NICE National Institute for Health and Care Excellence

Brentuximab vedotin for previously untreated systemic anaplastic large cell lymphoma (sALCL) [ID1586]

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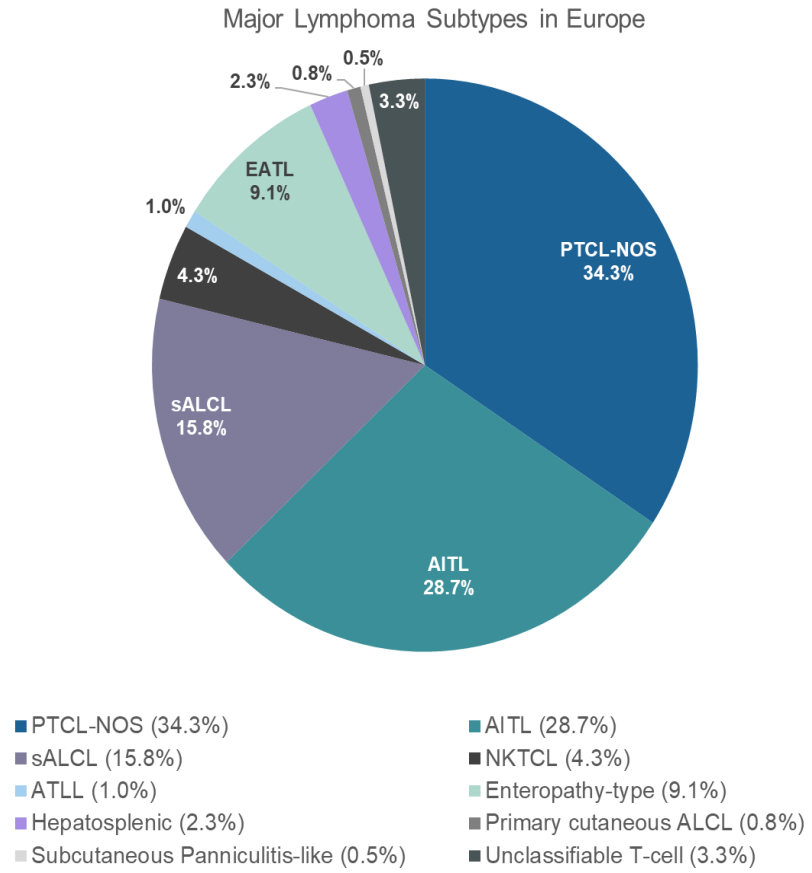
Company: Takeda

Peripheral T-Cell Lymphoma (PTCL): a type of Non-Hodgkin Lymphoma (NHL)

- The most common subtypes of PTCL are: PTCL-not otherwise specified, angioimmunoblastic T-cell lymphoma, and systemic anaplastic large cell lymphoma (sALCL).
- PTCL is an aggressive disease, complicated by frequent relapses, and primary refractory disease.
- The overall treatment goal is to use front-line therapy to induce a long-term remission, and potentially cure the underlying disease by attaining a deep, durable response.
- In the UK people are more commonly diagnosed with stage III/IV disease. For individuals who relapse after primary treatment, PFS and OS are extremely poor.

Distribution of PTCL Diagnosis in Europe



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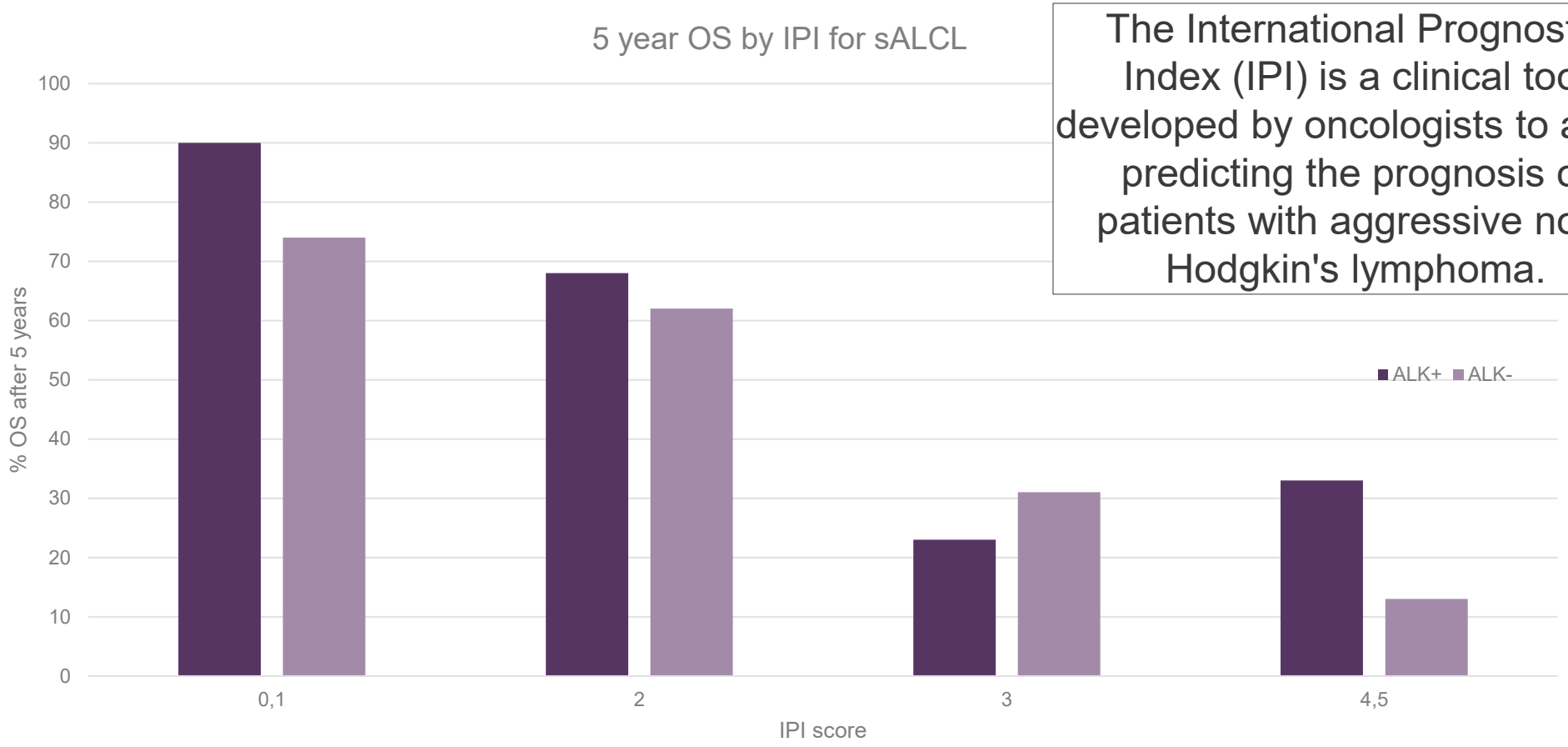
Expected survival for sALCL subtype



The International Prognostic Index (IPI) is a clinical tool developed by oncologists to aid in predicting the prognosis of patients with aggressive non-Hodgkin's lymphoma.

