EMA/336551/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

ADCETRIS

International non-proprietary name: Brentuximab vedotin

Procedure No. EMEA/H/C/002455/0000/11/109

Note

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

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	15 Jul 2023	15 Jul 2023	☐
☐	CHMP Rapporteur Assessment Report	08 Sep 2023	08 Sep 2023	☐
☐	CHMP Co-Rapporteur Assessment Report	08 Sep 2023	n/a	☐
☐	PRAC Rapporteur Assessment Report	15 Sep 2023	14 Sep 2023	☐
☐	CHMP Co-Rapporteur Assessment	20 Sep 2023	-	☐
☐	PRAC members comments	20 Sep 2023	-	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Sep 2023	21 Sep 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	28 Sep 2023	28 Sep 2023	☐
☐	CHMP members comments	02 Oct 2023	02 Oct 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	05 Oct 2023	05 Oct 2023	☐
☒	Request for supplementary information	12 Oct 2023	12 Oct 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur:	Peter Mol
PRAC Rapporteur:	Menno van der Elst
Contact person Rapporteur	Name: Anneruth Huttinga Tel: +31 88 224 8120

Procedure resources	
	Email: a.huttinga@cbg-meb.nl
Assessor Rapporteur	Name: Jessica Harskamp
Contact person - PRAC Rapporteur	Name: Anneruth Huttinga Tel: +31 88 224 8120 Email: a.huttinga@cbg-meb.nl
Assessor – PRAC Rapporteur	Name: Anne Slomp / Sara Khosrovani
EMA Product Lead	Name: Irene Papadouli Tel: +31 88781 8579 Email: Irene.Papadouli@ema.europa.eu
Procedure Assistant	Name: Irina Belonina Tel: +31 88781 6942 Email: Irina.Belonina@ema.europa.eu

Declarations

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

Table of contents

List of abbreviations

A+AVD	ADCETRIS® (brentuximab vedotin) in combination with doxorubicin (Adriamycin), vinblastine, and dacarbazine
A+CHP	ADCETRIS® (brentuximab vedotin) in combination with cyclophosphamide, doxorubicin, and prednisone
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
(s)ALCL	(systemic) anaplastic large-cell lymphoma
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
ATA	antitherapeutic antibody (ies)
ATLL	adult T-cell leukemia/lymphoma
CHMP	Committee for Medicinal Products for Human Use
CHOEP	cyclophosphamide, doxorubicin, Oncovin (vincristine), etoposide, prednisone
CHOP	cyclophosphamide, doxorubicin, Oncovin (vincristine), prednisone
CHP	cyclophosphamide, doxorubicin, prednisone
CR	complete remission
CSR	clinical study report
CT	computed tomography
CTCL	cutaneous T-cell lymphoma
EATL	enteropathy-associated T-cell lymphoma
ECHELON-1	clinical study C25003 of brentuximab vedotin (SGN-35)
ECHELON-2	clinical study SGN35-014 of brentuximab vedotin (SGN-35)
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU-RMP	European Union Risk Management Plan
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
HSTCL	hepatosplenic Tcell lymphoma

HR	hazard ratio
INV	investigator
IPI	International Prognostic Index
IRF	independent review facility
ITT	intent-to-treat
MAA	marketing authorization application
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MMAE	monomethyl auristatin E
MRU	medical resource utilization
nATA	neutralizing ATA
NCCN	National Comprehensive Cancer Network
NE	not estimable
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic(s) or progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMR	postmarketing requirement
PN	peripheral neuropathy
PR	partial remission
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma – not otherwise specified
QLQ-C30	(EORTC) Quality of Life Questionnaire – Core 30
RCT	randomized controlled trial
rwCR	real-world complete response
RWE	real-world evidence
rwOS	real-world overall survival
rwPFS	real-world progression-free survival
SAE	serious adverse event
SCT	stem cell transplantation

SD	stable disease
SGN-35	brentuximab vedotin, ADCETRIS
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TEAE	treatment-emergent adverse event

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 28 June 2023 an application for a variation.

The following changes were proposed:

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 (CHP) treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) for ADCETRIS based on the final overall survival results of Echelon-2 (SGN035-014). This 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. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 19.0 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.

The requested variation proposed 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.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0013/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0013/2021 was completed. On 13.12.2021 the PDCO issued an opinion on compliance for the PIP C(2021)9584 (final).

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 other than brentuximab vedotin for a condition related to the proposed indication.

Protocol assistance

The MAH has obtained scientific advice from the CHMP in May 2012 (EMA/288880/2012), with follow-up advice issued in September 2012 and October 2014 (see section 5.1.3).

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

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 (CHP) treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) for ADCETRIS based on the final overall survival results of Echelon-2 (SGN035-014). This 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. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 19.0 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.

☐is recommended for approval.

☐is not recommended for approval.

☒is subject to a request for supplementary information (please refer to the RSI section and the proposed Changes to the Product Information in a separate document) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)

☒ 60 days (36 days to assess)

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

The proposed target indication for this extension of indication is:

'CD30+ Peripheral T-cell Lymphomas (PTCLs)~~Systemic anaplastic large cell lymphoma~~

ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or CD30+ PTCL not otherwise specified (NOS) (see section 5.1).'

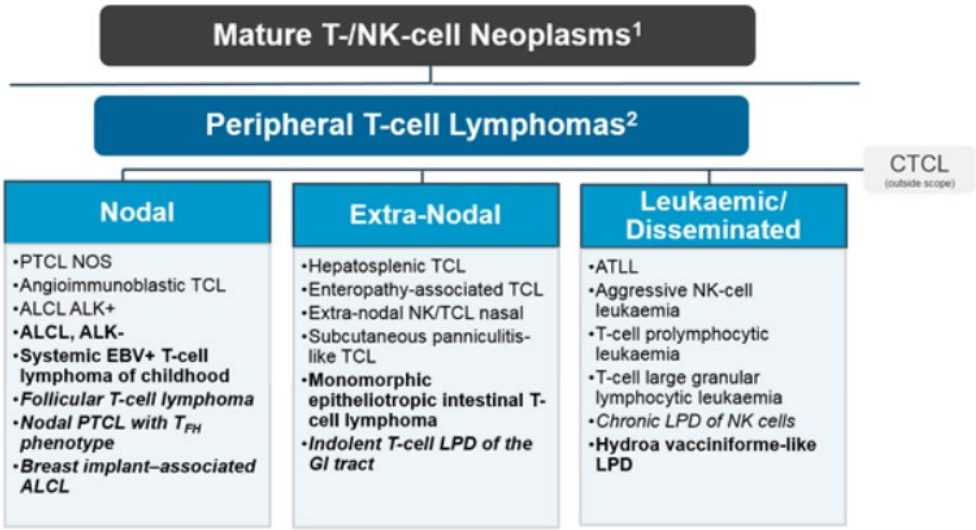
Peripheral T cell lymphomas (PTCLs) are a group of uncommon and heterogeneous malignant lymphoproliferative disorders that originate from post-thymic (peripheral) T cells or mature natural killer (NK) cells, which according to the recent (2016) WHO classification are recognized as separate entities.

Epidemiology

PTCL is a very rare condition with an estimated incidence of < 1 case per 100,000 people, which represents 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 Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS; 31-34%; Vose 2008, Laurent et al. 2017, Perry et al. 2016; Smith et al. 2015), angioimmunoblastic T cell lymphoma (AITL; 29%), anaplastic large cell lymphoma, primary systemic type (sALCL; ALK- 9%, ALK+6%) and enteropathy associated T cell lymphoma (EATL; 9%). Other subtypes are a.o. HSTCL, which is associated with Crohn's disease and constitutes 2.3% of the PTCL patients; adult T-cell leukemia/lymphoma (ATLL) constitutes in 1.0% of the PTCL cases.

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 (Figure 1). PTCL-NOS forms a heterogenous category of nodal and extranodal mature T-cell lymphomas that do not correspond to any specifically defined mature T-cell lymphoma entities in the current WHO classification. While it is reached as a diagnosis of exclusion, PTCL-NOS is recognized as a distinct medical entity.



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 is variable in PTCL-NOS. Among PTCL-NOS patients, one immunohistochemistry (IHC) study found that 82 of 141 cases (58%) had CD30 expression ≥1, and 32 of 141 cases (23%) had a score ≥3 (Bossard et al. 2014), while another study found that 45 of 87 cases (52%) had CD30 expression ≥2, and 27 of 81 cases (33%) had CD30 expression ≥3 (Sabattini et al. 2013).

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 genetics and clinical data.

The prognosis of PTCL is highly dependent on subtype and IPI score. 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. For patients with PTCL-NOS, the prognosis is relatively poor with a reported 5 year failure-free survival rate of 20% and 5-year overall survival (OS) rate of 32%. Within this generally poor prognosis, it appears that cure is possible for a small proportion of patients, possibly through subsequent SCT; 10-year OS shows 20% of patients still alive.

Management

The treatment of newly diagnosed PTCL patients depends on subtype, age, IPI and comorbidities. For nodal PTCL including PTCL-NOS,ALCL and AITL a 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.

Depending on the subtype, response duration of first line therapy may be 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 when patients are fit. For these patients, responses to subsequent therapy are often of modest duration.

3.1.2. 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.

3.1.3. The development programme/compliance with CHMP guidance/scientific advice

The main clinical data are derived from a randomised, controlled Phase 3 Study SGN35-014 (ECHELON-2). This study has been reviewed by the CHMP as a pivotal trial for the extension of indication to first line treatment of systemic anaplastic large cell lymphoma (sALCL) in March 2020 (II/0070). Long-term follow-up data for clinical trial Echelon-2 have been reviewed in November 2021 (II/0089). These updated data supported the positive benefit risk in sALCL. Long-term data of the ECHELON-2 study for the subgroup of PTCL-NOS patients form the basis of the current application.

For convenience, study design details and results of the overall study population are repeated in this report. Results for PTCL-NOS patients are presented separately from the overall study population.

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 and considerations on the HR assumption in the ECHELON-2 trial.

Further details regarding the advice in May 2012 (EMA/288880/2012):

- Regarding the proposed study population, it was noted that all ALK+ALCL patients, and possibly also those with ALK-ALCL with low IPI (⩽1), have a better prognosis and increased heterogeneity as compared to the trial population. The company was strongly advised to include informative numbers of patients with different subtypes. If the vast majority of patients were to have a prognostic better subtype

and the results upon subgroup analysis are not clear cut, certain subgroups might be excluded. The MAH maintained the criteria of 75±5% sALCL patients in the pivotal study.

- 6-8x CHOP was considered an appropriate control arm. The CHMP suggested to allow addition of etoposide in the control arm for younger patients with ALK+ALCL, which may lead to better EFS in these patients. The MAH chose to allow only CHOP treatment for the control arm.

- Primary endpoint PFS, secondary endpoints and sample size calculation were supported. PFS sensitivity analyses with radiotherapy as progression event were advised. The MAH incorporated this into other analyses, but did not present this as a separate analysis. Regarding PFS censoring, it was advised that undocumented PFS progression should be regarded as progression and not be censored. The MAH did not follow this advice, but did present a sensitivity analysis with this censoring rule.

In August 2012 a clarification letter to the advice from May 2012 was given (EMA/559606/2012):

- This letter was in line with the May 2012 advice, except regarding the possibility of unblinding at time of documented progression. Initially the CHMP did not agree with this approach, however, as brentuximab vedotin was to be an approved option for patients with r/r sALCL, the CHMP noticed that it would be unethical to withhold approved therapies from patients once they experience relapse in a trial.

A follow up advice was given in October 2014 (EMA /628945/2014):

- Based on low accrual rates and new external data pointing to an overestimation of the HR, the MAH planned to reduce the HR assumption from 0.6895 to 0.667 and increase the sample size from 300 to 360 patients, which would reduce the events needed from 238 to 191 events. This proposal was considered acceptable by the CHMP. The MAH eventually amended the sample size to 450, this amendment was not discussed with the CHMP.

- The MAH also proposed to conduct the primary analysis for PFS at 2 years after last patient enrolled if 191 events would not be reached before that time. The CHMP did not accept that proposal as these outcomes may be driven by early progressors. Nonetheless, the MAH amended the protocol (amendment 4, 15 May 2018) to allow analysis 2 years after last patient.

A pre-submission meeting with Rapporteur and Co-Rapporteur was held on 6th September 2022.

Fulfilment of MEA

The submission of the ECHELON-2 study also served to fulfil the commitment made by the marketing authorization holder (MAH), during the initial European marketing authorization application (MAA) in order to provide safety data in the sALCL population (MEA-015). As such, the 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).

3.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

3.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

3.3. Clinical aspects

3.3.1. Introduction

- 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

3.3.2. Pharmacokinetics

No new clinical pharmacokinetic or pharmacodynamic data have been submitted in this application, which is considered acceptable.

3.4. Clinical efficacy

3.4.1. Dose response study(ies)

No new dose-response studies have been submitted. The posology remains unchanged (i.e. the same as for the approved PTCL subtype systemic anaplastic large cell lymphoma (sALCL).

3.4.2. Main study

ECHELON-2: 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.

Methods

The study design is shown in Figure 2.

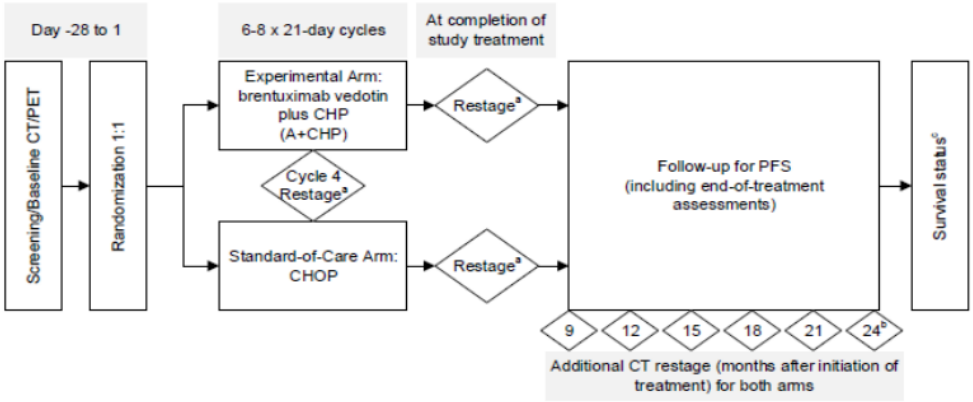


Figure 2. Study design

Study participants

Key inclusion criteria

- 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
    - 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

Key exclusion criteria

- 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 1. 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 2.

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 1. 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 2. 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 independent review facility (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 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 a 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 238 events (progression or death due to any cause) were 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) was anticipated. An additional 18-month follow-up period was 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 were to be randomized. The target proportion of patients with a diagnosis of sALCL per central pathology assessment was 75% (±5%).

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 analyses 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 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, $\alpha=0.025$ 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 3.

Table 3. 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 were planned, including, but 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 tumour 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 tumour 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 tumour assessment are considered to have had an event on the date of death or progression.

As exploratory analyses, PFS subgroup analyses were prespecified. These included subgroups by age, gender, race, geographic region, weight, prior cutaneous ALCL yes/no, baseline ECOG PS, disease indication (histologic subtype), ALK status in sALCL patients, disease stage, IPI score, randomisation strata, malignant cutaneous lesions at baseline yes/no, BM involvement at baseline yes/no, patients with central pathology confirmed histologic subtype/CD30 expression, patients with and without consolidative autologous or allogeneic SCT, cycles of study treatment received.

Key secondary endpoints: A fixed sequence testing procedure (Westfall 2001) was 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 had 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 was defined as the proportion of patients that develop ATA at any time during the study. ATA incidence was to be summarized by treatment group.

MRU: Medical resource utilization data included medical care encounters related to study treatment or treatment for lymphoma. Medical resource utilization (MRU) data was to be 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 focussed 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 & sALK positive sALCL will be pooled with the same IPI score and 'other types than ALK positive' sALCL (see the SAP).

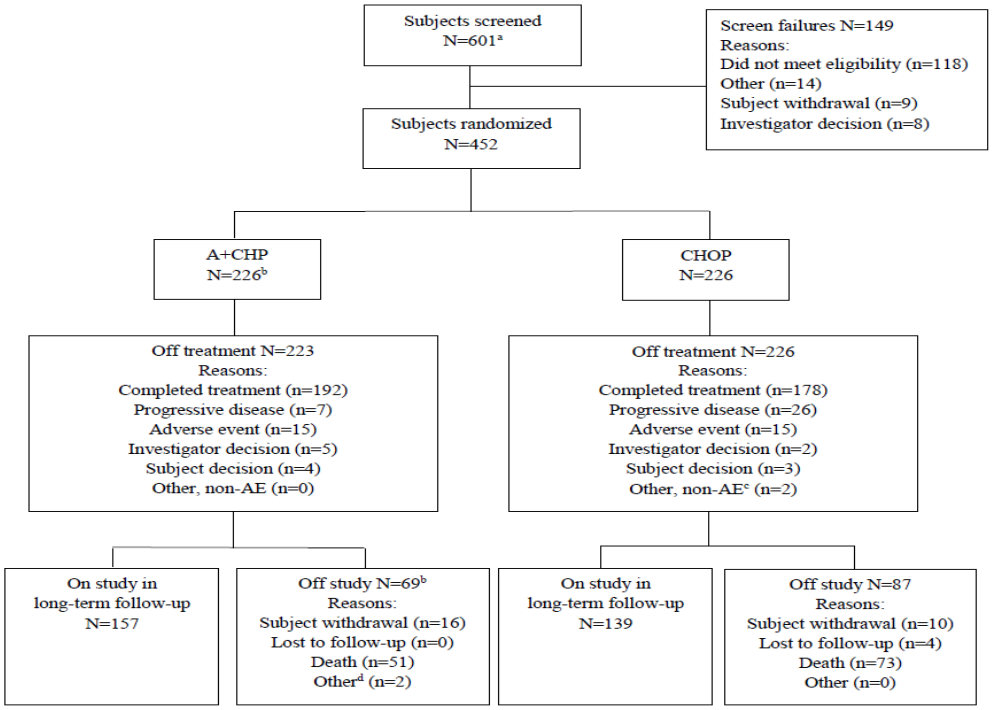
The primary analysis of PFS per IRF was specified to occur after the earliest of:

- A total of 238 events in the ITT analysis set have been recorded.
- August 2018, if 238 PFS events had 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. The disposition of subjects is summarized in Figure 3.



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.
Source: Table 14.1.1.5 and Listing 16.2.1.1

Figure 3. Summary of subject disposition as of August 2018

As of study closure in 2020 a total of 3 patients (1%) on the A+CHP arm and 5 patients (2%) on the CHOP arm were lost to follow-up (Table 4). In addition, 22 patients (10%) on the A+CHP arm and 16 patients (7%) on the CHOP arm withdrew consent, while 68 patients (30%) on the A+CHP arm and 89 patients (39%) on the CHOP arm died.