OS: overall survival, IPI: International Prognostic Index, sALCL: systemic anaplastic large cell lymphoma, ALK: anaplastic lymphoma kinase.

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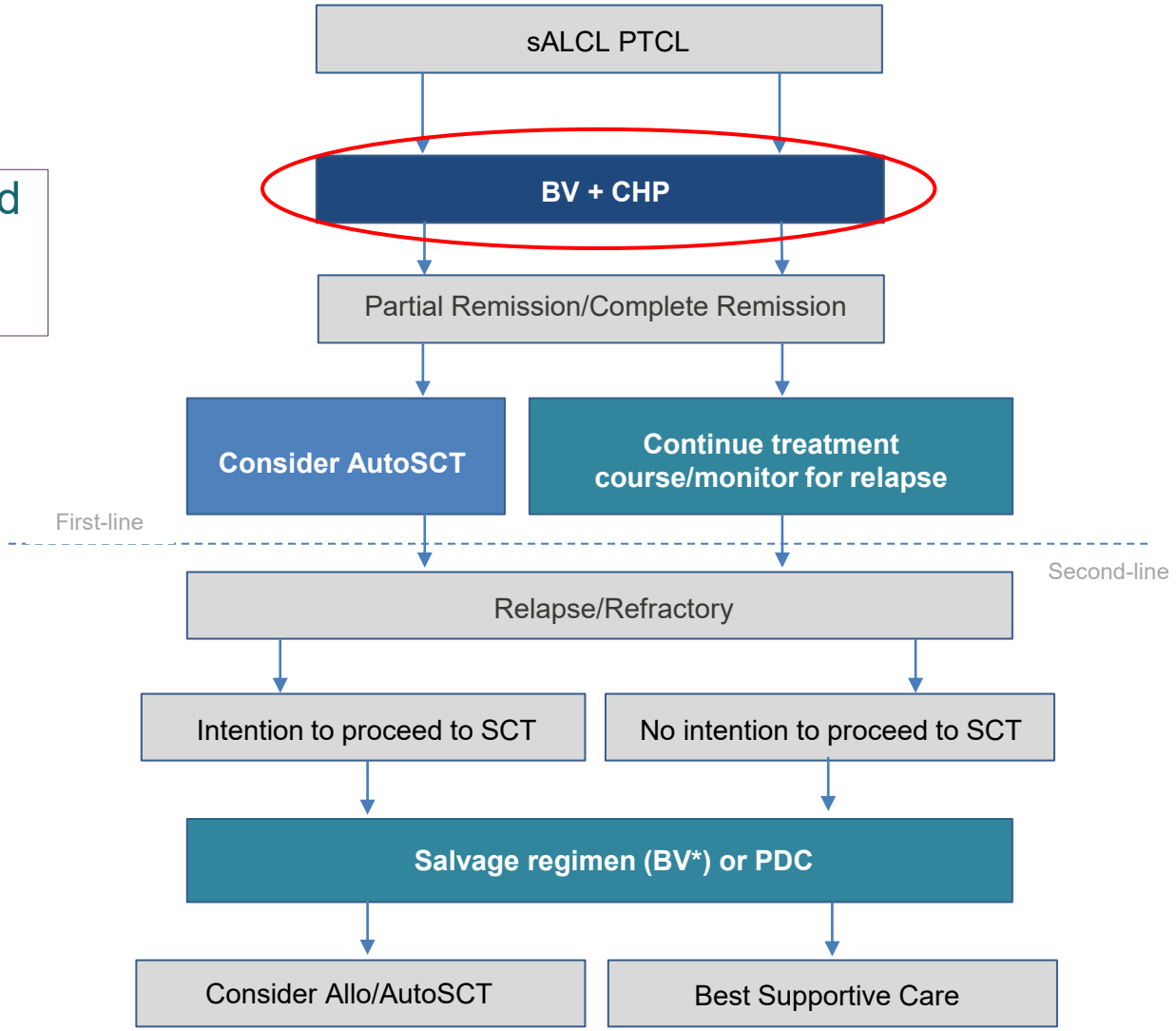
Brentuximab vedotin

Marketing authorisation (received May 2020)	**Brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)**
Mechanism of action	BV is an antibody drug conjugate composed of an anti-CD30 monoclonal antibody linked with a microtubule-disrupting, antimitotic drug compound, monomethyl auristatin E.
Administration	The recommended dose of BV is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks, to be administered in combination with CHP.
Price	• The NHS list price of BV is £2,500 per 50mg vial (ex VAT). • Based on a mean of 6.0 cycles, the cost for an average patient is estimated at approximately £47,619. • BV has a confidential patient access scheme (PAS) price.

Company's proposed treatment pathway

Source: adapted from company submission.



* BV is approved as second line monotherapy treatment for relapsed/refractory ALCL (TA478): assumption is that patients must be BV naïve and no-retreatment is permitted.

Patient perspectives and professional views

- PTCL and aggressive treatment regimens have a significant impact on the quality of life of patients and their carers.
- Patients are concerned about low response rates and lack of options for relapsed or refractory disease.
- Current treatments are often difficult to tolerate, significant side effects and risk of late effects. They also need repeated trips to hospital.
- Patients need to know “what’s next” and BV is seen as something that can get them to a stem cell transplant - “last throw of the dice”
- Perceived advantages of BV are the significant improvement in outcomes, having treatment as an outpatient and a more acceptable tolerability profile.

Professional views:

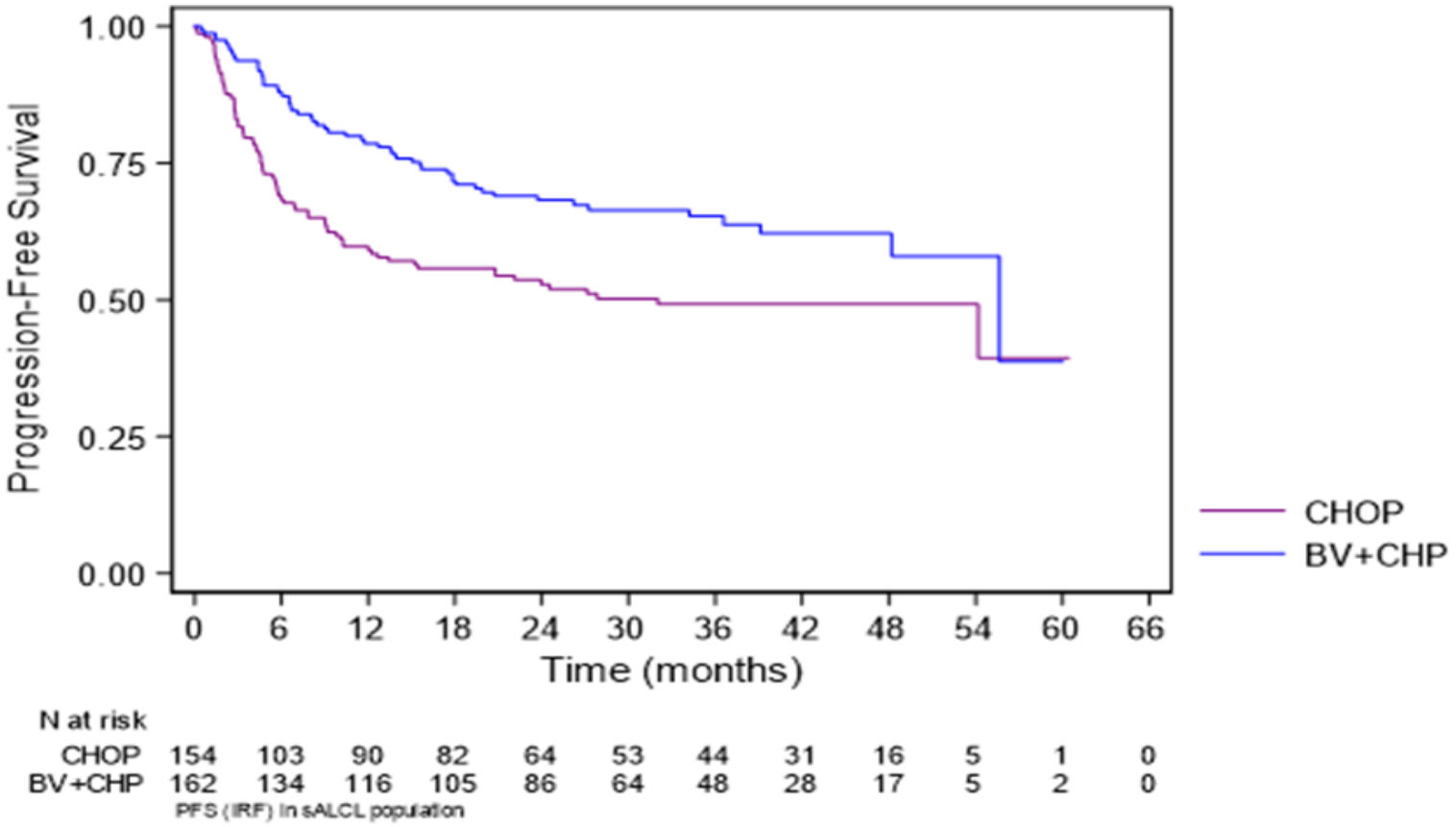
- More effective treatments are urgently needed.
- For the sALCL group this is a paradigm shift in survival outcomes that has not previously been seen in first-line therapy.
- Will replace current standard of care in NHS practice.

ECHELON-2 : Phase III trial

Population (n=452, 1:1 randomisation)	Patients aged ≥18 years with previously untreated CD30+ PTCL. 70% of patients in the trial were sALCL with an International Prognostic Index (IPI) score of ≥ 2.
Locations	132 sites in 17 countries (five of the trial sites were located in the UK).
Intervention	Brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (BV+CHP)
Comparator	Cyclophosphamide in combination with doxorubicin, vincristine and prednisone (CHOP)
Data cuts	August 2018 for PFS and OS. Final data cut expected late 2020.
Follow up	Median follow-up, primary analysis (PFS): 36.2 months (95% CI 35.9–41.8) Median follow-up, longer-term analysis (OS): 42.1 months (95% CI, 40.4−43.8)
PFS/OS (95% confidence interval)	Median PFS: BV+CHP: 48.2 (35.2, NR); CHOP: 20.8 (12.7, 47.6). PFS HR 0.71 (0.54, 0.93). Median OS: not reached in either group. OS HR 0.66 (0.46, 0.95).

ECHELON-2 : PFS results (sALCL)