Table 4. Patient disposition as of November 2020 (ITT population)

	A+CHP (N=226) n (%)	**CHOP (N=226) n (%)**	**Total (N=452) n (%)**
Number of patients off study	226 (100)	226 (100)	452 (100)
Reason for study discontinuation			
Patient withdrawal of consent	22 (10)	16 (7)	38 (8)
Loss to follow-up	3 (1)	5 (2)	8 (2)
Death	68 (30)	89 (39)	157 (35)
Other [a]	2 (1)	0	2 (0)
Study terminated per protocol by sponsor	131 (58)	116 (51)	247 (55)
Number of patients who participated in follow-up visits	194 (86)	185 (82)	379 (84)

Source: SGN35-014 CSR Addendum Table 1.

A+CHP: brentuximab vedotin (ADCETRIS), cyclophosphamide, doxorubicin, Oncovin (vincristine), prednisone; CHOP: cyclophosphamide, doxorubicin, Oncovin (vincristine), prednisone.

[a] "Other" includes "Patient was not eligible and should not have been randomized. Patient did not receive any treatment and therefore was removed from the study" and "change of diagnosis on 13 Sep 2016."

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). The study completed in 2020 with a final data cut-off date of 05 November 2020; data presented below are labeled as coming from the 15 August 2018 primary analysis or the 2020 long-term follow-up (LTFU) analysis current to study closure.

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 5.

Table 5. 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

A summary of demographics and subject characteristics is shown in Table 6, Table 7 and Table 8.

Table 6. 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)

a Patient 97205-0173 (A+CHP) is not included in the summary of ECOG, because baseline ECOG = 0 was collected on 11-SEP-2014 after treatment start date 06-SEP-2014.

Table 7. 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 8. 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

PTCL-NOS subpopulation

A summary of demographics and disease characteristics for patients with PTCL-NOS is shown in Table 9 and Table 10.

Table 9. Demographics (ITT Population Patients With PTCL-NOS)

	A+CHP (N=29) n (%)	CHOP (N=43) n (%)
Age (yrs)		
n	29	43
Mean (std dev)	62.8 (10.40)	61.8 (12.21)
Median	64.0	64.0
Min, Max	35, 77	38, 82
Gender, n(%)		
Male	20 (69)	25 (58)
Female	9 (31)	18 (42)
Ethnicity, n(%)		
Hispanic or Latino	2 (7)	1 (2)
Not Hispanic or Latino	21 (72)	35 (81)
Unknown	6 (21)	7 (16)
Race, n(%)		
Asian	5 (17)	9 (21)
Black or African American	3 (10)	0
Native Hawaiian or other Pacific Islander	0	0
White	18 (62)	28 (65)
Other	1 (3)	0
Unknown	2 (7)	6 (14)
Body Mass Index (kg/m^2)		
n	29	43
Mean (std dev)	25.3 (5.45)	26.7 (6.44)
Median	25.3	25.3
Min, Max	18, 38	16, 45
ECOG Performance Status (a), n(%)		
0	11 (38)	27 (63)
1	12 (41)	15 (35)
2	6 (21)	1 (2)

Source: /bdm/tbos/SGN-035/35-14/CSR/Adhoc/PostSubm_2019-01-28/Tables/T99.3.2.1.1-demo-itt-subgrp, run time 04 March 2019 16:39.
(a) Patient 97205-0173 (A+CHP) is not included in the summary of ECOG, because baseline ECOG = 0 was collected on 11-SEP-2014 after treatment start date 06-SEP-2014.

Table 10. Summary of Baseline Disease Characteristics (ITT Population Patients With PTCL-NOS)

	A+CHP (N=29)	CHOP (N=43)
Diagnosis per local assessment n (%)		
Peripheral T-cell lymphoma PTCL-NOS	29 (100)	43 (100)
Time from Diagnosis to First Dose (months)		
n	29	43
Mean (STD)	1.1 (0.9)	1.3 (1.0)
Median	0.9	1.0
Min, Max	0, 4	0, 4
Disease Staging at Diagnosis, n (%)		
Stage I	0	2 (5)
Stage II	4 (14)	9 (21)
Stage III	14 (48)	13 (30)
Stage IV	11 (38)	19 (44)
Baseline IPI Score, n (%)		
0	0	2 (5)
1	4 (14)	10 (23)
2	6 (21)	11 (26)
3	16 (55)	16 (37)
4	3 (10)	3 (7)
5	0	1 (2)
Serum LDH per local laboratory, n (%)		
≤1×ULN	10 (34)	16 (37)
>1×ULN	19 (66)	27 (63)
Extranodal Disease Involvement, n (%)		
≤1 site	21 (72)	32 (74)
>1 site	8 (28)	11 (26)
HTLV-1 Status, n (%)		
Positive	0	1 (2)
Negative	28 (97)	41 (95)
Intended Number of Cycles at Baseline, n (%)		
6	24 (83)	36 (84)
8	5 (17)	7 (16)
Intention of stem cell transplant following completion of study regimen, n (%)		
Yes	13 (45)	19 (44)
No	15 (52)	24 (56)
Baseline bone marrow biopsy lymphoma involvement		
Yes	6 (21)	9 (21)
No	23 (79)	34 (79)

Numbers analysed

Efficacy analyses were performed using the ITT analysis set, which included all 452 randomized patients; 226 patients randomized to A+CHP and 226 patients 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.

Subgroup efficacy analyses were performed for patients with PTCL-NOS (n=72, 16%), which included 29 patients randomised to A+CHP and 42 patients randomised to CHOP.

Outcomes and estimation

Primary Efficacy Analysis PFS per IRF

Data cut-off 2018 primary analysis

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. As the planned 238 PFS events had not been accrued at this time, the date was the trigger for the primary PFS analysis. PFS per IRF was significantly improved on the A+CHP arm compared with the CHOP arm. The median PFS was 48.2 months in the A+CHP arm vs. 20.8 months in the CHOP arm with a stratified HR of 0.71 [95% CI: 0.54, 0.93], p=0.011 (Table 11, Figure 4).

Table 11. 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

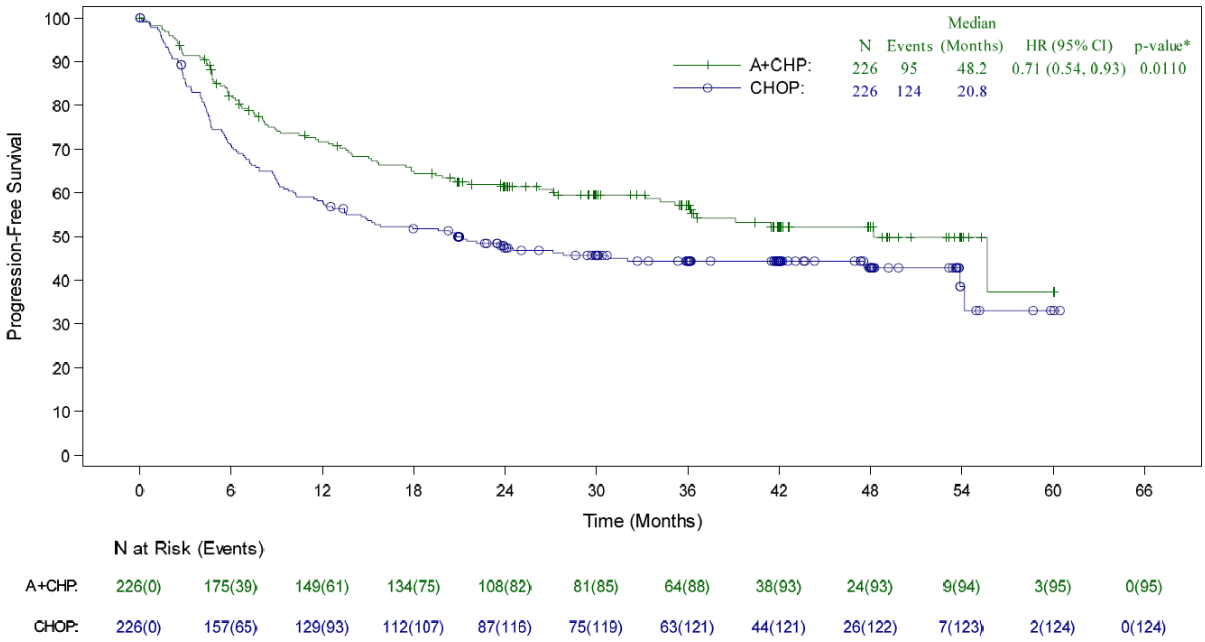
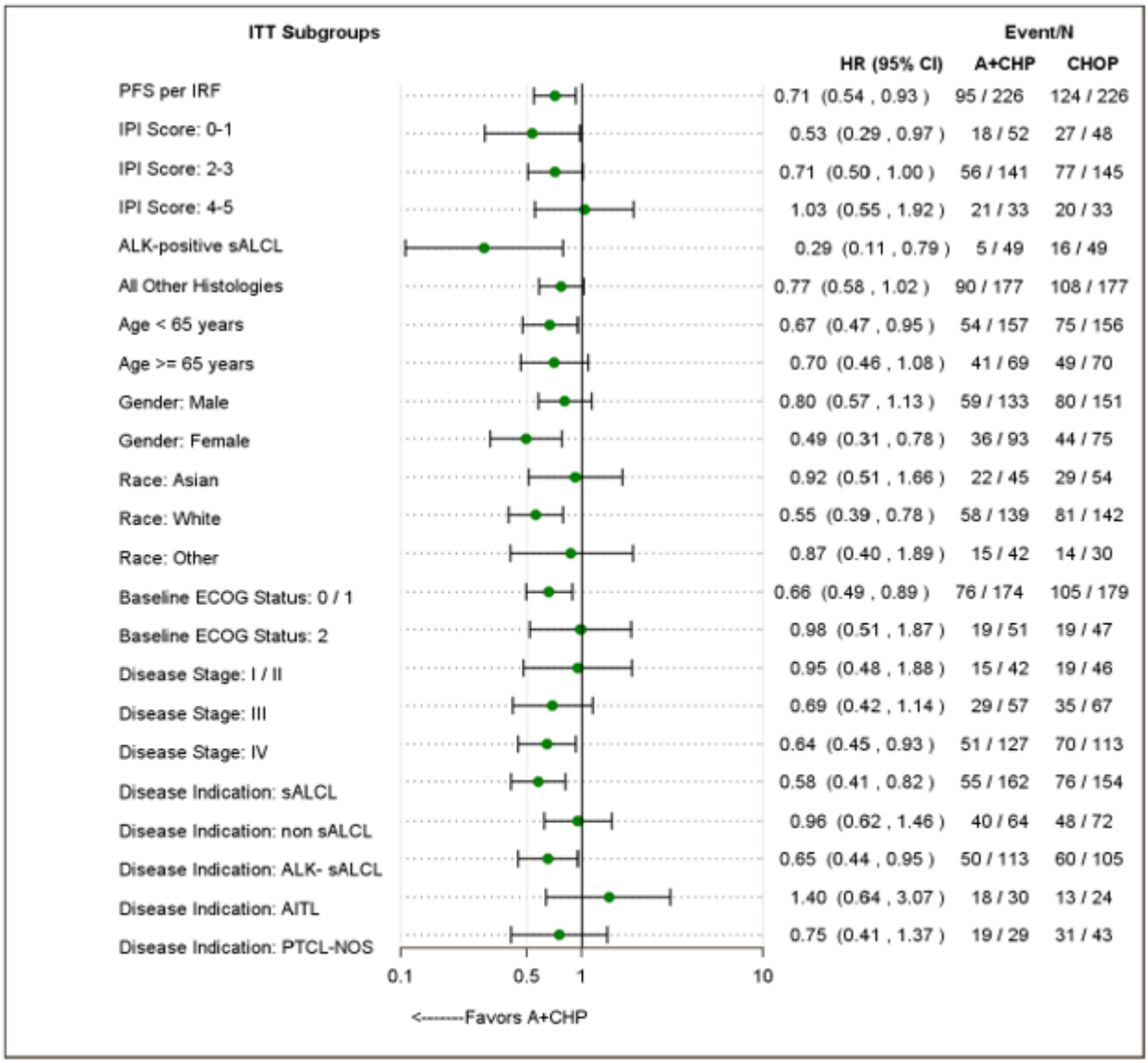


Figure 4. Kaplan-Meier plot of PFS per IRF (ITT)

The reasons for PFS censoring and PFS subgroup analyses for the ITT are shown in Table 12 and Figure 5.

Table 12. 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



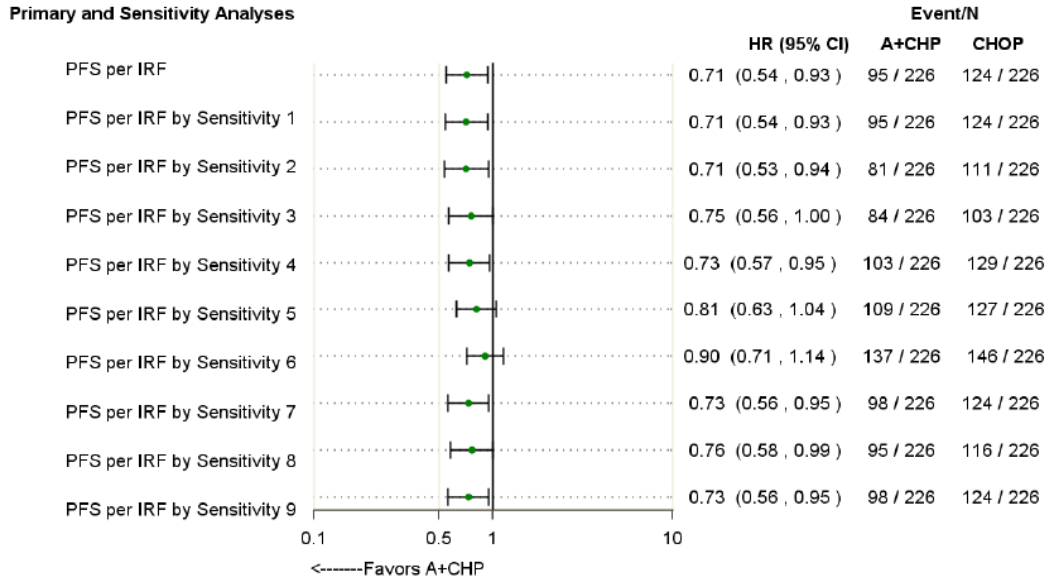
HR is calculated from the Cox regression model considering stratification factors at randomization
Source: Figure 14.2.1.23

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

Figure 5. PFS subgroup analyses (ITT)

For the PFS sensitivity analyses see Table 13, Table 14, Table 15 and Figure 6.

Table 13. PFS- primary and sensitivity analyses (ITT)



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. 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
9. (not prespecified) 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.

Table 14. 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%)

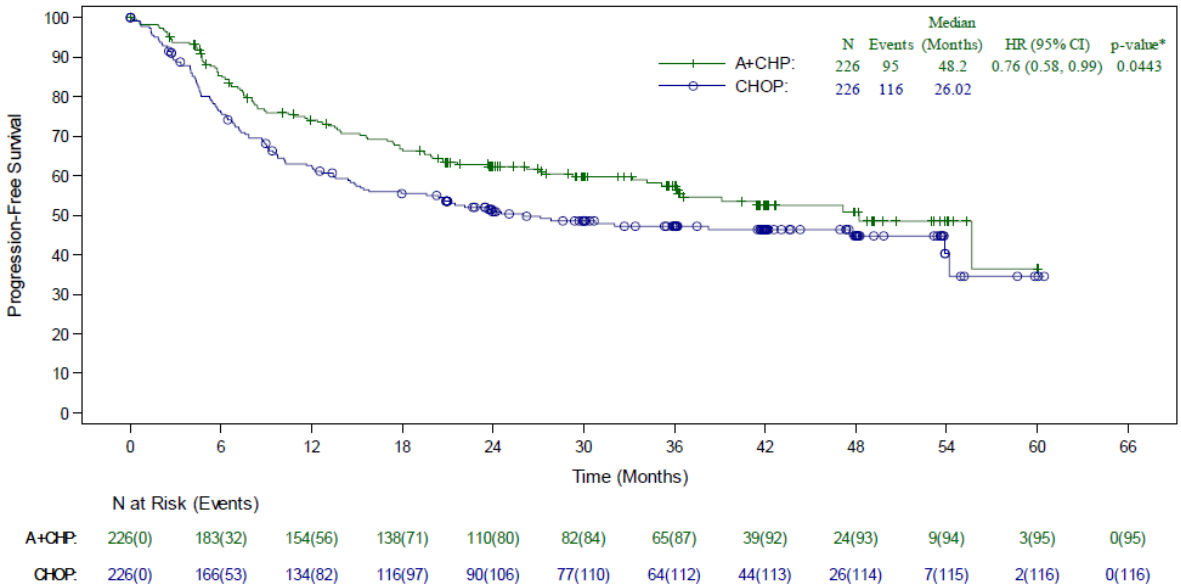


Figure 6. Progression-Free Survival per IRF by Treatment Arm, Sensitivity analysis 8 (ITT)

Table 15. Summary of Censoring Reasons for PFS per IRF, Sensitivity 8 (ITT)

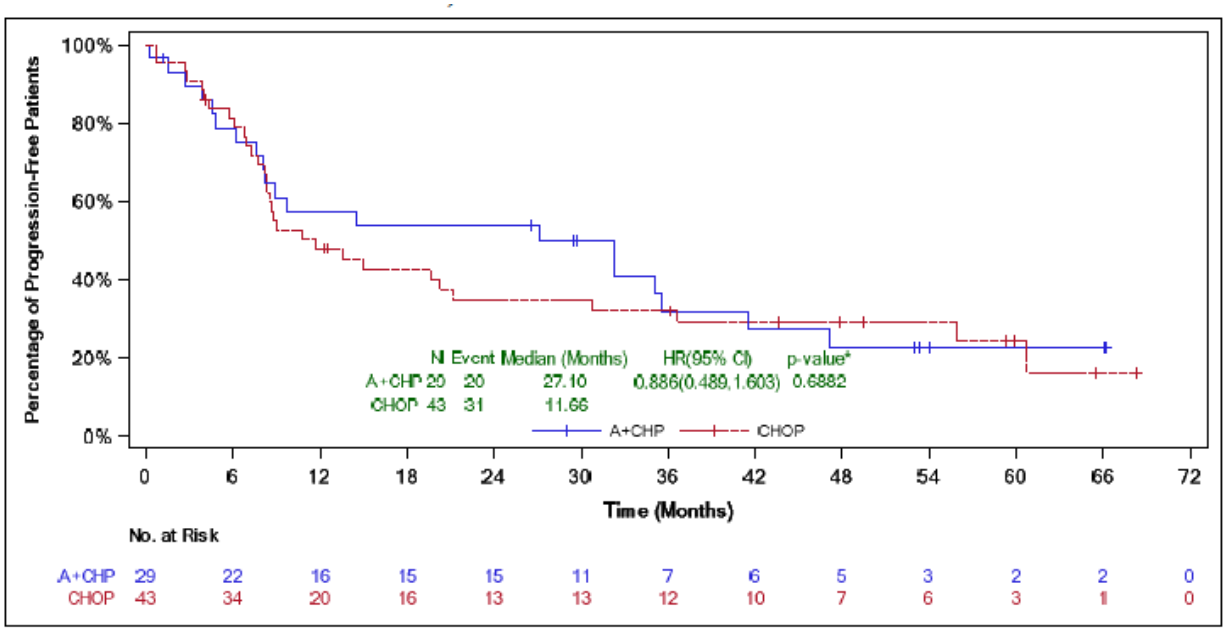
	A+CHP (N=226)	CHOP (N=226)	Total (N=452)
Censored, n (%)	131 (58)	110 (49)	241 (53)
No adequate baseline tumor assessment, or no adequate post-baseline tumor assessment	5 (2)	3 (1)	8 (2)
No documented progression, still on study	117 (52)	100 (44)	217 (48)
Off Study	9 (4)	7 (3)	16 (4)
Withdrawal of consent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