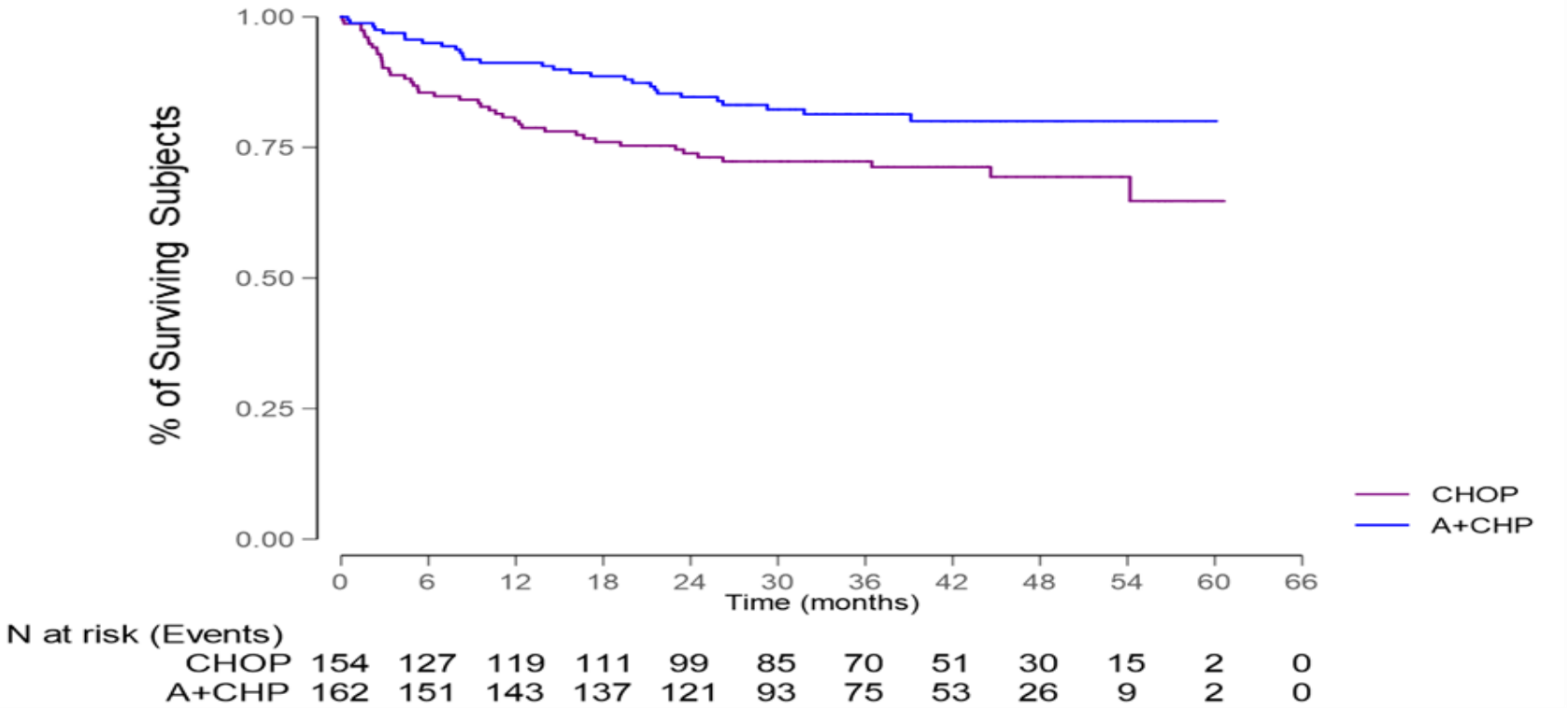
- Treatment with BV+CHP equated to a 41% reduction in the risk of a PFS event compared to those treated with CHOP alone (stratified HR 0.59 [95% CI 0.42 – 0.84], p=0.0031).



Abbreviations: BV+CHP: brentuximab vedotin+ cyclophosphamide, doxorubicin, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone.

ECHELON-2 : OS results (sALCL)

- Treatment with BV+CHP reduced the risk of death by 46% when compared with CHOP (HR 0.54 [95% CI 0.337–0.867], p=0.0096). 70% of relapsed patients in the CHOP arm received BV following relapse.



Abbreviations: A/BV+CHP: brentuximab vedotin+ cyclophosphamide, doxorubicin, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; SCT: stem cell transplant

ECHELON-2 : Objective Response Rates (sALCL)

- The ORR at end of treatment per IRF assessment was 88% (95% CI 81.6 to 92.3) for subjects on the BV+CHP arm compared with 71% (95% CI 62.9 to 77.8) for subjects on the CHOP arm (P=0.0001).

Response	BV+CHP (N=162)	CHOP (N=154)
Complete Remission	115 (71%)	82 (53%)
Not evaluable	9 (6%)	18 (12%)
Progressive disease	7 (4%)	19 (12%)
Partial response	27 (17%)	27 (18%)
Stable disease	4 (2%)	8 (5%)

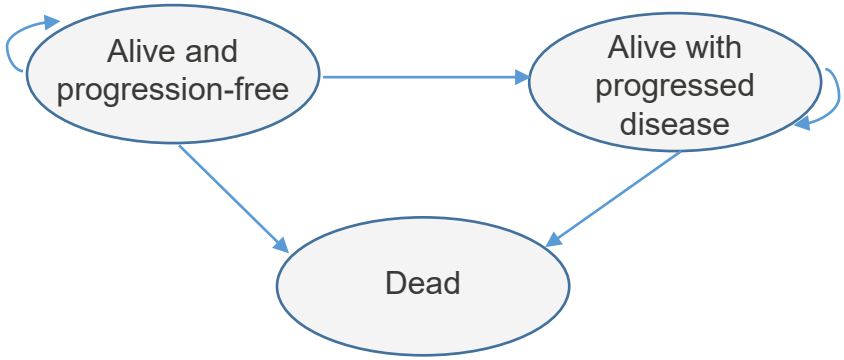
ORR: objective response rate, IRF: independent review facility

ECHELON-2 : Summary of adverse events (ITT population)

Adverse Event	BV+CHP Group (n=223)		CHOP group (n=226)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	103 (46%)	5 (2%)	87 (38%)	4 (2%)
Peripheral neuropathy	100 (45%)	8 (4%)	92 (41%)	6 (3%)
Neutropenia	85 (38%)	77 (35%)	85 (38%)	76 (34%)
Diarrhoea	85 (38%)	13 (6%)	46 (20%)	2 (1%)
Constipation	64 (29%)	2 (1%)	67 (30%)	3 (1%)
Alopecia	58 (26%)	0	56 (25%)	3 (1%)
Pyrexia	58 (26%)	4 (2%)	42 (19%)	0
Vomiting	57 (26%)	2 (1%)	39 (17%)	4 (2%)
Fatigue	54 (24%)	2 (1%)	46 (20%)	4 (2%)
Anaemia	46 (21%)	30 (13%)	36 (16%)	23 (10%)

ITT: intention-to-treat

Key economic information



- Partitioned survival model with 3 health states: *progression-free, progressed disease* and *death.*
- Economic analysis of BV+CHP compared with CHOP
- A lifetime horizon of 45 years applied in the model base case.
- 21-day cycle length (treatment cycle), with a half-cycle correction applied.
- NHS and Personal Social Services (PSS) perspective
- An annual discount rate of 3.5% for costs and benefits

Company base-case ICER (CHOP v BV+CHP)	£21,192 per QALY gained.
Technical team preferred ICER (CHOP v BV+CHP)	£22,047 per QALY gained.

Note: All ICERs include the confidential discount price for brentuximab vedotin.