PTCL-NOS subgroup

Table 16 Summary of Progression-Free Survival (PFS) per IRF ITT Analysis Set - PTCL-NOS

	A+CHP (N=29)	CHOP (N=43)	Total (N=72)
Number of patients with a PFS event, n (%)	19 (66)	31 (72)	50 (69)
Disease Progression per Cheson	15 (52)	23 (53)	38 (53)
Death	2 (7)	2 (5)	4 (6)
New Therapy[a]	2 (7)	6 (14)	8 (11)
Stratified Hazard ratio (95% C.I.) (A+CHP to CHOP)			0.75 (0.41, 1.37)
Stratified Log-rank p-value[b]			0.3493
Median PFS (months) (95% C.I.)[c]	21.16 (7.66, 36.24)	11.43 (6.80, 19.61)	12.09 (8.08, 21.16)
25th, 75th percentile	5.62, -	4.47, -	4.67, -
Observed min, max	0.03+, 60.02+	0.66, 55.16+	0.03+, 60.02+
Censored, n (%)	10 (34)	12 (28)	22 (31)
Estimated progression-free rate (95% C.I.)[c] at:			
6 months	75.0% (54.6%, 87.2%)	69.8% (53.7%, 81.2%)	71.8% (59.8%, 80.8%)
12 months	57.1% (37.1%, 72.9%)	46.5% (31.2%, 60.4%)	50.7% (38.6%, 61.6%)
24 months	50.0% (30.6%, 66.6%)	29.5% (16.6%, 43.5%)	37.7% (26.5%, 48.8%)
36 months	35.6% (17.6%, 54.2%)	27.0% (14.7%, 40.9%)	30.9% (20.4%, 42.1%)
48 months	25.5% (10.0%, 44.4%)	27.0% (14.7%, 40.9%)	27.3% (17.1%, 38.5%)
Median PFS follow-up (months) (95% C.I.)[d]	42.61 (29.47, 54.01)	43.60 (41.79, 53.16)	42.61 (41.46, 53.16)

Figure 7. ECHELON-2: Updated (2019) PFS per Investigator, EMA censoring rules (i.e. sensitivity analysis 8) (ITT Population – PTCL-NOS Subset)

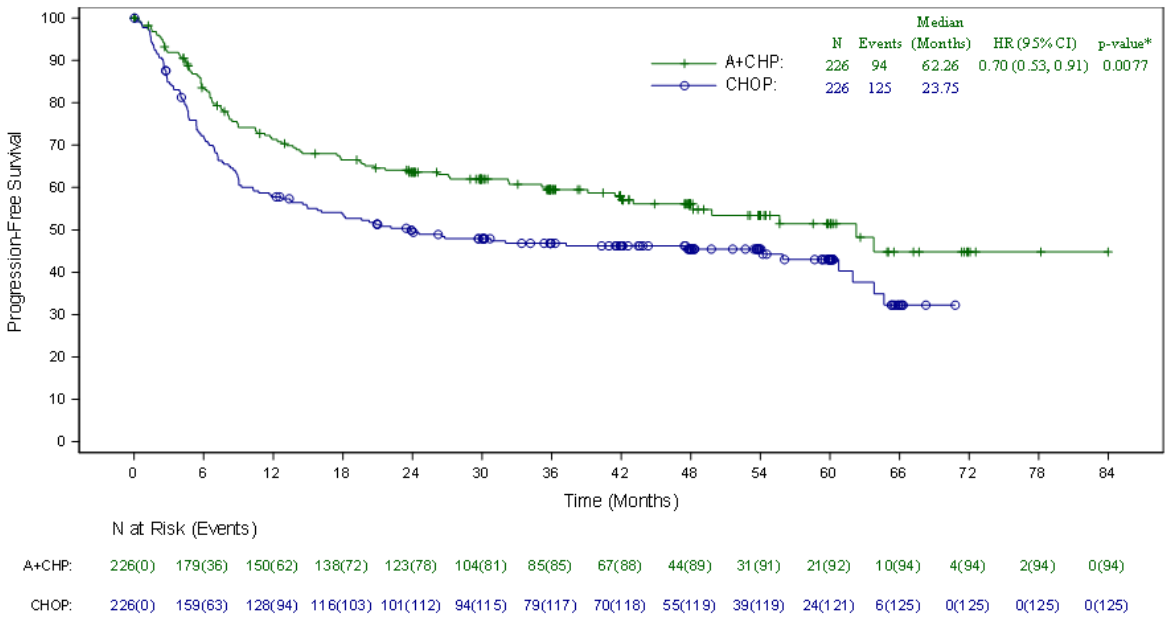


Source: (Table 96.1.2.1.2) /bdm/tbos/SGN-035/35-14/CSR/Adhoc/EMA_RSI_2019/Figures/F96.1.2.1.2-KM_PFS_INV_sen8_subgrp, run 07 October 2019, 10:43. Data snapshot: 25SEP2019.
* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization

Data cut-off 2020 long term follow-up

At the 05 November 2020 data cutoff for study closure, consistent with the primary analysis per IRF, 219 patients (48%) had experienced a PFS event per investigator; 94 of 226 A+CHP-randomized patients (42%) and 125 of 226 CHOP-randomized patients (55%). Median PFS was 62.26 months (95% CI: 41.99, –) on the A+CHP arm versus 23.75 months (95% CI: 13.57, 60.75) on the CHOP arm (stratified HR 0.70, 95% CI 0.53 to 0.91, descriptive p=0.0077, Table 17).

Table 17. Kaplan-Meier Plot of PFS per Investigator as of Study Closure (ITT Population, data cut-off 2020)



Source: SG035-014 CSR Addendum Figure 2.

* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0 1/2 3/4-5) at randomization.

PTCL-NOS subgroup

At the 05 November 2020 data cut-off for study closure, PFS per investigator data were mature for the PTCL-NOS subgroup. At that time, 51 of 72 PTCL-NOS patients (71%) had experienced a PFS per investigator event (19 of the 29 A+CHP-randomized patients [66%] and 32 of the 43 CHOP-randomized patients [74%]). The median PFS was 32.26 months on A+CHP vs. 10.74 months on CHOP, with a stratified HR of 0.79, 95% CI 0.43 to 1.43, descriptive p=0.429, Figure 8).

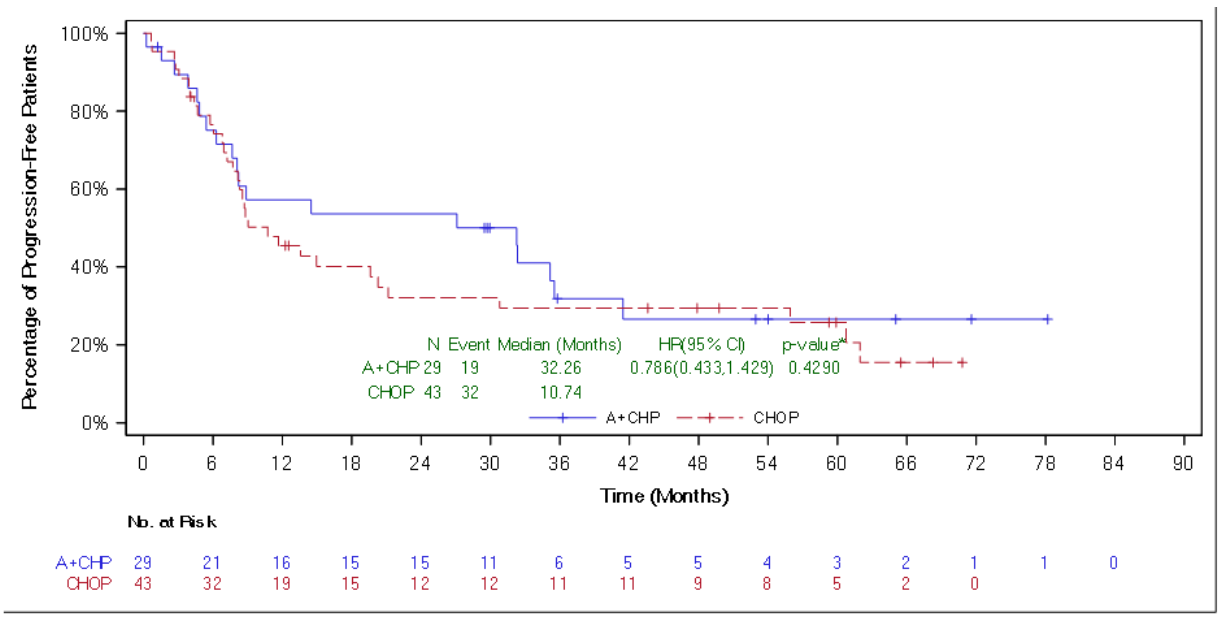


Figure 8. PFS per Investigator as of Study Closure (Subset of ITT Population With PTCL-NOS, data cut-off 2020)

Key secondary endpoints

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. The KM plot of PFS per IRF for subjects with sALCL is shown in Figure 9.

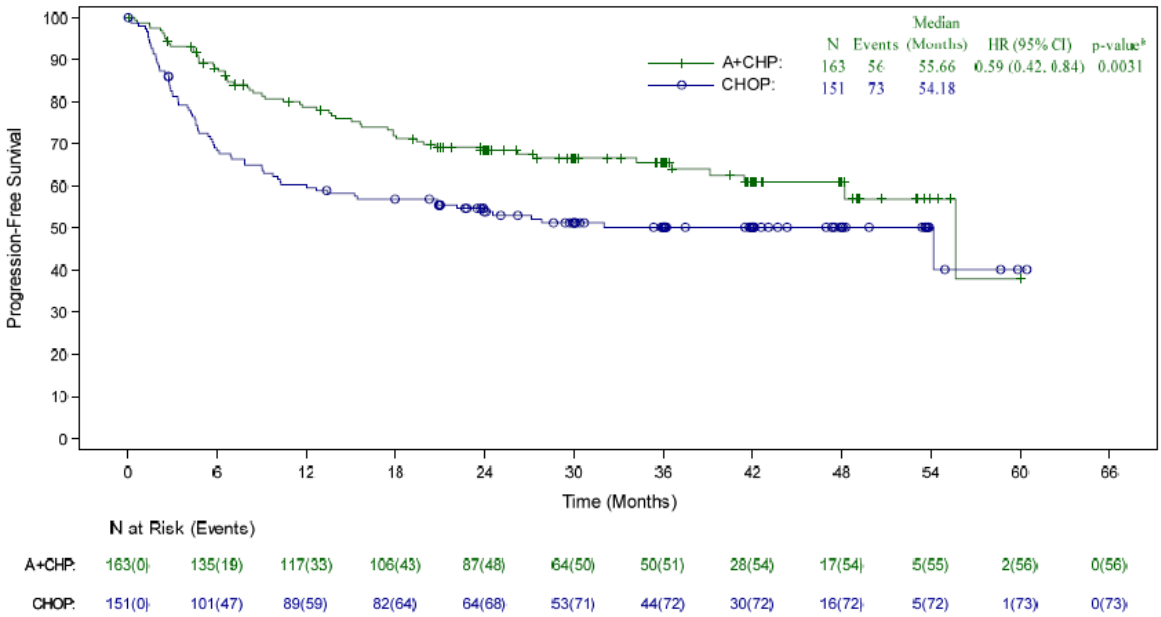


Figure 9. PFS per IRF for subjects with sALCL (ITT)

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 Odds ratio was 1.71 [1.16, 2.53], p-value 0.0069. 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.

In the non-sALCL subgroup there was no difference in CR rate between the A+CHP and CHOP arm (59.4% vs 61.1%) and for PTCL-NOS patients the CR rate was 65.5% with A+CHP vs. 58.1% with CHOP. In Figure 10 the CR subgroup analyses are shown.

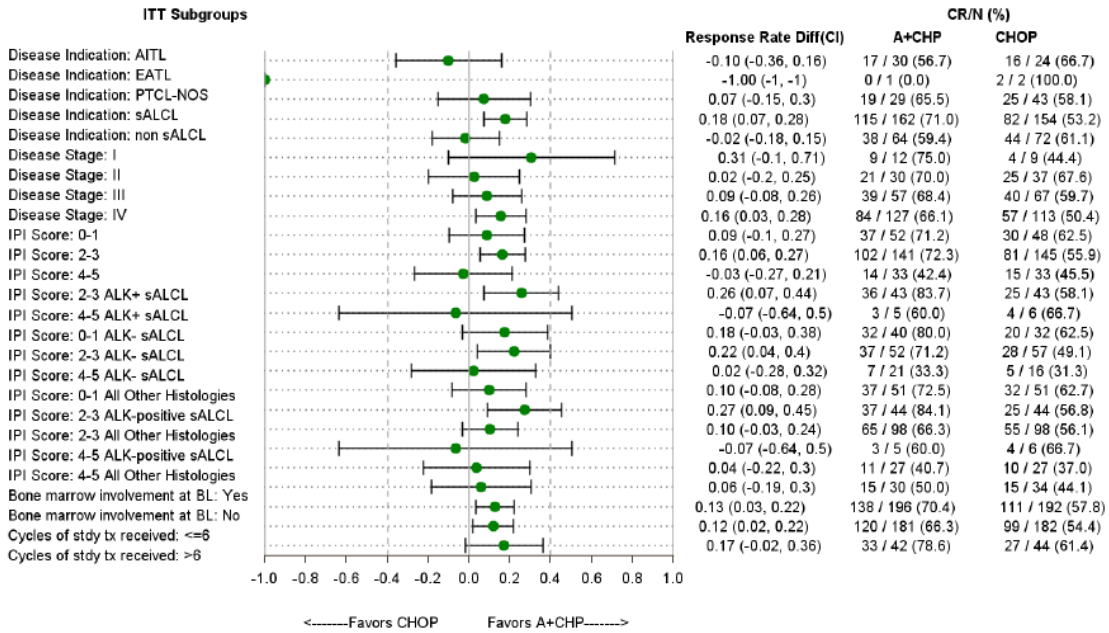


Figure 10. Difference in CR at EOT per IRF by prognostic factors (ITT)

Overall survival

Data cut-off 2018

The median OS observation time is 42.12 months at the 2018 data cut-off. 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 (Figure 11). The stratified HR was 0.66 (95% CI: 0.46, 0.95), p=0.0244. (OS critical p-value: 0.025.) In the subgroup of patients with PTCL-NOS, the OS HR was 0.83 (0.38, 1.80; Figure 12). Updated results of ad hoc OS analysis in this subgroup (HR 0.75, data cut-off Oct 2019) are shown in Figure 13.

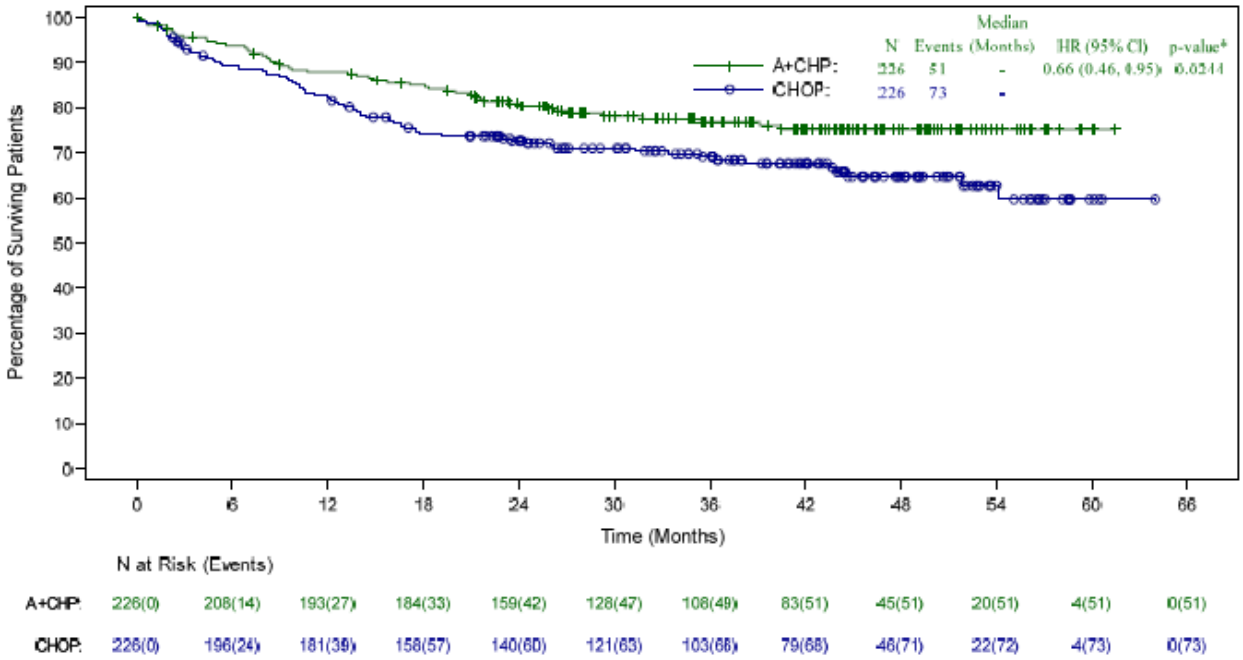


Figure 11. Kaplan Meier curve Overall survival (ITT)

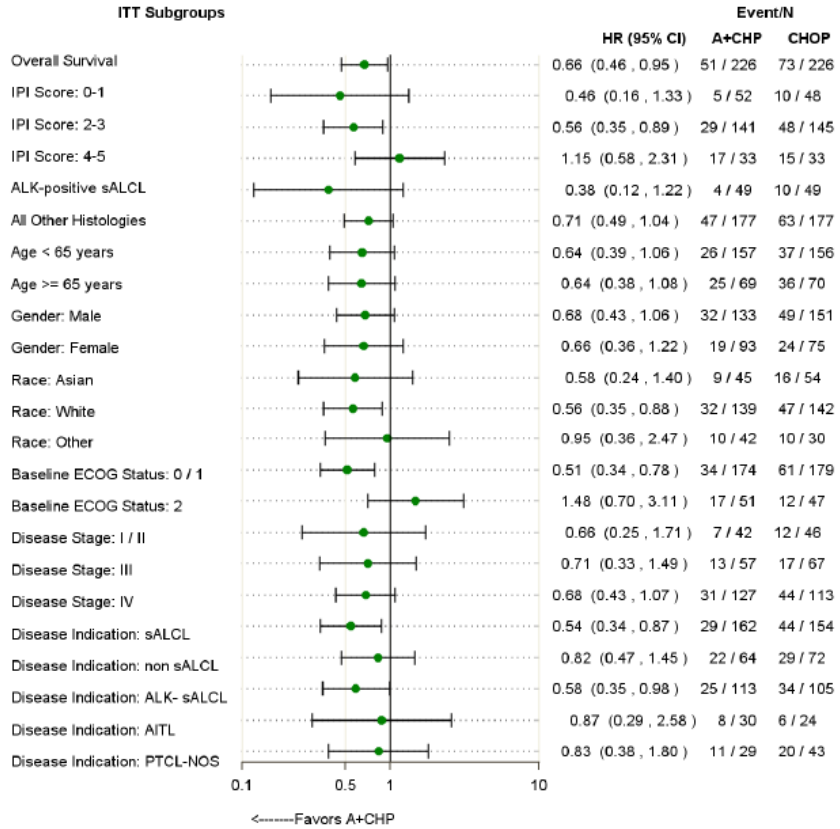
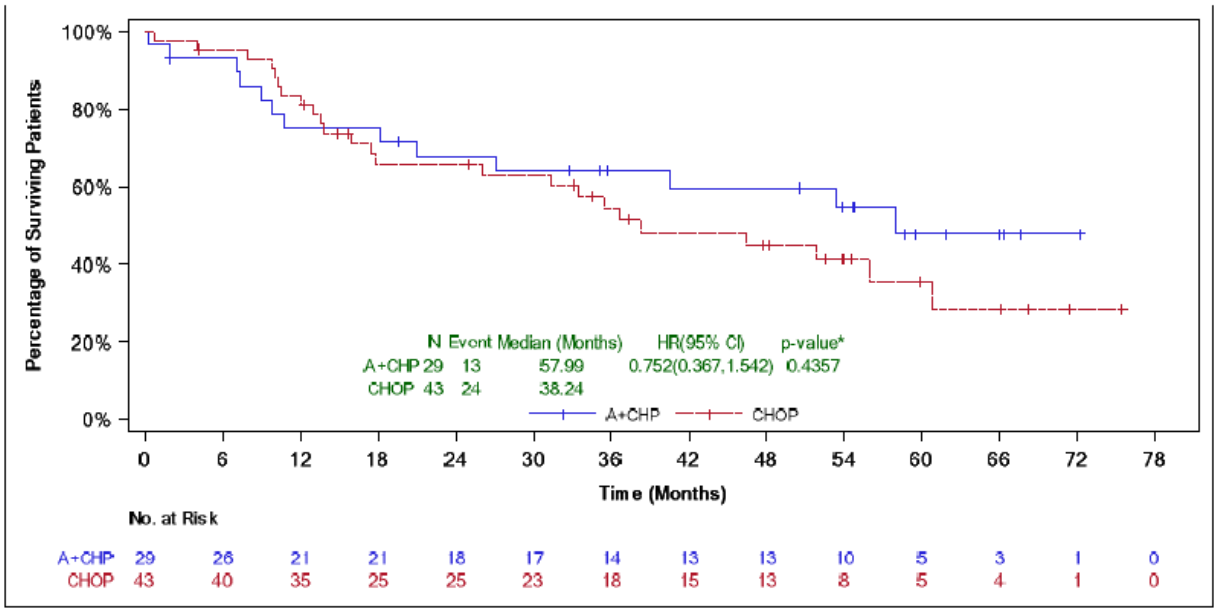


Figure 12. Subgroup analyses for OS (ITT)

PTCL-NOS subgroup

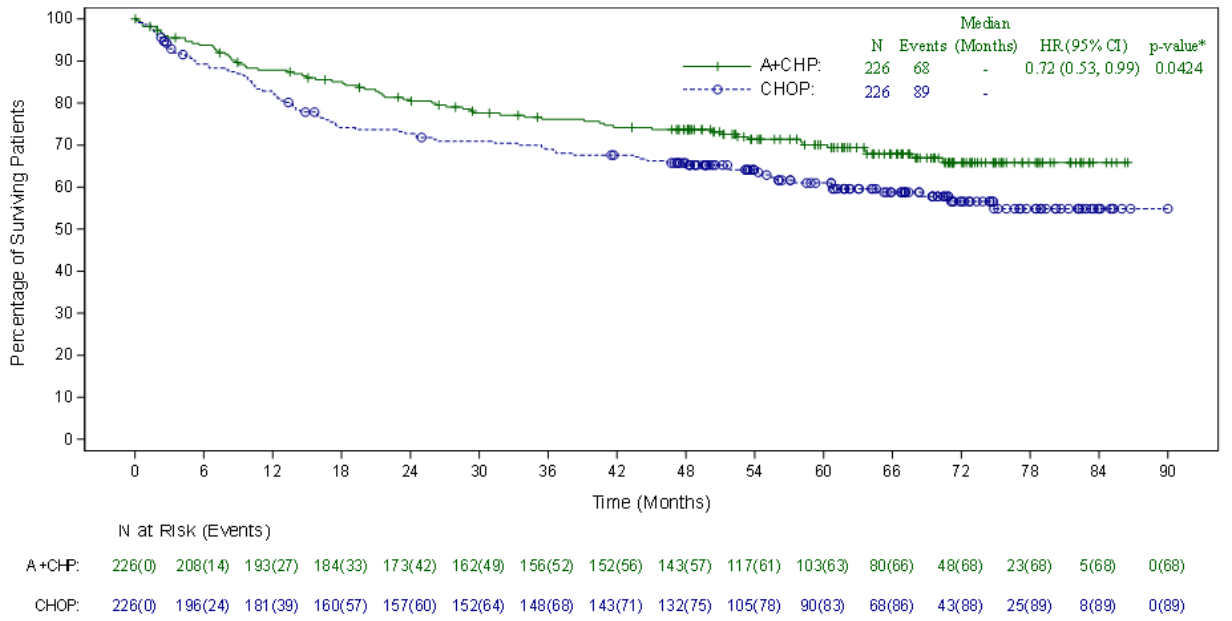
Figure 13. : ECHELON-2: Updated (2019) Overall Survival (ITT Population – PTCL-NOS Subset)



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.

Data cut-off 2020 long term follow-up

At the 5 November 2020 data cut-off for study closure, the stratified OS HR was 0.72 (95% CI 0.53 to 0.99, p=0.0424; Figure 14) in favour of A+ CHP. Median OS was still not reached, nor was the 75th percentile. The 25th percentile of OS in the A+CHP arm was 40.9 months as compared with 17.5 months in the CHOP arm.



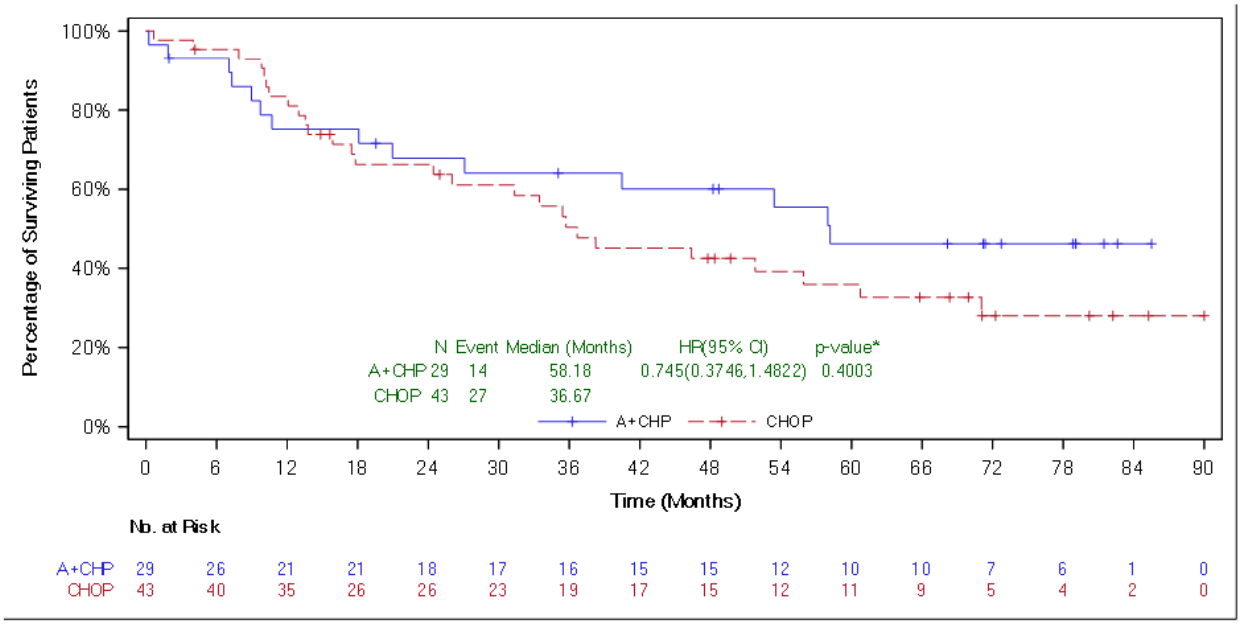
Source: SGN35-014 CSR Addendum Figure 4, database lock 05 November 2020.

*Computed from log-rank test using stratification factors (ALK+ sALCL: Yes/No and IPI score 0-1/2-3/4-5) at randomization.

Figure 14. Kaplan-Meier Plot of Overall Survival as of Study Closure (ITT Population, data cut-off 2020)

PTCL-NOS subgroup

At the 05 November 2020 data cut-off for study closure, OS data were mature for the PTCL-NOS subset. At that time, 43 of 72 PTCL-NOS patients (57%) had died (14 of the 29 A+CHP-randomized patients [48%] and 27 of the 43 CHOP-randomized patients [63%]). PTCL-NOS patients randomized to A+CHP showed a 25% reduction in the risk of death compared with CHOP-randomized patients (stratified HR 0.75, 95% CI 0.37 to 1.48, Figure 15). Median OS was 58.18 vs. 36.67 months, respectively.



Source: SGN35-014 CSR Addendum Figure 14.2.4.2.
Database lock date 05 November 2020.

Figure 15. OS as of Study Closure (Subset of ITT Population With PTCL-NOS, data cut-off 2020)

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 18). The Odds ratio was 1.99 [1.25, 3.16], 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%).

The ORR in non-sALCL patients is 71.9% vs 75% in the A+CHP versus the CHOP arm and in PTCL-NOS patients 79.3% vs. 74.4%, respectively (Figure 16).

Table 18. 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	

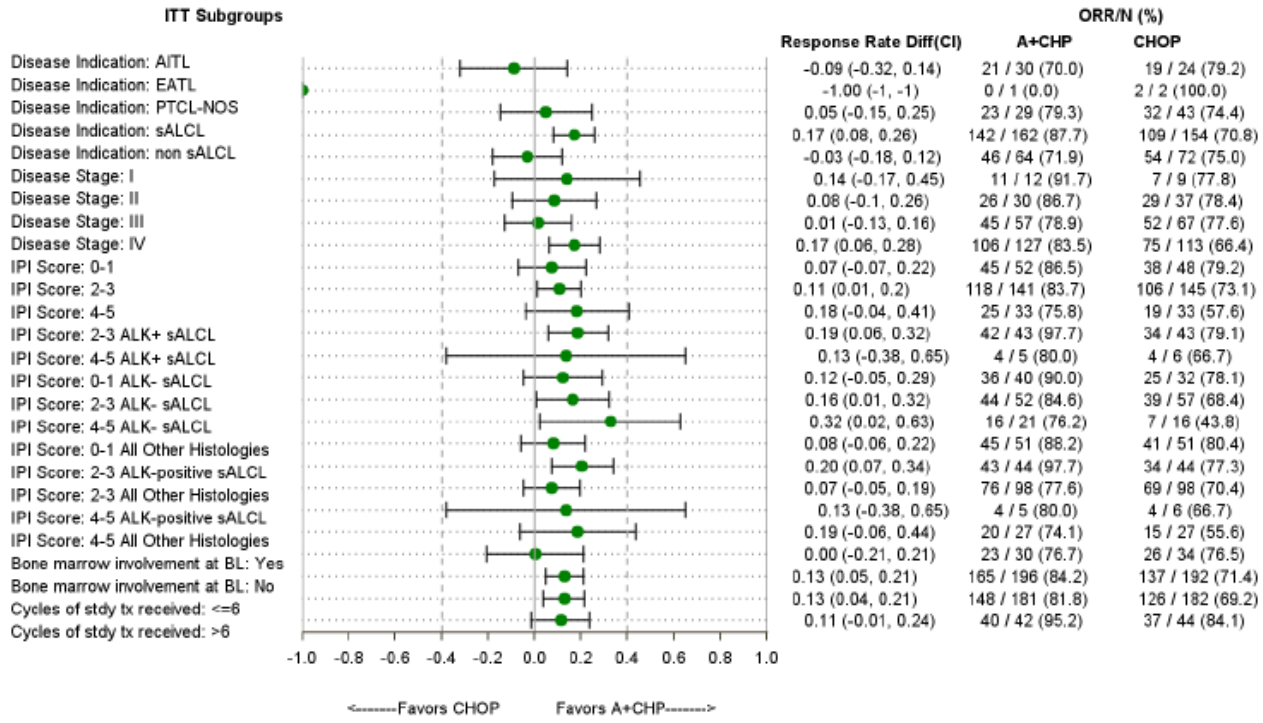


Figure 16. Difference in ORR at EOT per IRF and 95% CI for ORR Difference by Prognostic Factors (ITT)

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 at least 1 hospitalization visit at the primary 2018 data cut-off was 141 (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. The most frequent reason for hospitalization in the A+CHP arm was '*related to an AE that started during the treatment period and is ongoing'* (37% of patients in the A+CHP arm; 23% in the control arm) and in the control arm *'chemotherapy'* (28% with A+CHP vs. 38% with CHOP).

Quality of Life

- EORTC QLQ c-30: The mean total scores are shown in Figure 17. The mean total score and physical functioning scores were lower at baseline and trended lower on the A+CHP arm, but both rose above baseline levels with time on treatment; however there were no meaningful differences in the total score. Some statistically significant differences between the 2 arms in favour of CHOP were maintained across some cycles based on linear mixed models: total score (Cycle 2), role functioning (Cycles 2 through 6), social functioning (Cycles 2, 3, and 6), diarrhoea (Cycles 2 and 7), nausea & vomiting (Cycles 2 and 7) and pain (Cycles 2, 3, and 4). 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 up to Cycle 8 (Figure 18). The score was lower at the end of treatment visit for the A+CHP arm compared with the CHOP arm, but returned to baseline values during long-term follow-up. Results of the analysis using linear mixed models showed no differences between the treatment arms across the treatment cycles.

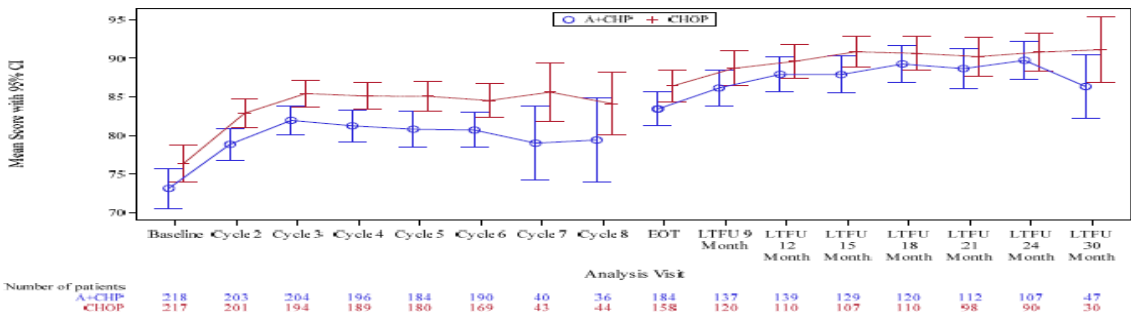


Figure 17. Mean score over time: QLQC-30 total score (ITT Population)

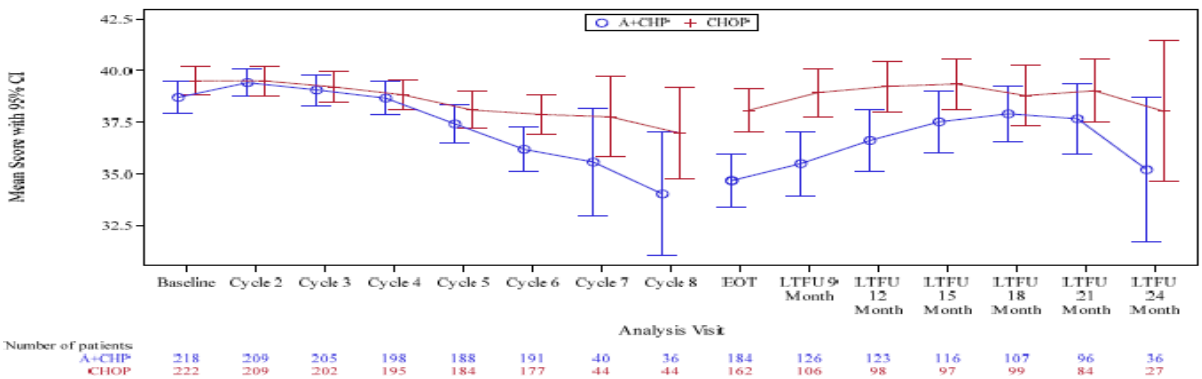


Figure 18. Mean score over time: FACT/GOG-NTX

- EQ-5D-3L:The mean score was lower in the A+CHP at baseline and generally trended lower during the study period (see Figure 19). The scores improved over time on both treatment arms. Analysis of the change in EQ-5D score from baseline using linear mixed models showed that overall, there was no difference between the treatment arms based on the US- and UK-based value sets.

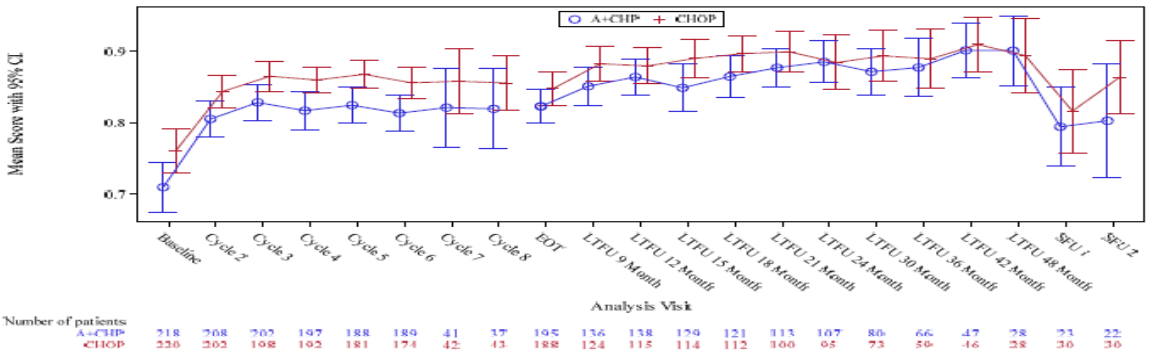


Figure 19. Mean score over time: EQ5D US TTO (ITT Population)

Ancillary analyses

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. (Table 19)

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

Table 19 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

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 (Table 20). Consolidative radiotherapy was received by 14 subjects (6%) on the A+CHP arm versus 6 subjects (3%) on the CHOP arm.

Table 20. 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)

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 had the potential to receive new subsequent therapy to treat residual or progressive disease. Subsequent systemic anticancer therapy was to treat residual or progressive disease was administered in 25% vs. 42%, respectively (

Table *21*).