Key issues:	Status
Issue 1 – Average age of PTCL patients in the economic model	
Is the mean age used in the company base case too low? If so, what age is appropriate for the economic model?	Resolved
Issue 3 – Utility model approach	
Is the time-to-death utility model preferable to the health state utility method?	Resolved
Issue 4 – Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	Resolved
Issue 5 – Number of 2nd line monotherapy BV cycles in the model	
Is a mean of 6 cycles for 2nd line BV appropriate?	Resolved
Issue 6 – Choice of joint or stratified modelling	
Are joint or stratified models more appropriate? *	Resolved
Issue 7 – Grade 3 and 4 Peripheral Neuropathy Management	
What is the treatment of Grade 3 or 4 peripheral neuropathy? *	Resolved
Issue 2 – Choice of extrapolation for long-term PFS and OS	
Which are the most clinically plausible extrapolations for PFS and OS?	For discussion

* Issues identified at technical engagement

Resolved issues

Issue:	Company	ERG	Tech team
Issue 1 – Average age of PTCL patients in the economic model	ECHELON-2 data does not diverge widely from the real-world data and is most appropriate for the updated base-case.	Accepts the mean age from ECHELON-2 for its updated base-case but argues this is likely to underestimate the ICER.	Agree that the age in the updated base-case is appropriate, and that the impact on the ICER as shown in the scenario analysis is modest.
Issue 3 – Utility model approach	In response to technical engagement, opted to switch from a HSUV approach to the 'time-to-death' (TTD) approach for the base-case estimation.	Agree with the company's choice to select the TTD approach for its base case.	Agree with the company and ERG that TTD is the most appropriate approach. Impact on the ICER is small.

Resolved issues

Issue:	Company	ERG	Tech team
Issue 4 – Utility age-adjustment	Company's original model allowed sALCL utilities to be higher than those of the general population. Agree with the ERG's model constraint (see ERG view).	Implemented a constraint in their preferred base-case whereby patient utility values cannot exceed the age-adjusted utility value of the general population.	The implemented constraint is appropriate.
Issue 5 – Number of 2nd line monotherapy BV cycles in the model	Company's original model assumed 8.2 cycles of subsequent-line BV for relapsed or refractory (R/R) sALCL in CHOP arm. Agree that 6 cycles is appropriate (see tech team view).	The clinical expert at the TA478 committee meeting highlighted that real-world evidence suggests that the median number of cycles for BV is 5 to 6.	Real-world evidence from the Systemic Anti-Cancer Therapy (SACT) dataset shows that the average number of cycles of BV monotherapy used 2nd line for R/R sALCL was 6.

Resolved issues

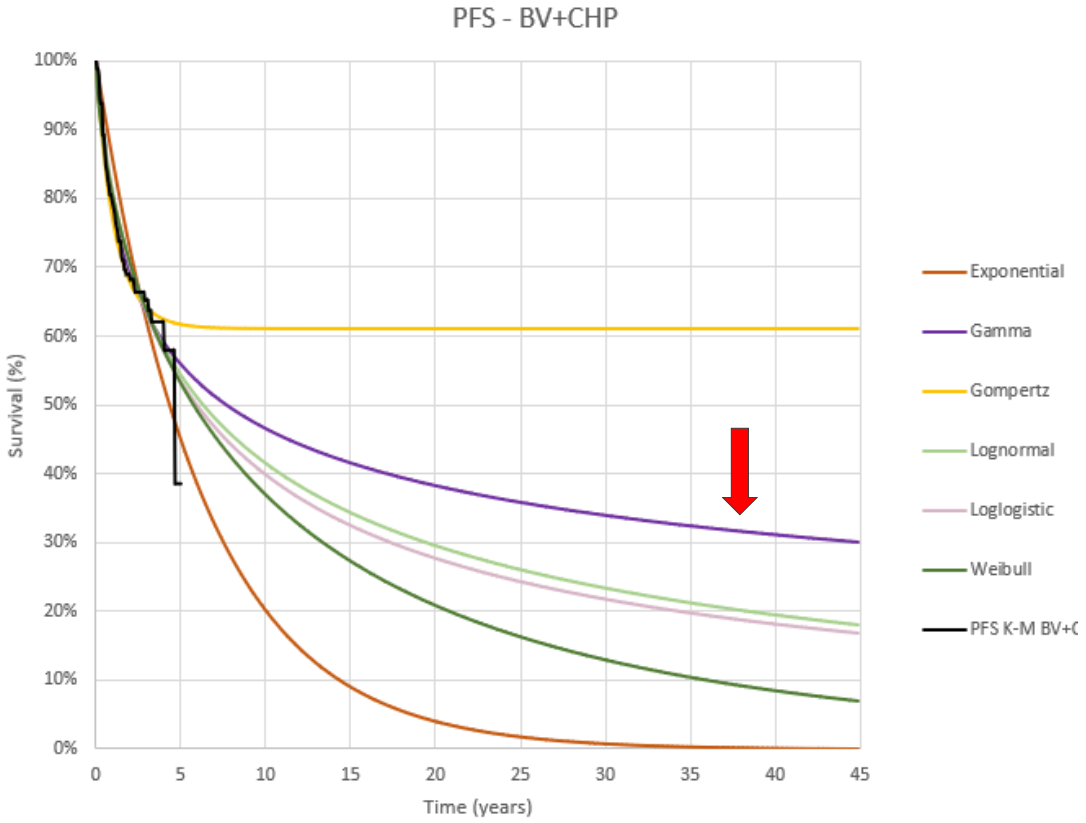
Issue:	Company	ERG	Tech team
Issue 6 – Choice of joint or stratified modelling	Believes that the joint modelling approach is appropriate and represents the best use of available data.	Considers that the joint modelling approach is appropriate, based on the log-cumulative hazard plots.	Q:Q plots (a method for comparing two probability distributions) were not assessed by the company. The effect on the ICERs is marginal.
Issue 7 – Grade 3 and 4 Peripheral Neuropathy Management	Clinical input regarding the current management of PN in the UK is that clinicians would either dose reduce or dose delay BV, or in higher grades of PN (Grade 3 or 4) would stop treatment with BV.	Originally questioned whether there should be consistency with TA478. Following technical engagement, the ERG accept the company's justification.	Not including costs for grades 3 & 4 peripheral neuropathy is appropriate.