Brentuximab vedotin was the most frequently used subsequent anticancer therapy in both arms (9% vs 21%). 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. Objective responses were attained by 13/23 subjects (57%) on the A+CHP arm and 24/49 subjects (49%) on the CHOP arm.

Table 21– 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.

2020 data cut-off long term follow-up

Similar to 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 (31% versus 45%). The time to subsequent therapy still favoured the A+CHP arm as shown by a HR of 0.57 (0.41, 0.77).

As of closure of the ECHELON-2 study, 50 of the 225 A+CHP patients with known SCT eligibility status at baseline (22%) were known to have received consolidative SCT vs. 39 of the 225 patients (17%) in the CHOP arm.

For the subgroup of patients with PTCL-NOS, consolidative SCT was received by 13 A+CHP patient (45%) and 19 CHOP patients (44%) at time of study closure. Brentuximab vedotin was received as first subsequent therapy by 5 PTCL-NOS patients in the A+CHP arm, of whom 2 patients responded with a CR and 1 with a PR, the other 2 patients had progressive disease. In the CHOP arm, 10 patients received subsequent brentuximab vedotin, with 3 patients responding with CR (3 patients had progressive disease, 4 patients were non evaluable or had unknown response).

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.

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 declared 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 Odds ratio for the CR rate per investigator (CR Odds ratio was 1.71 [1.16, 2.53], p-value 0.0069) was comparable to the IRF analysis. The Odds ratio for ORR rate per investigator was slightly lower than per IRF, but still in favour of A+CHP (ORR Odds ratio per investigator was 1.99 [1.25, 3.16], p-value=0.0032).

Summary of main study

The following table summarises 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 22 - 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: Duration of Run-in phase: Duration of Extension phase:	From 24-Jan-2013 till 15-Aug 2018 not applicable 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 (IRF based).
	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
Database lock	15-Aug-2018 for primary analysis 5-Nov-2020 for long term follow-up analysis		

Results and Analysis

Analysis description	**Primary Analysis (2018)**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	**A+CHP**	**CHOP**
	Number of subject	226	226
	PFS events Median PFS ITT (months)	95 (42%) 48.20	124 (55%) 20.80
	95% CI	35.2, -	12.7, 47.6
	Median OS	NE	NE
	95%CI	NE	NE
	ORR rate	83	72
	95%CI	77.7, 87.8	65.8, 77.9

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	A+CHP vs. CHOP
		Stratified HR	0.71
		95%CI	0.54, 0.93
		P-value	0.0110
	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
		Odds ratio	1.99
		95%CI	1.25, 3.16
		P-value	0.0032

Notes: Results for subgroup of patients with **PTCL-NOS** (n=29 A+CHP vs. n=43 CHOP) at 2018 primary data cut-off:

PFS: Stratified HR 0.75 (0.41, 1.37)
OS: Stratified HR 0.83 (0.38, 1.80)
ORR: 79.3% vs. 74.4%

Analysis description	**Long term follow-up Analysis (2020)**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	**A+CHP**	**CHOP**
	Number of subject	226	226
	PFS events Median PFS in ITT (months)	94 (42%) 62.26	125 (55%) 23.75
	95% CI	41.99, -	13.57, 60.75
	Median OS	NE	NE
	95%CI	NE	NE

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	A+CHP vs. CHOP
		Stratified HR	0.70
		95%CI	0.53, 0.91
		P-value	0.0077
	Secondary endpoint OS	Comparison groups	A+CHP vs. CHOP
		Stratified HR	0.72
		95%CI	0.53, 0.99
		P-value	0.0424

Notes: Results for subgroup of patients with **PTCL-NOS** (n=29 A+CHP vs. n=43 CHOP) with LTFU 2020 data cut-off:

PFS: Stratified HR 0.79 (0.43, 1.43; p=0.4290); median PFS per investigator 32.26 months on A+CHP vs. 10.74 months on CHOP.
OS: Stratified HR 0.75 (0.37, 1.48; p=0.4003), median OS 58.18 months vs. 36.67 months)

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

See hybrid analysis in section '*supportive studies*'.

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 (30.9%) 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 aged ≥18 years.

Pregnancy and lactation

No data is available in pregnant or lactating woman.

Supportive studies

Supportive data are derived from real world evidence (a chart review study, including a hybrid analysis with ECHELON-2 patients) and clinical Phase 2 study SGN35-012.

Chart Review Study: A retrospective longitudinal physician panel-based chart review study of patients with PTCL who were treated in the real-world setting with standard first-line therapies, including cyclophosphamide, doxorubicin, and prednisone, A+CHP and CHOP.

The study was conducted to evaluate the efficacy and safety of A+CHP to standard CHOP for the treatment of previously untreated patients with peripheral T-cell lymphoma (PTCL). Results of a post-hoc analysis on a subgroup of patients with CD30+ PTCL-NOS and treated with A+CHP or CHOP were presented as supportive data for this application.

Study design

The study was double-blinded (physicians were blinded to study sponsor and study sponsor was blinded on physicians recruited to participate).

The *index date* was defined as the initiation of first-line therapy with A+CHP or CHOP from November 2018 to March 2021 (Figure 20). November 2018 marked the date of the FDA approval of brentuximab vedotin in combination with chemotherapy for first-line treatment of patients with CD30+ PTCL. March 2021 was selected to allow for at least 6 months of follow-up. The study was conducted between October 2021 and November 2021. The baseline period was defined as the period up to 12 months before the index date, during which patient demographic and clinical characteristics were assessed. Treatment patterns and outcomes were assessed during the *observation period*, defined as the time from index to the earliest of death, loss to follow-up, or date of chart abstraction.

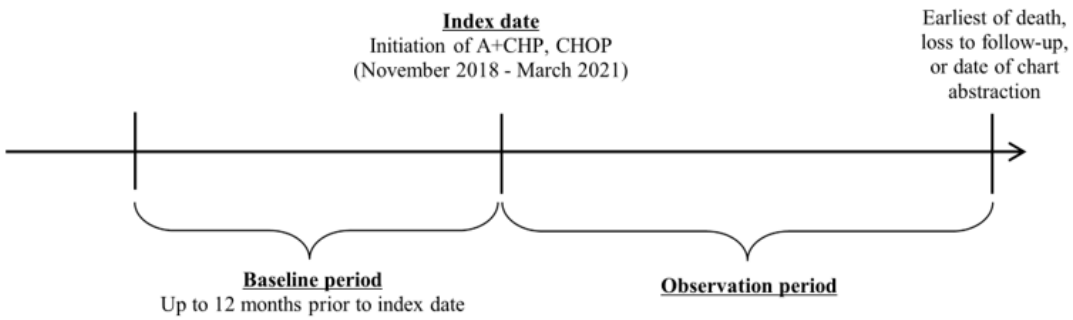


Figure 20. Chart Review Study Design Scheme

Statistical analyses

RW treatment response to first-line therapy (ie, CR, PR, stable disease, PD) was summarized as proportions with associated 95% CIs. rwORR was described as the proportion of patients who achieved an objective response (ie, CR or PR). DOR for first-line therapy was evaluated among patients who achieved an objective response and was described using KM analysis; median DOR and 95% CIs were reported. rwPFS was defined as the time from treatment initiation of first-line treatment until the earliest of disease progression, death within that line of therapy, or initiation of a second-line of therapy. Patients were censored if there was no death, initiation of second-line, or progression recorded, in which case the date

of the end of data was used as the censoring date. TTNT, rwPFS, and OS were estimated using KM methodology, and median time to events along with 95% CIs were reported. Given the nature of the chart data, the number and frequency of follow up assessments could differ between patients. The sequence of response, disease progression, and death during follow-up was visualized using swimmer plots. Results were stratified by type of therapy (A+CHP or CHOP).

Data source

Eligible oncologists/haematologists were originally recruited through Medefield America Limited LLC, a physician panel vendor, based on their medical specialty. Eligible oncologists/haematologists abstracted data from medical charts of eligible patients using an online electronic case report form (eCRF). The eCRF had an underlying program that required the oncologist/hematologist to select patient charts according to a randomized sequence of letters. The eCRF collected de-identified patient information including patient demographic and clinical characteristics, treatment patterns, and clinical outcomes. The included patient population was not a random or total sample of all patients with PTCL-NOS treated with brentuximab vedotin in the US. Thirty eight physicians contributed data on 96 eligible patients who had CD30 positive PTCL-NOS.

Eligibility criteria

Eligible physicians randomly selected up to five patients meeting the following key eligibility criteria.

Inclusion criteria

- Confirmed diagnosis of PTCL.
- Age 18 years or over at the time of PTCL diagnosis.
- Initiated first-line treatment with A+CHP or CHOP during November 2018 to March 2021.
- At least 6 months of follow-up following first-line treatment initiation, except in the event of death (patients could be alive or dead at time of data abstraction).

Exclusion criteria

- Enrolled in a clinical trial for first-line treatment of PTCL.
- Any prior diagnoses of another malignancy within five years of PTCL diagnosis.

Results

Patient characteristics

Ninety six patients had CD30+ PTCL-NOS; Of these 96 patients with CD30+ PTCL-NOS, 71 received A+CHP (74%) and 25 received CHOP (26%) as first-line treatment. Average age at diagnosis was similar between the cohorts (~ 61 years, Table 23). Most patients were male (~71% in both arms) and white (A+CHP 62%, CHOP 52%).

The A+CHP cohort was healthier than the CHOP cohort. A higher percentage of A+CHP patients had Stage II PTCL (38% vs. 16%) and a lower percentage had Stage III PTCL (30% vs. 56%) than the CHOP patients (Table 24). Most patients receiving A+CHP had Grade 1 ECOG performance (73%), while the CHOP group had an equal percentage (48% each) of patients with Grade 1 and 2. The IPI score of the patients in the A+CHP group tended to be lower than those in the CHOP group (median 2.0 vs. 3.1. A

higher percentage of CHOP patients had extranodal disease in their liver than A+CHP patients (64% vs. 32%).

Laboratory results - The A+CHP group had higher average haemoglobin values than that of the CHOP group (mean: 12.8 g/dL [SD: 7.2] vs 10.2 g/dL [SD: 1.4]), and a lower percentage of patients who received A+CHP had anemia compared with patients who received CHOP (35.0% vs 83.3%). In addition, a higher percentage of patients treated with A+CHP normal LDH compared with CHOP patients (62.0% vs 16.0%) with the same pattern observed for normal albumin (63.6% vs 36.4%).

Transplant eligibility - Among the CHOP cohort, 14 patients (56%) were evaluated to be transplant eligible at baseline compared with 28 patients (39%) in the A+CHP cohort. The primary reason for ineligibility in the A+CHP group was performance status (67%, compared with 45% of the CHOP group), while the primary reason for ineligibility in the CHOP group was advanced age (55%, compared with only 17% of the A+CHP group).

Comparison with ECHELON-2 - Fewer A+CHP treated chart review study patients were diagnosed with advanced (Stage III/IV) PTCL-NOS or had an IPI score ≥3 compared to the ECHELON-2 A+CHP treated PTCL-NOS subgroup (43.7% vs 86%, and 46% vs. 65%, respectively). The number of extranodal sites of PTCL-NOS was comparable between the A+CHP study populations. An ECOG PS of 0-1 was reported for 79% of patients in the A+CHP arm of the chart review study and 84.5% of A+CHP treated patients of the ECHELON-2 trial. Transplant eligibility at baseline was not available for the ECHELON-2 trial.

Table 23. Baseline patient demographic characteristics among patients with CD30 positive PTCL-NOS[1]

	A+CHP	CHOP	*P* value
	N = 71	N = 25	A+CHP vs CHOP
Age at diagnosis date (years)			
Mean ± SD	61.2 ± 9.7	60.2 ± 9.0	0.468
Median (IQR)	61.4 (54.1, 68.8)	60.9 (52.4, 65.8)	0.468
Age at index date (years)[1]			
Mean ± SD	61.4 ± 9.8	60.3 ± 9.0	0.398
Median (IQR)	61.5 (54.5, 69.0)	60.9 (52.5, 65.9)	0.398
Sex, N (%)			
Male	50 (70.4)	18 (72.0)	0.833
Female	21 (29.6)	7 (28.0)	0.833
Race, N (%)[2]			
White	44 (62.0)	13 (52.0)	0.217
Black or African American	12 (16.9)	11 (44.0)	<0.001
Asian	8 (11.3)	1 (4.0)	0.164
Hispanic or Latino	7 (9.9)	0 (0.0)	0.023
BMI (kg/m^2)			
Patient BMI available, n (%)	61 (85.9)	23 (92.0)	0.263
Mean ± SD	25.3 ± 2.4	26.3 ± 3.5	0.153
Median (IQR)	25.7 (24.3, 26.6)	26.3 (24.2, 27.6)	0.153
Insurance type, N (%)[2]			
Commercial	46 (64.8)	11 (44.0)	0.010
Medicare supplement insurance	9 (12.7)	5 (20.0)	0.207
Medicaid	9 (12.7)	4 (16.0)	0.555
Medicare only	9 (12.7)	5 (20.0)	0.207
Military	1 (1.4)	1 (4.0)	0.278
Uninsured	0 (0.0)	0 (0.0)	1.000
Unknown	0 (0.0)	0 (0.0)	1.000

P values <0.05 are significant

Notes:

[1] The index date is defined as date of initiation of first-line therapy with A+CHP or CHOP.

[2] Patients may identify with multiple options, so the sum may exceed total N or 100%.

Table 24. Patient and Disease Characteristics in the Subset of Patients With CD30+ PTCL-NOS

	ECHELON-2		Chart Review	
	A+CHP (N=29)	CHOP (N=43)	A+CHP (N=71)	CHOP (N=25)
Disease staging at diagnosis, n (%)				
Stage I	0	2 (5)	13(18.3)	4 (16.0)
Stage II	4 (14)	9 (21)	27 (38.0)	4 (16.0)
Stage III	14 (48)	13 (30)	21 (29.6)	14 (56.0)
Stage IV	11 (38)	19 (44)	10 (14.1)	3 (12.0)
ECOG performance status, n (%)				
0	11 (38)	27 (63)	8 (11.3)	0
1	12 (41)	15 (35)	52 (73.2)	12 (48.0)
2	6 (21)	1 (2)	10 (14.1)	12 (48.0)
3	0	0	1 (1.4)	1 (4.0)
Baseline IPI score, n (%)				
0	0	2 (5)	0	0
1	4 (14)	10 (23)	2 (5)	1 (5)
2	6 (21)	11 (26)	20 (50)	3 (15)
3	16 (55)	16 (37)	13 (33)	11 (55)
4	3 (10)	3 (7)	3 (8)	3 (15)
5	0	1 (2)	2 (5)	2 (10)
Mean (std dev)	2.6 (0.9)	2.3 (1.1)	2.6 (0.9)	3.1 (1.0)
Median (IQR)	3.0	2.0	2.0 (2.0, 3.0)	3.0 (3.0, 3.5)
Number of extranodal sites, n(%)				
≤1 site	21 (72)	32 (74)	50 (82)	19 (76)
>1 site	8 (28)	11 (26)	11 (18)	6 (24)
Mean (std dev)	NA	NA	0.7 (0.9)	0.8 (1.0)
Median (IQR)	NA	NA	0 (0.0, 1.0)	0 (0.0, 1.0)
HTLV-1 status, n (%)				
Positive	0	1 (2)	3 (4)	0
Negative	28 (97)	41 (95)	17 (2)	6 (24)
Time from diagnosis to treatment (months)				
Mean (std dev)	1.1 (0.9)	1.3 (1.0)	2.3 (3.4)	1.2 (2.4)
Median	0.9	1.0	0.8	0.6
Stem cell transplant eligibility at baseline (Chart review), n (%)				
Yes	NA	NA	28 (39)	14 (56)
No	NA	NA	36 (51)	11 (44)
Intention of stem cell transplant following completion of regimen (E2), n (%)				
Yes	13 (45)	19 (44)	NA	NA
No	16 (55)	24 (56)	NA	NA
Stem cell transplant recipient, n (%)				
Yes	13 (45)	19 (44)	10 (14)	0
No	16 (55)	24 (56)	61 (86)	25 (100)

Source: E2 CSR; In-house data; Chart Review Study.

A+CHP: brentuximab vedotin plus cyclophosphamide, doxorubicin and prednisone; CD30+: CD30 positive; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; E2: ECHELON-2 study; ECOG: Eastern Cooperative Oncology Group; HTLV-1: human T-cell leukemia virus-1; IPI: International Prognostic Index; IQR: interquartile range; max: maximum; min: minimum; NA: not applicable or not assessed; PTCL-NOS: peripheral T-cell lymphoma–not otherwise specified; std dev: standard deviation.

[a] The index date is defined as date of initiation of first-line therapy with A+CHP or CHOP.

[b] In the chart review study, "Hispanic or Latino" category was captured as part of the race variable.

Treatment patterns

The average time on treatment was slightly longer in the A+CHP cohort vs. CHOP (median 6.7 vs. 5.8 months). The median number of cycles administered was 5 vs. 6, respectively.

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.

3.4.3. Discussion on clinical efficacy

An extension of indication (EoI) is requested for adcetris in combination with cyclophosphamide, doxorubicin and prednisone (CHP) for previously untreated adult patients with CD30+ PTCL not otherwise specified (NOS).

Design and conduct of clinical studies

The main clinical data are derived from randomised, controlled Phase 3 Study SGN35-014 (ECHELON-2). This study investigated brentuximab vedotin + CHP versus CHOP for treatment-naive CD30 positive PTCL patients. The CHMP has previously reviewed the ECHELON-2 trial as a pivotal study for the EoI to first line treatment of systemic anaplastic large cell lymphoma (sALCL) in March 2020 (II/0070). Long-term follow-up data for clinical trial Echelon-2 has been reviewed in November 2021 (II/0089). These updated data supported the positive benefit risk in sALCL. Long-term follow-up data of the ECHELON-2 study for a subgroup of PTCL-NOS patients form the basis of the current application.

The initially applied indication in the II/0070 procedure included all PTCL disease entities, i.e. treatment-naive CD30 positive PTCL patients. The PTCL entities that were allowed in the study were sALCL (ALK+ IPI score ≥2 and all ALK-), PTCL-NOS, AITL, ATTL, EATL and HSTCL. As per protocol, most patients had sALCL (70%). The number of patients with other PTCL entities was relatively small, hampering interpretation of efficacy considering the limited benefit of A+CHP over CHOP in some entities (e.g. HR point estimate crossed 1 for AITL patients). Moreover, extrapolation of efficacy to underrepresented PTCL entities was not considered acceptable by the CHMP and the consulted Scientific Advisory Group (SAG) for Oncology due to marked heterogeneity at clinical, pathological, histogenetic and molecular levels as well as variable prognoses. Moreover, most of PTCL entities not included in the study would not be eligible for treatment with a CHOP-based regimen under current recommendations. As such, the broad PTCL indication that was initially requested was restricted to the largest subgroup in the study, i.e. sALCL.

The current extension of indication comprises a smaller subgroup of the same study, i.e. PTCL-NOS. Despite representing a smaller subgroup in the study, PTCL-NOS is the most prevalent PTCL entity in clinical practice. It may be considered that a stand-alone B/R is not needed for a smaller PTCL disease entity, when there is an established benefit risk profile for the larger disease entity in the study (sALCL) and there are similarities between the disease entities (i.e., similarities in treatment paradigm, clinical course, mechanism of action and CD30 expression). This should be further discussed by the MAH (see **MO** below).

The WHO classification of lymphoid malignancies has changed twice since the inception of the ECHELON-2 trial. The diagnosis PTCL-NOS is still a diagnosis of exclusion but the differential diagnoses which must be excluded in order to make the diagnosis of PTCL-NOS have been amended in the latest WHO classification from 2022. Clarification is requested on how the changes in the current WHO classification impact which patients would be eligible for ECHELON-2 were it enrolling today compared to the cohort of patients that was actually enrolled (**OC**).

The ECHELON-2 study design as well as results for the overall study population and PTCL-NOS population at the primary analysis data cut-off 15 August 2018 were agreed during the II/0070 EoI.

The primary PFS analysis censored patients for post-treatment chemotherapy, 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, the PFS sensitivity analysis in accordance with EMA guidance was considered important.

Furthermore, real world data has been presented based on a retrospective chart review study conducted in the US. In the US, brentuximab vedotin has been authorised for use in patients with previously untreated sALCL or other CD30+ PTCL including PTCL-NOS since 2018. Results of a post-hoc analysis on a subset of patients with newly diagnosed CD30+ PTCL-NOS treated with A+CHP or CHOP in real-world setting were submitted as supportive data. The chart review study was designed to select a sample of PTCL patients at the physician level and not the total population of US patients who had been treated, which hampers interpretation of results. It is not clear whether the decision to treat patients with A+CHP or CHOP was consistent within physician (i.e. a physician either treated all of their patients with A+CHP or CHOP, perhaps based on the guidelines followed within the practice) or whether some physicians used both treatments (**OC**).

As suggested at the pre-submission meeting, the MAH developed 3 models to incorporate real world data for CD30+ PTCL-NOS patients (chart review data) with ECHELON-2 data for the PTCL-NOS subgroup using hybrid analyses, which is acknowledged. The MAH performed three different analyses: propensity score analysis with Inverse probability of treatment weighting (IPTW), and two Bayesian analyses (commensurate priors and mixed prior model).

Efficacy data and additional analyses

The ITT population consisted of 452 patients, of whom 72 (16%) had PTCL-NOS. Unfortunately, these patients were not evenly distributed across treatment arms: a lower percentage was included in the A+CHP arm (n=29, 13% of the A+CHP arm) compared to the CHOP arm (n=43, 19% of the CHOP arm). As per protocol most patients had sALCL (70%; ALK- 48%, ALK+22%). Other entities studied were AITL 12%, ATLL (n=7; 2%) and EATL (n=3;1%). No HSTCL patients were included. In the PTCL-NOS population, the ECOG performance status was worse in the A+CHP arm (38% ECOG 0, 21% ECOG 2 vs 63% ECOG 0 and 2% ECOG 2 in the CHOP arm) and there was a higher percentage of patients with Stage III-IV disease (86% vs 74%) or IPI score ≥3 (65% vs 46%). These imbalances would be in favour of the control arm and are as such unlikely to bias the treatment effect in favour of A+CHP.

2018 primary analysis ITT - The primary endpoint PFS per IRF showed a statistically significant advantage of A+CHP over CHOP in the overall study population. Median PFS was 48.20 months for A+CHP vs. 20.80 months with CHOP with a stratified HR of 0.71 [0.54, 0.93], p=0.011. The difference in PFS rate at 1 year (71.7% vs 58.2%) and 2 years (61.4% vs. 47.4%) with flattening of the KM curves is indicative of long-term benefit. The observed effect size is deemed clinically relevant, as also concluded in the II/0070 procedure. The primary analysis was supported by several sensitivity analyses, including analysis 8 that was in accordance with EMA guidance. The key secondary endpoints of CR rate (68% vs 56%, p=0.0066) and ORR rate (83% versus 72%, p=0.0032) both measured at the end of treatment, as well as immature OS results (HR 0.66 [0.46, 0.95], p=0.0244) supported the primary endpoint. Median duration of response was similar between the two arms. It is encouraging that response rate outcomes are driven by differences in CRs.

2020 long term follow-up analysis ITT - As of study closure with data cut-off 5 November 2020, PFS per investigator was consistent with the primary analysis per IRF for the ITT: median PFS 62.26 vs 23.75 months, stratified HR 0.70 [0.53, 0.91], descriptive p=0.0077. The stratified OS HR shifted from 0.66 to 0.72 [0.53, 0.99, p=0.0424], but was still in favour of A+ CHP. Notably, an OS benefit has not previously been shown for first line PTCL patients compared to CHOP. Median OS was not reached.

PTCL-NOS - In the subgroup of patients with PTCL-NOS that reflects the current applied indication, the HR for PFS per IRF at the 2018 primary analysis was 0.75 [0.41, 1.37]. The ORR was 79.3% vs 74.4% at the end of treatment. With longer follow-up in 2020, median PFS per investigator was 32.3 vs 10.7 months and the stratified HR remained similar (0.79 [0.43, 1.43], descriptive p=0.429). A sensitivity analysis following EMA censoring guidance (#8) with the 2020 data cut-off is missing (**OC**). The OS HR shifted from 0.83 [0.38, 1.80] with the 2018 data cut-off to 0.75 ([0.37, 1.48], p=0.4003) with longer follow-up in 2020. Median OS in 2020 was 58.2 vs 36.7 months for the A+CHP and CHOP arms, respectively. A trend for positive results in the PTCL-NOS subgroup is supported by the mode of action and could be considered clinically relevant in this substitution trial setting. However,the number of included PTCL-NOS patients is relatively limited and unevenly distributed across treatment arms, hampering interpretation of observed efficacy results. As the presented real-world data cannot be accepted as supportive evidence due to methodological issues (see below), relevant data are not fundamentally different from those at the time of the previous assessment. The Applicant should justify that the results of the ITT population are relevant for PTCL- NOS patients, insofar that homogeneity of response across the disease entities sALCL and PTCL-NOS, may be assumed. Therefore, the MAH is requested to further elaborate on the similarity between sALCL and PTCL-NOS, preferably with further external scientific data.

Real world data - In total 96 PTCL-NOS patients were selected for inclusion in the chart review, of whom 71 patients (74%) received A+CHP and 25 (26%) CHOP. A+CHP was administered to a healthier patient population compared to the CHOP regimen, as reflected by Ann Arbor disease stage, ECOG performance status, IPI score and lab results like haemoglobin and LDH levels. It is also noted that a higher percentage of patients who received A+CHP had commercial insurance compared with those who received CHOP, potentially reflecting a more general selection bias. The chart review A+CHP treated PTCL-NOS population also had lower Ann Arbor disease stage and IPI score compared to the A+CHP treated PTCL-NOS patients enrolled in ECHELON-2.

Phase 2 study - In addition, a clinical Phase 2 study SGN35-012 was submitted, investigating brentuximab vedotin monotherapy in relapsed or refractory NHL. In a subgroup of 22 patients with PTCL-NOS, the ORR was 33% with a CR rate of 14%. Results for AITL patients were better, whereas opposite results were observed for the AITL and PTCL-NOS subgroups in the pivotal trial. As this was a non-comparative study, actual benefit also in terms of time dependent endpoints remains unclear. Therefore, and as it concerns monotherapy in a later line setting, this study is not considered supportive for the current applied indication.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable as the indication pertains to adult patients.

3.4.4. Conclusions on the clinical efficacy

The results from the pivotal ECHELON-2 trial show a clinically relevant PFS advantage of A+CHP over CHOP for the study population mainly consisting of sALCL patients. This is supported by secondary efficacy parameters, including OS. The applied indication is based on a positive trend in a relatively small subgroup of PTCL-NOS patients of the ECHELON-2 trial. As the presented real-world data cannot be accepted as supportive evidence due to methodological issues, relevant data are not fundamentally different from those at the time of the previous assessment. The Applicant should justify that the results of the ITT population are relevant for PTCL-NOS patients, insofar that homogeneity of response across the diagnostic entities sALCL and PTCL-NOS included, may be assumed. Therefore, the MAH is requested to further elaborate on the similarity between sALCL and PTCL-NOS, preferably with further external scientific data.'

3.5. Clinical safety

Introduction

Safety results from Study SGN35-014 (ECHELON-2) are presented as well as additional safety results for the PTCL-NOS subpopulation from 2 additional clinical studies, SGN35-011 and SGN35-012.

Study SGN35-014 ended on 02 October 2020 (the date of the last patient's last assessment) and final safety results based on the 05 November 2020 database lock. Safety assessments have been previously reported during the II/0070 procedure with the exception of updated data on deaths, safety data in the PTCL-NOS subgroup and updated data on resolution of peripheral neuropathy (PN) which have been presented during the II/0089 procedure.

Safety assessments included adverse events (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; serious adverse events (SAEs); and deaths reported in the study. Safety assessments included adverse events (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; serious adverse events (SAEs); and deaths reported in the study.

During the II/0070 procedure supportive safety data was provided for Study SGN35-011 and SGN35-012. Study SGN35-011 (NCT01309789) was a phase 1, open-label, 3-arm, dose-escalation study designed to define maximum tolerated dose, pharmacokinetics, immunogenicity, and antitumor activity of brentuximab vedotin when given sequentially and in combination with standard doses of CHP for the frontline treatment of patients with CD30+ mature T-cell and natural killer (NK)-cell neoplasms. Study SGN35-012 (NCT01421667; EudraCT Number: 2013-003946-17) was a phase 2, open-label, multicenter study designed to evaluate the efficacy and safety of single-agent brentuximab vedotin in patients with CD30+ non-Hodgkin lymphoma (NHL).

Patient exposure

The ECHELON-2 safety population included all patients who received any amount of brentuximab vedotin or any component of CHOP. 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. In total, 70% of patients in the A+CHP arm and 62% of patients in the CHOP arm received 6 cycles of study treatment, 18% resp. 19% received 8 cycles of study treatment.

Adverse events

A summary of overall safety in the safety population and PTCL-NOS patients is presented in Table 28.

Table 25 ECHELON-2: Overall Safety Summary (Safety Population; PTCL-NOS Subpopulation)

	Safety Population		**PTCL-NOS Subpopulation**	
n (%)	**A+CHP (N=223)**	**CHOP (N=226)**	**A+CHP (N=29)**	**CHOP (N=43)**
Patients with any TEAE [a]	221 (99)	221 (98)	28 (97)	42 (98)
Patients with blinded study treatment-related event [b]	201 (90)	193 (85)	25 (86)	39 (91)
Patients with CHP treatment-related event [b]	198 (89)	205 (91)	25 (86)	40 (93)
Maximum TEAE severity [a]				
Grade 1	15 (7)	23 (10)	0	5 (12)
Grade 2	59 (26)	52 (23)	2 (7)	8 (19)
Grade 3	77 (35)	67 (30)	14 (48)	16 (37)
Grade 4	62 (28)	63 (28)	10 (34)	12 (28)
Grade 5	8 (4)	16 (7)	2 (7)	1 (3)
Patients with any SAE	87 (39)	87 (38)	17 (59)	18 (42)
Patients with any blinded treatment-related [b] SAE	58 (26)	45 (20)	11 (38)	13 (30)
Patients with any CHP treatment–related SAE [b]	62 (28)	53 (23)	14 (48)	14 (33)
Patients who discontinued treatment due to AE	14 (6)	15 (7)	4 (14)	1 (2)
Patients who discontinued treatment due to blinded study treatment–related AE [b]	10 (4)	10 (4)	3 (10)	1 (2)
Patients who discontinued treatment due to CHP treatment–related AE [b]	8 (4)	7 (3)	2 (7)	1 (2)

n (%)	Safety Population		PTCL-NOS Subpopulation	
	A+CHP (N=223)	CHOP (N=226)	A+CHP (N=29)	CHOP (N=43)

Source: SGN35-014 Table 14.3.1.18 (E2 safety population); Table 22.2.6.1 (PTCL-NOS).

A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; AE: adverse event; ALCL: anaplastic large cell lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHP: cyclophosphamide, doxorubicin, prednisone; E2: ECHELON-2; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Table included only AEs that were reported during the safety evaluation period, defined as Study Day 1 through 30 days after the last dose of any component of the regimen. MedDRA Version 21.0 was applied.

Blinded study treatment was either brentuximab vedotin or vincristine.

[a] TEAEs were 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).

[b] Related to treatment as assessed by the investigator.

TEAEs of any Grade

Treatment-emergent adverse events that occurred in ≥10% of subjects in the A+CHP treatment arm are summarized in Table 29.

Table 26 Study SGN35 014: TEAEs Reported for at Least 10% of Patients in Either Treatment Arm by PT (Safety Population)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Patients 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)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Patients with at least 1 TEAE	221 (99)	221 (98)
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)
Back pain	16 (7)	22 (10)

Source: SGN35-014 Table 14.3.1.20.

A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; AE: adverse event; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.

MedDRA Version 21.0 was applied.

TEAEs of any Grade in PTCL-NOS patients

Within the PTCL-NOS safety subpopulation, at least 1 TEAE of any grade was reported for 28 patients (97%) in the A+CHP arm and 42 patients (98%) in the CHOP arm.

The TEAEs of any grade reported for at least 20% of patients with PTCL-NOS in the A+CHP arm were nausea (52% of patients); pyrexia (45%); diarrhoea and peripheral sensory neuropathy (41% each); constipation (38%); febrile neutropenia and neutropenia (31% each); fatigue (28%); dizziness and alopecia (24% each); and anaemia and vomiting (21% each).

The TEAEs of any grade reported for at least 20% of patients with PTCL-NOS in the CHOP arm were constipation and neutropenia (37% each); nausea and peripheral sensory neuropathy (33% each); fatigue (26%); and pyrexia, diarrhoea, febrile neutropenia, dyspnoea, and stomatitis (21% each).

Treatment related TEAEs

Treatment related TEAEs in the safety population are reported on in Table 30.

Table 27 Study SGN35 014: Treatment Related TEAEs Reported for at Least 10% of Patients in Either Treatment Arm by PT (Safety Population)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Patients with at least 1 treatment-related TEAE	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)
Diarrhoea	36 (16)	16 (7)
Fatigue	36 (16)	36 (16)
Febrile neutropenia	35 (16)	28 (12)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Patients with at least 1 treatment-related TEAE	201 (90)	193 (85)
Vomiting	32 (14)	25 (11)
Anaemia	30 (13)	23 (10)
Decreased appetite	26 (12)	16 (7)
Pyrexia	22 (10)	14 (6)

Source: SGN35-014 Table 14.3.1.27.

A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.

MedDRA Version 21.0 was applied.

Blinded study treatment was brentuximab vedotin or vincristine. TEAEs related to blinded study treatment could also be related to other components of the treatment regimen.

Treatment related TEAEs in PTCL-NOS patients

At least 1 treatment-related TEAE of any grade was reported for 25 patients (86%) in the A+CHP arm and 39 patients (91%) in the CHOP arm.

The treatment-related TEAEs of any grade reported for ≥20% of patients with PTCL-NOS in the A+CHP arm were peripheral sensory neuropathy (38% of patients); nausea (34%); febrile neutropenia and neutropenia (28% each); diarrhoea, constipation, and fatigue (24% each); and alopecia (21%).

The treatment-related TEAEs of any grade reported for ≥20% of patients with PTCL-NOS in the CHOP arm were peripheral sensory neuropathy (33% of patients); neutropenia (28%); nausea and constipation (23% each); and febrile neutropenia and fatigue (21% each).

Grade 3 or Higher TEAEs: ECHELON-2 Safety Population

Within the ECHELON-2 safety population, at least 1 Grade 3 or higher TEAE was reported for 147 patients (66%) in the A+CHP arm and 146 patients (65%) in the CHOP arm (Table 31).

Table 28 Study SGN35 014: Grade 3 or Higher TEAEs Reported for at Least 2% of Patients in Either Treatment Arm by PT (Safety Population)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Any Grade 3 or higher TEAE	147 (66)	146 (65)
Neutropenia	77 (35)	76 (34)
Febrile neutropenia	41 (18)	33 (15)
Anaemia	30 (13)	23 (10)
Leukopenia	16 (7)	14 (6)
Diarrhoea	13 (6)	2 (1)
Thrombocytopenia	13 (6)	9 (4)
Pneumonia	12 (5)	5 (2)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Any Grade 3 or higher TEAE	147 (66)	146 (65)
Hypokalaemia	8 (4)	3 (1)
Peripheral sensory neuropathy	8 (4)	6 (3)
Sepsis	6 (3)	4 (2)
Nausea	5 (2)	4 (2)
Dyspnoea	4 (2)	4 (2)
Hyperglycaemia	4 (2)	1 (0)
Pulmonary embolism	4 (2)	7 (3)
Pyrexia	4 (2)	0
Urinary tract infection	4 (2)	1 (0)
Hypertension	2 (1)	7 (3)
Fatigue	2 (1)	4 (2)
Vomiting	2 (1)	4 (2)
Hypotension	1 (0)	4 (2)
Anaplastic large cell lymphoma T- and null cell types	0	12 (5)

Source: SGN35-014 Table 14.3.1.29.

A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; PT: Preferred Term; TEAE: treatment-emergent adverse event.

MedDRA Version 21.0 was applied.

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%).

Grade 3 or Higher TEAEs in PTCL-NOS patients

In total, at least 1 Grade 3 or higher TEAE was reported for 26 patients (90%) in the A+CHP arm and 29 patients (67%) in the CHOP arm. Grade 3 or higher febrile neutropenia, leukopenia, thrombocytopenia, and diarrhoea were reported for a higher proportion of patients in the A+CHP arm than the CHOP arm.

The Grade 3 or higher TEAEs reported for at least 10% of patients with PTCL-NOS in the A+CHP arm were febrile neutropenia and neutropenia (31% of patients each); diarrhoea, leukopenia, and thrombocytopenia (14% each); and anaemia and pneumonia (10% each).

The Grade 3 or higher TEAEs reported for at least 10% patients with PTCL-NOS in the CHOP arm were neutropenia (30% of patients), febrile neutropenia (21%), and anaemia (12%).

Serious adverse event/deaths/other significant events

SAEs

Treatment-emergent SAEs were reported for the same proportion of patients across treatment arms in the ECHELON-2 safety population. At least 1 SAE was reported for 87 patients each (39% of patients in

the A+CHP arm and 38% of patients in the CHOP arm). Febrile neutropenia was the most commonly reported SAE for patients in both treatment arms (Table 32).

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 29 Study SGN35 014: SAEs Reported for at Least 2 Patients in Either Treatment Arm by PT (Safety Population)

PT, n (%)	**A+CHP (N=223)**	**CHOP (N=226)**
Patients with any SAE	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)
Diarrhoea	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
Nausea	1 (0)	4 (2)
Vomiting	1 (0)	3 (1)
Leukopenia	1 (0)	3 (1)
Septic shock	1 (0)	2 (1)
Staphylococcal infection	1 (0)	2 (1)

PT, n (%)	A+CHP (N=223)	CHOP (N=226)
Tachycardia	1 (0)	2 (1)
Anaplastic large cell lymphoma	0	11 (5)
Multiple organ dysfunction syndrome	0	3 (1)
Neutropenic sepsis	0	3 (1)
Escherichia sepsis	0	2 (1)
Gastric ulcer	0	2 (1)
Metastases to central nervous system	0	2 (1)
Skin infection	0	2 (1)
Stomatitis	0	2 (1)

Source: SGN35-014 Table 14.3.1.50.