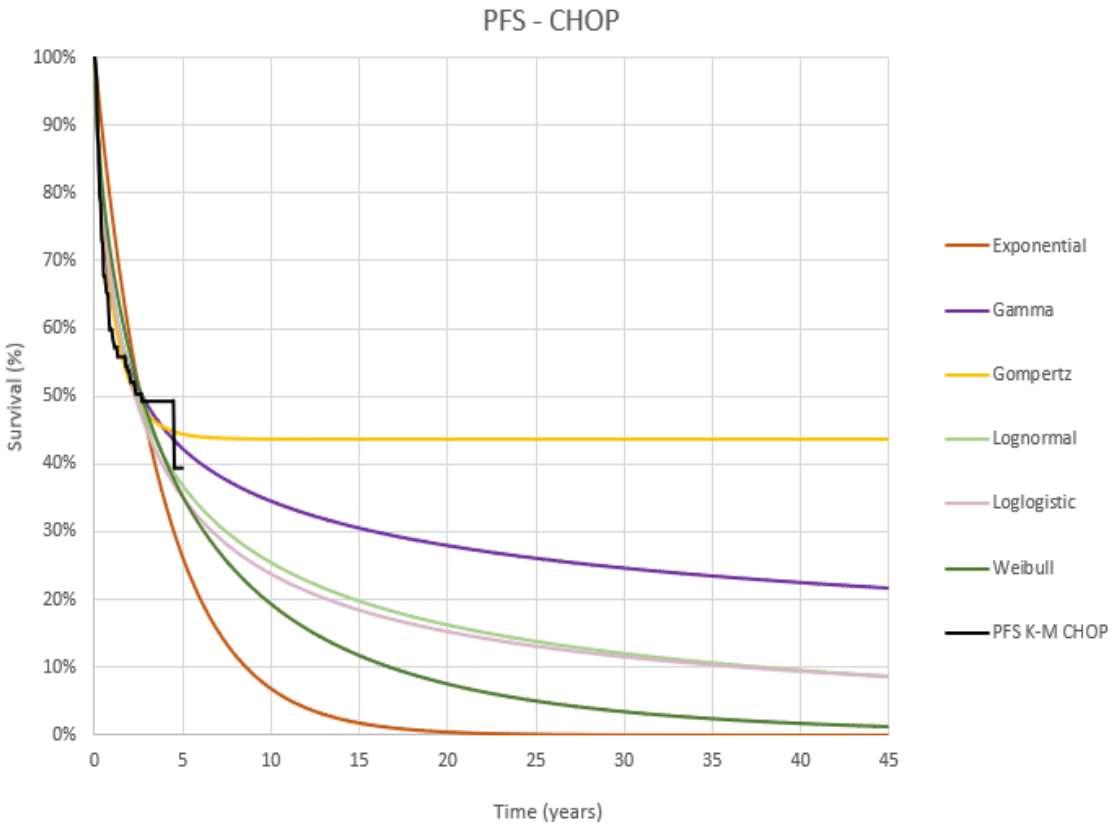
Issue 2 – Choice of extrapolation for long-term PFS and OS

- **Company:** Selected a generalised gamma distribution to extrapolate long-term PFS and OS. The hazard rates of the generalized gamma extrapolations reflect a short-term increase in risk, followed by a substantial decrease thereafter. Clinical experts confirmed that this is reflective of the clinical population.
- **ERG:** Note that this short-term increase followed by a decreasing risk trend is also observed in lognormal extrapolations, which should also be considered as plausible **(ERG scenario analysis on slide 23)**.
- **Clinical experts:** Whilst acknowledging the difficulty in selecting between different distributions for the intention-to-treat population, clinical experts considered the lognormal extrapolation to be more plausible.
- **Technical team:** Agree with the company that the generalised gamma distribution for both PFS and OS represents the highest impact on the ICER and is therefore the most conservative option for decision making. But there remains uncertainty about long term survival gains.

This issue is for discussion

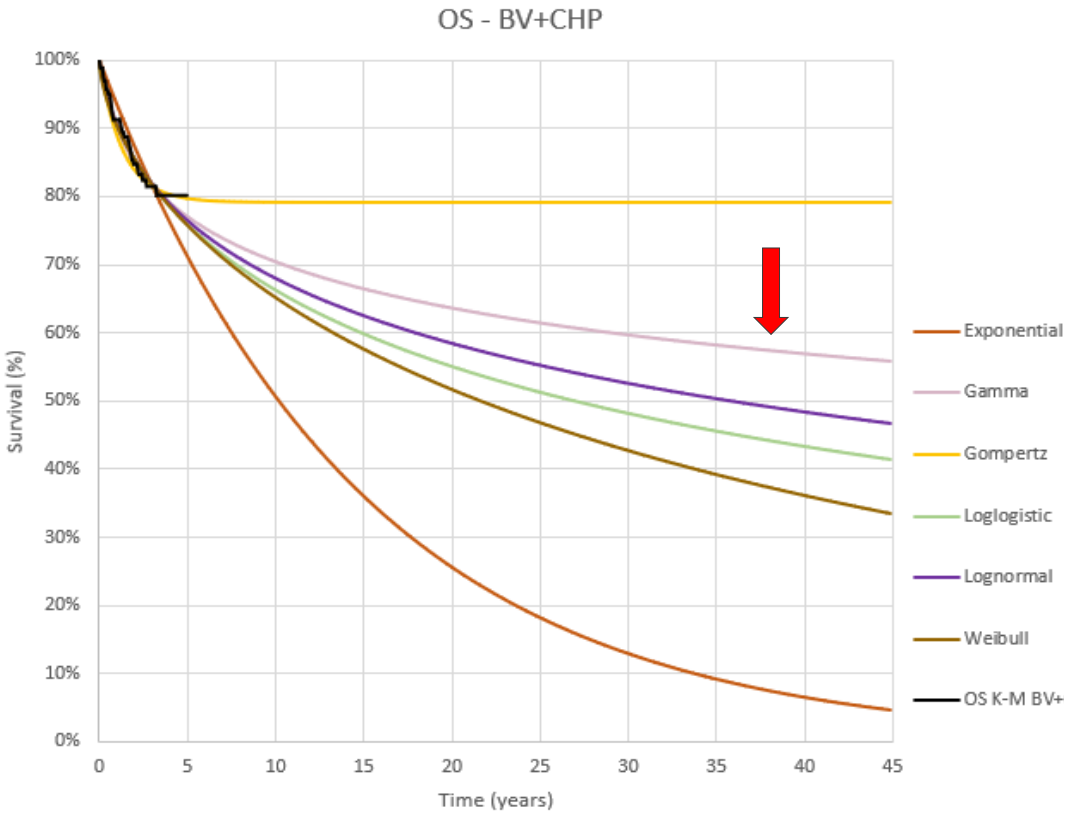
Issue 2 – Choice of extrapolation for long-term PFS (sALCL)

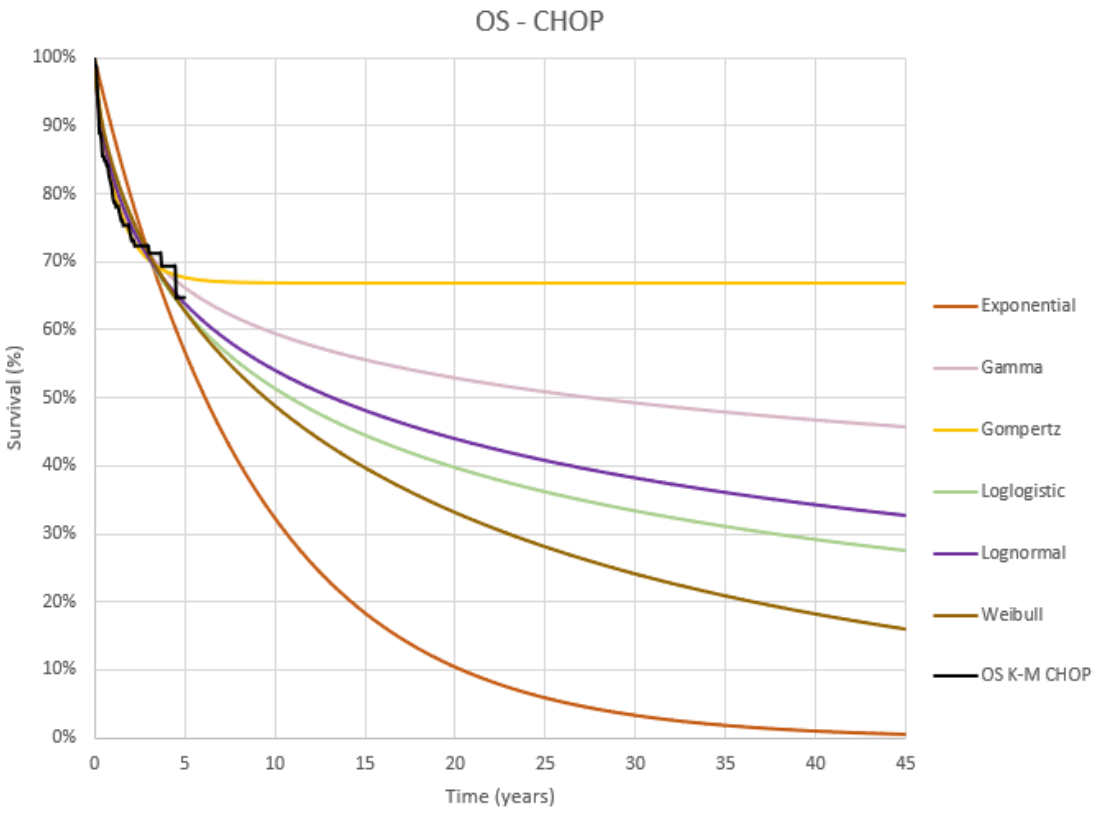




Standard parametric extrapolations for OS and PFS (without background mortality applied). Red arrow shows company and ERG preferred curve (generalised gamma).

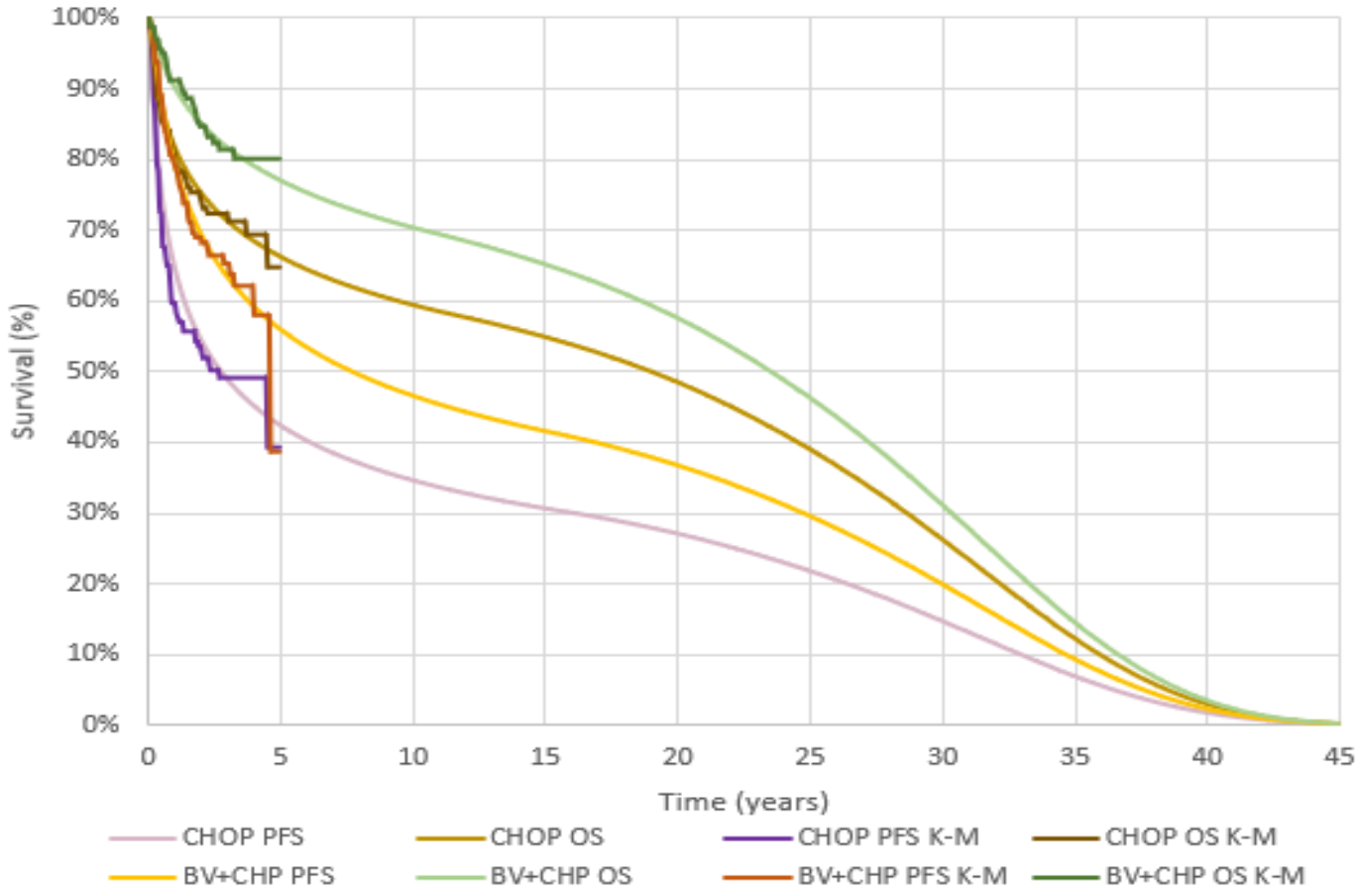
Issue 2 – Choice of extrapolation for long-term OS (sALCL)





Standard parametric extrapolations for OS and PFS (without background mortality applied)
Red arrow shows company and ERG preferred curve (generalised gamma).