A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; SAE: serious adverse event.

MedDRA Version 21.0 was applied.

SAEs in PTCL-NOS patients

Within the PTCL-NOS safety subpopulation, at least 1 SAE was reported for 17 patients (59%) in the A+CHP arm and 18 patients (42%) in the CHOP arm. Febrile neutropenia was the most commonly reported SAE across treatment arms. Febrile neutropenia was reported for 8 patients each across the 2 treatment arms (28% in the A+CHP arm and 19% in the CHOP arm). Pyrexia was reported as an SAE for 3 patients (10%), and sepsis, pneumonia, respiratory failure, pneumonitis, deep vein thrombosis, and diarrhoea were reported as SAEs for 2 patients each (7%) in the A+CHP arm. Pyrexia and neutropenic sepsis were reported for 2 patients each (5%) in the CHOP arm.

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. At the time of study closure, a total of 156 deaths were reported for the ECHELON-2 safety population, which included 67 patients in the A+CHP arm (30%) and 89 patients (39%) in the CHOP arm. Among the 67 deaths reported for patients in the A+CHP arm, 47 deaths (21%) were considered disease related, 14 were considered non-disease related, and disease relationship was unknown for 6 patients. Among the 89 deaths reported for the patients in the CHOP arm, 63 deaths (28%) were considered disease related, 14 were considered non-disease related, and disease relationship was unknown for 12 patients.

On-study death, defined as death within 30 days of last dose of any component of the treatment regimen, was reported for 8 patients (4%) in the A+CHP arm and 13 patients (6%) in the CHOP arm. The causes of on-study death for the A+CHP arm were acute renal failure, cardiac arrest, PTCL-NOS, pneumonia, aspiration pneumonia, pulmonary cavitation, sepsis, and ventricular fibrillation, and each was reported for 1 patient each. The causes of on-study death for the CHOP arm were sALCL, reported for 4 patients; sepsis, reported for 2 patients; and cardiac arrest, multiple organ dysfunction syndrome, arrhythmia, febrile neutropenia, hydrocephalus, and septic shock, reported for 1 patient each. The cause of death was reported as unknown for 1 patient in the CHOP arm. On-study death was considered treatment related for 4 patients in the A+CHP arm and 6 patients in the CHOP arm. During the II/0070 procedure the CSR for SGN35-014 indicated that causes of death for the 4 subjects with treatment related on-study deaths on the A+CHP arm were cardiac arrest, pneumonia aspiration, pulmonary cavitation, and ventricular

fibrillation. In the CHOP arm death non-disease related deaths were due to multi organ failure and sepsis (2 patients), unknown death, cardiac arrest and cardiac arrhythmia.

Death during post study follow up was reported for 9 patients with PTCL-NOS (4%) in the A+CHP arm and 15 patients with PTCL-NOS (7%) in the CHOP arm. All deaths reported during this period were considered disease related and attributed to PTCL-NOS (disease progression and associated complications).

Deaths in PTCL-NOS patients

Among patients in the PTCL-NOS safety subpopulation, 11 (37.9%) deaths were reported for the A+CHP arm and 16 (37.2%) deaths for the CHOP arm at study closure. The cause of death was reported as PTCL-NOS for 10 patients (4%) in the A+CHP arm and 15 patients (7%) in the CHOP arm.

On-study death was reported for 2 patients with PTCL-NOS in the A+CHP arm and 1 patient with PTCL-NOS in the CHOP arm. The causes of on-study death for the 2 patients in the A+CHP arm were reported as sepsis (1 patient), and progression of PTCL-NOS and leptomeningeal disease (1 patient). Sepsis was considered drug related; PTCL-NOS leptomeningeal disease were considered not drug related. The cause of on-study death for the patient in the CHOP arm was reported as multiple organ dysfunction syndrome, which was considered drug related.

Death during PTFU was reported for 9 patients with PTCL-NOS (4%) in the A+CHP arm and 15 patients with PTCL-NOS (7%) in the CHOP arm. All deaths reported during PTFU were considered disease related and attributed to PTCL-NOS (disease progression and associated complications).

Selected AEs of clinical interest

Peripheral Neuropathy

The MedDRA PTs identified from the comprehensive review of the PN (SMQ) broad (MedDRA Version 21.0) were peripheral sensory neuropathy, paraesthesia, peripheral motor neuropathy, muscular weakness, peripheral sensorimotor neuropathy, hypoaesthesia, dyasesthesia, areflexia, burning sensation, peroneal nerve palsy, polyneuropathy, autonomic neuropathy, gait disturbance, muscle atrophy, and neuralgia.

Within the ECHELON-2 safety population, at least 1 PN event of any grade was reported for 117 patients (52%) in the A+CHP arm and 124 patients (55%) in the CHOP arm. Peripheral sensory neuropathy was the most commonly reported PT in the PN (SMQ) broad across treatment arms.

The most commonly reported PN events of any grade for the A+CHP arm were peripheral sensory neuropathy (45% of patients); and paraesthesia and peripheral motor neuropathy (4% each). The most commonly reported PN events of any grade for the CHOP arm were peripheral sensory neuropathy (41% of patients); paraesthesia and peripheral motor neuropathy (8% each); and muscular weakness (4%). Grade 3 PN was reported for 7 patients (3%) in the A+CHP arm and 8 patients (4%) in the CHOP arm. Grade 4 PN was reported for 1 patient in the A+CHP arm (SGN35-014).

Pre-existent peripheral neuropathy was reported for the same proportion of patients across the 2 treatment arms in the ECHELON-2 safety population (both arms 11%).

Resolution of PN was defined as an event status of recovered/resolved, recovered/resolved with sequelae, or returned to baseline or lower severity as of the latest assessment for pre-existing events. For events that were not resolved, improvement was defined as a decrease in severity by at least 1 grade from the worst grade at the latest assessment. Resolution or improvement was reported for a higher proportion of patients over the period from the end of treatment (EOT) through study closure. Data on resolution of PN at the primary analysis and at study closure are shown in Table 33.

Table 30 ECHELON-2: Resolution of Treatment-Emergent Peripheral Neuropathy (SMQ) Adverse Events (Safety Population; Subset With Treatment-Emergent Peripheral Neuropathy)

	Primary Analysis		Study Closure	
Subset of Patients With Treatment-Emergent PN, n (%)	**A+CHP (N=117)**	**CHOP (N=124)**	**A+CHP (N=117)**	**CHOP (N=124)**
Patients with resolution of all PN AEs	58 (50)	79 (64)	71 (61)	82 (66)
Patients with improvement of PN AEs	14 (12)	15 (12)	13 (11)	15 (12)
Patients with no improvement or resolution of PN AEs	45 (38)	30 (24)	33 (28)	27 (22)
Number of PN events, n	158	167	158	168
Number of PN events resolved	91/158 (58)	114/167 (68)	105/158 (66)	117/168 (70)
Number of PN events improved	7/158 (4)	6/167 (4)	6/158 (4)	8/168 (5)
Number of PN events neither improved nor resolved	60/158 (38)	47/167 (28)	47/158 (30)	43/168 (26)
Patients with ongoing PN AEs at last follow-up	61 (52)	45 (36)	47 (40)	42 (34)
Grade 1 at last follow-up	44 (38)	32 (26)	33 (28)	30 (24)
Grade 2 at last follow-up	15 (13)	12 (10)	13 (11)	11 (9)
Grade 3 at last follow-up	2 (2)	1 (1)	1 (1)	1 (1)

Source: SGN35-014 Table 14.3.1.69.

A+CHP: brentuximab vedotin (Adcetris), cyclophosphamide, doxorubicin, prednisone; AE: adverse event; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; PN: peripheral neuropathy.

This table only includes AEs reported within safety analysis period, as defined as Day 1 up to 30 days after the last dose of any component of the regimen.

Resolution of PN events was reported at a median of 22.1 weeks (range, 0-315 weeks) and improvement at a median of 28.0 weeks (range, 5-123 weeks) for the A+CHP arm; in the CHOP arm, resolution was reported at a median of 12.1 weeks (range, 0-220 weeks) and improvement at a median of 22.5 weeks (range, 2-215 weeks).

Within the PTCL-NOS subpopulation, at least 1 PN (SMQ) event of any grade was reported for 14 patients (48%) in the A+CHP arm and 22 patients (51%) in the CHOP arm. Peripheral sensory neuropathy was the most commonly reported PT across the 2 treatment arms. Peripheral sensory neuropathy was reported for 12 patients (41%) and was the only PN event reported for more than 1 patient in the A+CHP arm. Peripheral sensory neuropathy was reported for 14 patients (33%), paraesthesia for 5 patients (12%), peripheral motor neuropathy for 4 patients (9%), and muscular weakness for 2 patients in the CHOP arm (5%).

Febrile neutropenia

Within the ECHELON-2 safety population, febrile neutropenia was reported for 41 patients (18%) in the A+CHP arm and 33 patients (15%) in the CHOP arm, including Grade 3 febrile neutropenia for 36 patients (16%) in the A+CHP arm and 26 patients (12%) in the CHOP arm. Grade 4 AEs in 5 patients (2%) in the A+CHP arm and 6 patients in the CHOP arm (3%) and one grade 5AE in the CHOP arm.

Within the PTCL-NOS subpopulation, febrile neutropenia was reported for 9 patients each (31% for the A+CHP arm; 21% for the CHOP arm) across the 2 treatment arms, which included Grade 3 febrile neutropenia for 7 patients each (24% for the A+CHP arm; 16% for the CHOP arm) and Grade 4 neutropenia for 2 patients each (7% for the A+CHP arm; 5% for the CHOP arm).

Laboratory findings

Laboratory findings were not presented for this EoI. During the II/0070 procedure it was reported that 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. 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.

Safety in special populations

Age

During the II/0070 procedure 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.

A subgroup analysis by age for patients within the PTCL-NOS subpopulation showed that patients aged <60 years generally had a better safety profile than those aged ≥60 year, though there were very few patients in each group.

Disease type

During the II/0070 procedure the safety profile was analysed 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.

In the II/0070 procedure it was established that 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.

Safety related to drug-drug interactions and other interactions

Results from a cross-study comparison of the observed PK in patients with PTCL in ECHELON-2 with previous PK data from brentuximab vedotin when administered as monotherapy showed that serum and plasma PK characteristics of ADC and MMAE, following administration of A+CHP were similar to that of brentuximab vedotin when administered as monotherapy.

Discontinuation due to adverse events

During the II/0070 procedure the following data were presented regarding discontinuations, dose delays and dose reductions due to AEs. 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. One subject in the CHOP arm discontinued due to febrile neutropenia.

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.

Post marketing experience

As of 25 April 2023, brentuximab vedotin has been approved in 80 countries and regions. As of the 18 February 2023 data-lock point for the currently approved Periodic Benefit-Risk Evaluation Report, the overall cumulative estimated patient exposure to brentuximab vedotin was 129,667 patients, including 3394 patients from company-sponsored clinical studies, 4397 patients from investigator-sponsored studies, 2979 patients from various compassionate use programs, and approximately 118,897 patients from the postmarketing setting (sponsor in-house data; Periodic Benefit-Risk Evaluation Report for Brentuximab Vedotin 21 April 202). No ADR overview was presented.

Supportive studies

During the II/0070 procedure the following data on studies Study SGN35-011 and Study SGN35-012 was presented.

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, including 2 patients with PTCL-NOS, 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.

3.5.1. Discussion on clinical safety

Safety was presented from ECHELON-2 (SGN35-014) a randomized, double-blinded, double-dummy, active-comparator, multicenter study in patients with previously untreated PTCL who received A+CHP or CHOP. Most safety assessments have been previously reported during the II/0070 procedure with August 15, 2018 as cut-off date. In the II/0070 procedure an extension of the indication to adult patients with previously untreated sALCL was granted based on the ECHELON-2 study data, but not for other PTCL types. Final safety results based on the 05 November 2020 database lock containing updated data for deaths and updated data on resolution of PN have been presented during the II/0089 procedure. Additionally in this application safety data specific for the PTCL-NOS subgroup is presented.

Exposure

The ECHELON-2 safety population included all patients who received any amount of brentuximab vedotin or any component of CHOP. The safety population consisted of 223 patients in the A+CHP arm and 226 patients in the CHOP arm. Similar exposure was observed for A+CHP compared to CHOP in terms of median number cycles (6) and duration of study treatment weeks (18).

AEs

The type and frequency of TEAEs reported is the same as in the II/0070 procedure and summarized here for easy reference. 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 the A+CHP and CHOP arm were nausea (respectively 46% vs. 38%), peripheral sensory neuropathy (45% vs. 41%), diarrhoea (38% vs. 20%), neutropenia (38% vs. 38%), constipation (29% vs. 30%), alopecia (26% vs. 25%), pyrexia (26% vs. 19%), and vomiting (26% vs. 17%). Thus, largely similar type and frequencies of AEs were observed for both regimens except for the occurrence of TEAE GI adverse events as well as pyrexia which are reported in higher frequencies in the A+CHP arm compared to CHOP. Treatment related events generally occurred at a numerically slightly higher or comparable frequencies in the A+CHP arm compared to CHOP. Noteworthy is the frequency of treatment-related diarrhoea which was observed more often in the A+CHP arm compared to CHOP (16% vs.7% in the CHOP arm). Severe AEs (66% versus 65%) and SAEs (39% versus 38%) were comparable between the A+CHP and CHOP arm. The most frequent brentuximab vedotin-related ≥ Grade 3 AEs and vincristine-related ≥ Grade 3 AEs were comparable between the A+CHP and CHOP arm (neutropenia 30% versus 27% and febrile neutropenia 14% versus 12% respectively.) Slightly more brentuximab vedotin-related SAEs (26%) were observed compared to vincristine-related SAEs (20%) although this could not be attributed to one type of SAE.

Deaths

At the time of study closure, a total of 67 deaths in the A+CHP arm (30%) and 89 deaths (39%) in the CHOP arm were reported. Most deaths in both arms were considered disease related.

On-study death (within 30 days of last dose) was reported for 8 patients (4%) in the A+CHP arm and 13 patients (6%) in the CHOP arm. On-study death was considered treatment related for 4 patients in the A+CHP arm (cardiac arrest, pneumonia aspiration, pulmonary cavitation, and ventricular fibrillation) and 6 patients in the CHOP arm (multi organ failure and sepsis (2 patients), unknown death, cardiac arrest and cardiac arrhythmia). The majority of deaths occurred ≥30 days of the last dose of any component of the treatment regimen. These deaths were mostly disease-related. Deaths during the post study follow up were all disease related for 9 patients with PTCL-NOS (4%) in the A+CHP arm and 15 patients with

PTCL-NOS (7%) in the CHOP arm. The total number of deaths between the August 15, 2018 data cut-off date and the post treatment follow up differ from the number of deaths at study closure (**OC**).

AEs of interest

PN was reported at similar rates for patients in the A+CHP arm (N=117; 52%) and patients in the CHOP arm (N=124; 55%). The most commonly reported PN events of any grade for the A+CHP arm was peripheral sensory neuropathy (45% of patients). At study closure resolution of all PN (61%) and improvement of PN (11%) was slightly lower in the A+CHP arm compared to the CHOP arm, respectively 66% and 12% in the. Also the time to resolution was better for patients in the CHOP arm (12 weeks) compared to patients in the A+CHP arm (28 weeks). PN led to very few discontinuations (2 subjects; 1% in each arm) and thus was well tolerated.

Febrile neutropenia was reported in comparable rates in patients in the A+CHP arm (18%) and patients in the CHOP arm (15%). No patients discontinued all study treatment due to febrile neutropenia in the A+CHP arm. Advanced age was a risk factor for febrile neutropenia. This has been adequately reported in the label, as well as the recommendation for primary prophylaxis with G-CSF, beginning with the first dose.

Tolerability

There were few discontinuations of all study medication in both treatment arms (A+CHP:6% versus CHOP 7%) and a very small amount of patients discontinued brentuximab vedotin or vincristine (2% in both arms). There were more dose delays due to AEs for brentuximab vedotin compared to vincristine (26% versus 12%). Also in few patients doses of brentuximab vedotin were reduced because of AEs (9%) on the A+CHP arm, comparable to the dose reductions of vincristine because of AEs (11%) on the CHOP arm. Thus, overall, the tolerability of A+CHP may be slightly worse compared to CHOP, but appears manageable with dose delays and dose reductions. Discontinuations of all study medication was infrequent including discontinuations due to PN, febrile neutropenia or GI tract complaints. Overall, A+CHP seems to be well tolerated.

PTCL-NOS

The sample of PTCL-NOS patients treated A+CHP is small (N=29). More patients were randomized to the CHOP arm (N=43). The type and frequency of frequent AEs is more or less comparable for PTCL NOS patients compared to overall population in the A+CHP (and CHOP) arm. In the II/0070 procedure it was established that SAEs occurred more frequent in non-sALCL disease types compared to sALCL patients (56% versus 32%), and also compared to CHOP treated non-sALCL patients (56% versus 42%), while the numbers were similar between both arms in sALCL patients. This can also be said for PTCL-NOS patients based on the data provided in this procedure. In the II/0070 procedure it was established that the difference is driven by a higher incidence of febrile neutropenia and infections occurring more often in non-sALCL patients treated with A+CHP compared to non-sALCL patients treated with A+CHP or CHOP treated patients. The same notion for febrile neutropenia can be made for PTCL-NOS patients in this procedure. During the II/0070 procedure the SAG was consulted on whether differential toxicity between sALCL and other PTCL_NOS entities is expected and the SAG indicated that this was not expected. They also indicated 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. The SAG will be requested whether specifically the population of PTCL-NOS patients can be expected to tolerate A+CHP as well as the population of sALCL patients. Or whether there are constitutive differences between the two (three) disease entities which could impact each group's ability to tolerate the treatment under investigation.

Supportive studies

The safety observed in Phase 1 study SGN35-011 generally support the safety observed in the pivotal study. 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.

3.5.2. Conclusions on clinical safety

The safety profile for patients with the combination of A +CHP was generally consistent with the known AE profile for patients treated with brentuximab vedotin in combination with chemotherapy. No new safety signals were identified. The toxicity profile of A+CHP is largely comparable to CHOP with the exception of higher frequency of TEAE GI adverse events in the A+CHP arm and slightly more brentuximab vedotin-related SAEs compared to vincristine-related SAEs, although this could not be attributed to one type of SAE. A+CHP appears to be well tolerated and is manageable with dose delays, dose reductions and primary prophylaxis with G-CSF. The safety data for PTCL-NOS patients is based on a small sample. There appear to be more SAEs in PTCL-NOS patients treated with A+CHP compared to the safety population of A+CHP driven by a higher incidence of febrile neutropenia, these numbers may be influenced by other factors and haematological toxicity can easily be managed by adding G-CSF, as primary prophylaxis. Thus, from a safety point of view there are no objections to treatment of PTCL-NOS patients other than that safety is based on a very small sample. Nonetheless, the SAG will be requested whether specifically the population of PTCL-NOS patients can be expected to tolerate A+CHP as well as the population of sALCL patients.

3.5.3. 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.

4. Risk management plan

The MAH submitted an updated RMP version 19.0 (dated 26 June 2023) with this application. The (main) proposed RMP changes were the following:

- Part I Product Overview: Indication extension to include "sALCL and PTCL-NOS" as proposed.
- Part II Safety Specification (Module SI Epidemiology of the indication(s) and target population(s): Updated epidemiology details related to PTCL indication.

The summary of safety concerns for brentuximab vedotin is unchanged:

Summary of safety concerns	
Important identified risks	1. Peripheral neuropathy (sensory and motor) 2. Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia) 3. Infections (including bacteraemia, sepsis, septic shock and opportunistic infections) 4. Infusion-related reactions 5. Hyperglycaemia

Summary of safety concerns	
Important potential risks	1. Severe hepatotoxicity 2. Pulmonary toxicity
Missing information	1. Long term safety

The proposed changes to the RMP are assessed below.

PRAC Rapporteur's assessment

Parts I and II of the RMP were updated to include the new proposed CD30+ Peripheral T Cell Lymphoma Not Otherwise Specified (PTCL-NOS) indication and epidemiology and exposure information related to PTCL / PTCL-NOS. These changes are acceptable, provided that the new indication will be approved by the CHMP.

Based on the CHMP Rapporteur's clinical safety assessment of the proposed indication, the safety profile for patients with the combination of A+CHP was generally consistent with the known AE profile for patients treated with brentuximab vedotin in combination with chemotherapy. Although the safety data for PTCL-NOS patients is based on a very small sample, no new safety signals were identified. It is therefore agreed that the summary of safety concerns, pharmacovigilance activities, and risk minimisation measures remain unchanged at this point.

Furthermore, Part II of the RMP was updated with recent epidemiology and exposure data for existing indications, and the characterisation of risks in Part II: Module SVII.3 was updated with recent ADR data. Furthermore, editorial changes were made throughout the RMP. These changes were also submitted in RMP version 18.0 in the ongoing procedure II/0107 and assessed there. The below was noted for amendment at the next regulatory opportunity, which is the current procedure:

"Please ensure consistency of tables V.1 and V.3 and the PI with regard to routine risk communication of severe hepatotoxicity and pulmonary toxicity. For severe hepatotoxicity, the MAH is requested to remove the reference to SmPC section 4.2 from table V.1, in line with the information in table V.3 and Part VI of the RMP. For pulmonary toxicity, the proposed changes are agreed, but the MAH is asked to also add SmPC section 4.5 which provides information about the risk of pulmonary toxicity due to interaction with bleomycin. Part VI of the RMP should be updated accordingly."

The new proposed indication is not yet reflected in Part VI: Summary of the risk management plan of RMP version 19.0. The MAH is requested to update Part VI with the new indication.

4.1. Overall conclusion on the RMP

☒The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in Annex 1 are submitted.

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2 and 5.1 of the SmPC are proposed to be updated. The Package Leaflet (PL) would be updated accordingly.

5.1.1. 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: The variation contains no changes that may affect the readability of the package leaflet.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The proposed target indication for this extension of indication is:

'**CD30+ Peripheral T-cell Lymphomas (PTCLs)** ~~Systemic anaplastic large cell lymphoma~~

ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) **or CD30+ PTCL not otherwise specified (NOS)** (see section 5.1).'

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 and therapeutic strategies the WHO 2016 classifies these disorders as separate disease entities. PTCL types represent 10%–15% of all non-Hodgkin's lymphoma's and is very rare with an incidence of < 1 case per 100,000. The most frequent in the EU are: PTCL-NOS (34.3%), AITL (28.7%), sALCL (ALK- 9.4%, ALK+ 6.4) and EATL (9.1%). sALCL patients per definition have CD30 expression ≥75% of the tumour cells, however, the level of expression (i.e. percentage of positive cells and intensity) varies among patients with other histologies including PTCL-NOS.

6.1.2. 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.

The prognosis of PTCL is also highly dependent on type of PTCL and IPI score. The subtype ALCL ALK+ usually has a more favorable prognosis (5 year OS 70%). Also ALK− ALCL (5 year OS 49%) has a better prognosis compared to PTCL-NOS and AITL (both 5 year OS 32%). Other subtypes included in the study usually have a poor prognosis.

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

6.1.3. 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. The protocol stipulated that 75± 5% of the enrolled subjects needed to have a diagnosis of sALCL.

The ITT analysis set consisted of 452 subjects, 226 in the A+CHP arm and 226 in the CHOP arm. Most patients had sALCL (n=316, 70%; ALK- in 48% and ALK+ in 22%). The other PTCLs studied were PTCL-NOS (n=72, 16%), AITL (n=42, 12%), ATLL (n=7; 2%) and EATL (n=3; 1%). No HSTCL patients were included.

This study has been reviewed by CHMP as pivotal trial for the extension of indication to first line treatment of systemic anaplastic large cell lymphoma (sALCL) in March 2020 (II/0070). Further long-term data of the ECHELON-2 study for the subgroup of PTCL-NOS patients form the basis of the current application.

Supportive data is derived from real world evidence. This included a retrospective US chart review study of PTCL patients treated in real-world setting with standard first-line therapies (among others A+CHOP and CHOP). Moreover, a hybrid analysis of real world data and ECHELON-2 patients was performed, using 3 different models developed by the MAH (propensity score analysis-PSA, commensurate prior analysis-CPA and mixture prior analysis-MPA).

6.2. Favourable effects

ECHELON-2

ITT population (n=452)

The primary endpoint PFS per IRF showed a statistically significant advantage of A+CHP over CHOP in the overall study population at the primary analysis data cut-off in 2018. The median PFS was 48.20 months for A+CHP vs. 20.80 months with CHOP with a stratified HR of 0.71 [0.54, 0.93], p=0.011. The estimated PFS rate at 1 year was 71.7% vs. 58.2% and at 2 years 61.4% vs. 47.4%. The primary analysis was supported by several sensitivity analyses. At the 2020 long term follow-up data cut-off, PFS per investigator was consistent with the primary analysis per IRF for the ITT: median PFS 62.26 vs. 23.75 months, stratified HR 0.70 [0.53, 0.91], descriptive p=0.0077.

Key secondary endpoints CR rate (68% versus 56%, p=0.0066) and ORR rate (83% versus 72%, p=0.0032) both measured at the end of treatment, as well as OS (HR 0.66 [0.46, 0.95], p=0.0244) favoured A+CHP over CHOP at the primary analysis data cut-off in 2018. At the 2020 data cut-off for study closure, the stratified OS HR was 0.72 [0.53, 0.99, p=0.0424] in favour of A+ CHP. Median OS was not reached.

Fewer patients received subsequent new anticancer treatment in the A+CHP arm compared to the CHOP arm at the primary analysis data cut-off (29% vs. 42%) and 2020 LTFU data cut-off (31% versus 45%).

PTCL-NOS subgroup (n=72)

At the primary data cut-off in the subgroup of PTCL-NOS patients, the stratified HR for PFS per IRF was 0.75 [0.41, 1.37]. At the 2020 long term follow-up data cut-off, median investigator based PFS was 32.26 vs. 10.74 months, with a stratified HR of 0.79 [0.43, 1.43], descriptive p=0.429.

For PTCL-NOS patients the CR rate was 65.5% with A+CHP vs. 58.1% with CHOP. The ORR was 79.3% vs. 74.4%, respectively.

At the primary data cut-off, the OS HR was 0.83 [0.38, 1.80]. At the 2020 data cut-off for study closure, median OS was 58.18 vs. 36.67 months with a HR of 0.75 [0.37, 1.48], descriptive p=0.4003.

6.3. Uncertainties and limitations about favourable effects

- The applied indication is based on a positive trend in a relatively small subgroup of PTCL-NOS patients of the ECHELON-2 trial. As the presented real-world data cannot be accepted as supportive evidence due to methodological issues, relevant data are not fundamentally different from those at the time of the previous assessment. It is uncertain whether results of the ITT population are relevant for PTCL-NOS patients, insofar that homogeneity of response across the disease entities sALCL and PTCL-NOS, may be assumed.
- Pivotal data for the applied indication in PTCL-NOS is derived from a small subgroup of the ECHELON-2 trial, with uneven distribution of PTCL-NOS patients between the A+CHP and CHOP treatment arms. Differences in baseline disease characteristics between the treatment arms were noted. These imbalances would be in favour of the control arm and are as such unlikely to bias the treatment effect in favour of A+CHP.
- Real world data, i.e., a chart review study and hybrid analyses, seem to be in line with the ECHELON-2 trial. However, differences in baseline disease characteristics and transplant decisions for patients included in the chart review study and between the A+CHP treated patients of the ECHELON-2 trial and the chart study hamper interpretation of these data. Interpretation is furthermore hampered by challenges related to using the chart study to augment the ECHELON-2 trial data. In particular the small number of patients included in the propensity-score analysis from the chart study (due to missing data) is of concern. Additional clarification regarding patient selection, transplant decisions and missing data is requested (OCs).

6.4. Unfavourable effects

Safety data from ECHLON-2 have been previously presented in the II/0070 procedure with August 15, 2018 as cut-off date. Final safety results based on the 05 November 2020 database lock are currently presented and additionally entail updated data for deaths, updated data on resolution of PN and safety data specific for the PTCL-NOS subgroup.

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. Largely similar type and frequencies of AEs were observed for the A+CHP arm compared to CHOP arm except for the occurrence of TEAE GI adverse events (nausea (46% vs. 38%), vomiting (26% vs. 17%), diarrhoea (38% vs 20%)) as well as pyrexia (26% vs. 19%). Treatment related events generally occurred at a numerically slightly higher or comparable frequencies in the A+CHP arm compared to CHOP, except for treatment-related diarrhoea (16% vs. 7% in the CHOP arm).

Grade 3 and higher TEAEs (66% versus 65%) and SAEs (39% versus 38%) were comparable between the A+CHP and CHOP arm. Brentuximab vedotin-related SAEs were reported for 26% of the subjects on the A+CHP arm; vincristine-related SAEs were reported for 20% of the subjects on the CHOP arm. AEs resulted in discontinuation of all study drugs for 14 A+CHP patients (6%) and 15 CHOP patients (7%) and a very small number of patients discontinued brentuximab vedotin or vincristine only (2% in both arms). Dose delays due to AEs were observed at a higher frequency for brentuximab vedotin compared to vincristine (26% versus 12%).

A similar frequency and severity of treatment-related peripheral neuropathy (PN) events were reported across treatment arms (52% of patients in the A+CHP arm and 55% in the CHOP arm). Most of PN events across treatment arms were Grade 1. At study closure all PN resolved/ improved in 72% and of the patients in the A+CHP arm. In the CHOP arm these numbers were slightly higher (78%). Febrile

neutropenia was reported in comparable rates in patients in the A+CHP arm (18%) and patients in the CHOP arm (15%).

The sample of PTCL-NOS patients treated A+CHP is N=29 versus CHOP arm N=43. The type and frequency of frequent AEs is more or less comparable for PTCL NOS patients compared to overall population in the A+CHP (and CHOP) arm.

6.5. Uncertainties and limitations about unfavourable effects

There are few patients with PTCL-NOS treated with A+CHP.

More SAEs (59% versus 39%) driven by febrile neutropenia SAEs (28% versus 14%) were observed in PTCL-NOS patients treated with A+CHP compared to the total safety population treated with A+CHP. Also more SAEs were observed compared to PTCL-NOS patients treated with CHOP (42%) as well as the safety population treated with CHOP (38%).

6.6. Effects Table

Table 31 - Effects Table for ADCETRIS in combination with CHP is indicated for adult patients with previously untreated sALCL or CD30+ PTCL NOS (data cut-off: 15 aug 2018)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression free survival – median ITT - At 1 year - At 2 years PTCL-NOS*	Months	48.2 [35.2, -] 71.7 [65.1, 77.2] 61.4 [54.4, 67.6] 32.26	20.8 [12.7, 47.6] 58.2 [51.4, 64.3] 47.4 [40.6, 53.8] 10.74	PFS HR 0.71 [0.54, 0.93], p=0.011. At study closure: median PFS 62.3 vs 23.8 months with HR 0.70 [0.53, 0.91]. Results of ITT population mainly driven by sALCL population (70%). PFS rates at 1 and 2 years most representative due to plateau formation in KM curves. PTCL-NOS sample is small and no stratification was performed on this subtype. PFS HR 0.75 [0.41, 1.37] at primary analysis and 0.79 [0.43, 1.43] at study closure.	Section 5.4
CR rate	Complete response at end of treatment ITT PTCL-NOS	%	68 [61.2, 73.7] 65.5	56 [49.0, 62.3] 58.1	CR rate difference p=0.0066 ORR results are in line and driven by CR rate.	
OS*	Overall survival - median ITT PTCL-NOS	Months	NE 58.18	NE 36.67	Updated OS HR 0.72 [0.53, 0.99], p=0.0424. OS HR 0.75 [0.37, 1.48]	
Unfavourable Effects						
GI AEs	Gastro-intestinal tract AEs - Nausea - Diarrhoea - Vomiting	%	 46 38 26	 38 20 17	Data derived from a double-blind RCT for a substitution therapy and thus considered reliable. Exposure was comparable between the study arms.	Section 3.5.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					PTCL-NOS sample is small and no stratification was performed on this subtype. The type and frequency of frequent AEs is more or less comparable for PTCL NOS patients compared to overall population in the A+CHP (and CHOP) arm.	
related SAE	SAEs related to blinded treatment		26	20	At least 1 SAE (independent of relation) was reported for 39% and 38% of the patients	
PN	Peripheral neuropathy	%	52	55	PN led to discontinuation of all study drugs in N=2 subjects; 1%) in each arm	Section 3.5.3.5.
FN	Febrile neutropenia	%	18	15	No discontinuations due to febrile neutropenia in the A+CHP arm (N=1 in the CHOP arm).	Section 3.5.
Discontinuations	Discontinuations of all study drugs due to AEs	%	6	7	Similar discontinuation rate reflects manageable safety profile for A+CHP	Section 3.5.
Dose delays	Dose delays due to AEs	%	26	12	Tolerability may be worse for A+CHP compared to CHOP but manageable as seen by discontinuations	Section 3.5.

Abbreviations: CHP=cyclophosphamide, doxorubicin and prednisone; HR= hazard ratio, sALCL= systemic anaplastic large cell lymphoma; OS= overall survival, PFS= progression free survival, PTCL-NOS= peripheral T-cell lymphoma – not otherwise specified; TEAE= treatment-emergent adverse event; SAE=serious adverse event; AE= adverse event; RCT=randomized controlled trial; PN= Peripheral neuropathy; FN= Febrile neutropenia

Notes: * at study closure, Nov 2020.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The pivotal study ECHELON-2 demonstrated a clinically relevant effect in PFS of A+CHP over CHOP in the overall study population of CD30+ PTCL patients (PFS HR 0.71). The difference in PFS rate at 1 and 2 years with flattening of the KM curves is indicative of long term benefit. PFS results are supported by sensitivity analyses and the key secondary endpoints CR rate and OS benefit with an updated HR of 0.72.

The initially applied indication in the II/0070 procedure included all PTCL disease entities, i.e. treatment-naive CD30 positive PTCL patients. The number of patients with other PTCL entities was relatively small,

hampering interpretation of efficacy considering the limited benefit of A+CHP over CHOP in some entities. Moreover, extrapolation of efficacy to all underrepresented PTCL entities was not considered acceptable by CHMP. Most of PTCL entities not included in the study would not be eligible for treatment with a CHOP-based regimen under current recommendations. As such, the broad PTCL indication was restricted to the largest subgroup in the study, i.e. sALCL.

The current extension of indication comprises a smaller subgroup of the same study, i.e., PTCL-NOS. In the subgroup of patients with PTCL-NOS from the ECHELON-2 trial, PFS (HR 0.75), and updated OS (HR 0.75) results are comparable to the effect in the overall population. The observed treatment effect in PTCL-NOS patients might be considered clinically relevant in this substitution trial setting. However, the number of investigated PTCL-NOS patients is relatively limited.

RWD from the USA where A is approved for PTCL-NOS seem to point in the same direction, but considered to be of limited support at present due to differences in baseline disease characteristics and transplant decisions for patients included in the chart review study and challenges related to using the chart study to augment the ECHELON-2 trial data.

As the presented real-world data cannot be accepted as supportive evidence due to methodological issues, relevant data are not fundamentally different from those at the time of the previous assessment. The Applicant should justify that the results of the ITT population are relevant for PTCL-NOS patients, insofar that homogeneity of response across the disease entities sALCL and PTCL-NOS, may be assumed. Therefore, the MAH is requested to further elaborate on the similarity between sALCL and PTCL-NOS, preferably with further external scientific data.

The toxicity profile of A+CHP is largely comparable to CHOP with the exception of higher frequency of GI adverse events in the A+CHP arm and slightly more brentuximab vedotin-related SAEs compared to vincristine-related SAEs, although this could not be attributed to one type of SAE. There may be worse tolerability for A+CHP compared to CHOP, but this is considered to be manageable with dose delays and did not result in more discontinuations of study medication. There appear to be more SAEs in PTCL-NOS patients treated with A+CHP compared to the total safety population of A+CHP driven by a higher incidence of febrile neutropenia. The SAG (during the II/0070 procedure) considered that differential toxicity between sALCL and other PTCL_NOS entities is not expected and these numbers may be influenced by other factors and haematological toxicity can easily be managed by adding G-CSF, as primary prophylaxis. Thus, therefore safety seems to be acceptable for PTCL-NOS patients, however, the SAG will be requested to specifically discuss whether the population of PTCL-NOS patients can be expected to tolerate A+CHP as well as the population of sALCL patients.

6.7.2. Balance of benefits and risks

The applied indication is based on a positive trend in a relatively small subgroup of PTCL-NOS patients of the ECHELON-2 trial. As the presented real-world data cannot be accepted as supportive evidence due to methodological issues, relevant data are not fundamentally different from those at the time of the previous assessment. The Applicant should justify that the results of the ITT population are relevant for PTCL-NOS patients, insofar that homogeneity of response across the disease entities sALCL and PTCL-NOS, may be assumed. Therefore, the MAH is requested to further elaborate on the similarity between sALCL and PTCL-NOS, preferably with further external scientific data.Safety of A+CHP is largely comparable to CHOP and therefore considered acceptable in PTCL-NOS patients.

6.7.3. Additional considerations on the benefit-risk balance

The SAG-O will be consulted on the following questions:

1. Can the overall results from the ITT population, mainly consisting of sALCL patients, be extrapolated to PTCL-NOS patients? Please discuss differences and similarities between PTCL-NOS and sALCL and discuss whether comparable treatment responses are demonstrated in patients with PTCL-NOS and sALCL.
2. Based on the results of ECHELON-2, does the SAG consider that it has been shown that the population of PTCL-NOS patients can be expected to tolerate A+CHP as well as the population of sALCL patients for which it is already approved? Or are there constitutive differences between the two (three) disease entities (age/comorbidity/differential expression of drug target/others?) which could impact each group's ability to tolerate the treatment under investigation and which have not been sufficiently well delineated in the relatively small population of PTCL-NOS patients enrolled in ECHELON-2?

6.8. Conclusions

The overall B/R of brentuximab vedotin is considered negative, due to a major concern regarding the limited number of investigated PTCL-NOS patients and need for justification that the results of the ITT population are relevant for PTCL-NOS patients.