Issue 2 – Choice of extrapolation for long-term PFS and OS (sALCL)



Survival extrapolations fitted to the generalised Gamma distribution (background mortality applied)

Issue 2 – Timepoints at which OS is driven by background mortality hazards

OS distribution	CHOP (years)	BV + CHP (years)
Generalised gamma (base-case)	13.05	12.02
Exponential	33.00	29.04
Gompertz	5.40	4.77
Log-logistic	19.03	17.02
Lognormal	17.54	15.01
Weibull	23.06	19.03

Cost effectiveness results

- ERG's updated deterministic base-case (with PAS price)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CHOP	[redacted]	11.64	[redacted]	[redacted]	1.95	[redacted]	£22,047
BV+CHP	[redacted]	13,58	[redacted]				

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year; LYs = life years

The ERG agreed with most of the changes made by the company to their updated base-case, with the following exceptions:

- Correct implementation of the time-to-death (TTD) utility approach in the model.
- Mortality multiplier: 1.28 to reflect 6.5% increased mortality risk.

ERG scenario analysis – OS

- OS (PFS = generalised gamma, with PAS price)

	Inc. costs (£)	Inc. QALYs	Inc. LYs (undiscounted)	ICER
Generalised gamma	[redacted]	[redacted]	[redacted]	£22,074
Exponential	[redacted]	[redacted]	[redacted]	£17,215
Gompertz	[redacted]	[redacted]	[redacted]	£20,585
Log-logistic	[redacted]	[redacted]	[redacted]	£17,778
Log-normal	[redacted]	[redacted]	[redacted]	£18,358
Weibull	[redacted]	[redacted]	[redacted]	£16,448

ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; PAS = patient access scheme; QALYs = quality adjusted life years; LYs = life years.

ERG scenario analysis – treatment waning

- PFS = generalised gamma and OS = generalised gamma (with PAS price)

Treatment effect duration	Inc. costs (£)	Inc. QALYs	Inc. LYs (undiscounted)	ICER
5 years	[redacted]	[redacted]	[redacted]	£23,446
10 years	[redacted]	[redacted]	[redacted]	£22,316
45 years (base-case)	[redacted]	[redacted]	[redacted]	£22,074

ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; PAS = patient access scheme; QALYs = quality adjusted life years; LYs = life years.

The equivalent ICERs for all other alternative OS models are lower.

Other considerations

- **End of life:** No case was made that BV + CHP meets the NICE end of life criteria.
- **Cancer Drugs Fund:** BV + CHP has not been put forward as a candidate for the CDF.
- **Innovation:** this is the first time in decades that any first-line regimen has been found to be superior to the long-established standard of care, CHOP.
- **Equality issues:** None raised.

Key issues:	Status
Issue 1 – Average age of PTCL patients in the economic model	
Is the mean age used in the company base case too low? If so, what age is appropriate for the economic model?	Resolved
Issue 3 – Utility model approach	
Is the time-to-death utility model preferable to the health state utility method?	Resolved
Issue 4 – Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	Resolved
Issue 5 – Number of 2nd line monotherapy BV cycles in the model	
Is a mean of 6 cycles for 2nd line BV appropriate?	Resolved
Issue 6 – Choice of joint or stratified modelling	
Are joint or stratified models more appropriate? *	Resolved
Issue 7 – Grade 3 and 4 Peripheral Neuropathy Management	
What is the treatment of Grade 3 or 4 peripheral neuropathy? *	Resolved
Issue 2 – Choice of extrapolation for long-term PFS and OS	
Which are the most clinically plausible extrapolations for PFS and OS?	For discussion

* Issues identified at technical engagement

Back-up slides

Issue 1 – Average age of PTCL patients in the economic model

- **Data:**
  - 1) Mean age of 316 sALCL patients in ECHELON-2 trial: 52 years
  - 2) Mean age of [redacted] sALCL patients in UK Haematological Malignancy Research Network [HMRN] registry data: [redacted] years
  - 3) Median age of 39 sALCL patients reported in Gleeson et al. (2018): 52.2 years (mean not available but expected to be lower)

- **Company:** ECHELON-2 data does not diverge widely from the real-world data and is most appropriate for the updated base-case.

- **Clinical experts:** Indicated that 55 years is an appropriate age for the sALCL population whereas the third expert suggested using 57.5 or 58 years based on UK ALCL-specific data (Martinez et al. 2019).

- **ERG:** Accepts the mean age from ECHELON-2 for its updated base-case, but argues this is likely to underestimate the ICER.

This issue is resolved.

Issue 3 – Utility model approach

- **Company:** In the original submission, three approaches were considered: 1) a health-state utility (HSUV), 2) time-to-death and 3) using the HSUV model but replacing the progression coefficient with the relapsed/refractory utility values from Swinburn et al. (used in TA478). In response to technical engagement the company opted to switch from a HSUV approach to the 'time-to-death' (TTD) approach for the base-case estimation, in line with the ERG's preferred analysis.
- **ERG:** Agree with the company that all three approaches have advantages and limitations and agree with the company's choice to select the TTD approach for its base case.
- **Technical team:** The impact on the ICER is minor.

This issue is resolved.

Issue 4 – Utility age-adjustment

- **The ERG:** Age-related decrement of 0.002, derived from the EQ-5D data from the ECHELON-2 trial, meant that in the long term, progression free patients in the model had higher utility values than the age-adjusted utilities of the general population as calculated in Ara and Brazier 2010. The ERG considered this implausible and implemented a constraint in their preferred base-case whereby utilities could not exceed these age-adjusted general population utility values.
- **Clinical experts:** Agree that it is appropriate to constrain patient's utility values to not exceed the general population's age-adjusted utility value.
- **The company:** Agree with the ERG's amendment to the model.

This issue is resolved.

Issue 5 – Number of 2nd line monotherapy brentuximab vedotin cycles in the model

- **Company:** The base case assumption regarding the number of cycles of brentuximab vedotin that patients in the CHOP arm with relapsed/refractory sALCL would receive at relapse was set to 8.2 cycles, as per the SGN35-0004 trial and reported in TA478.
- **ERG:** It was unclear to the ERG whether or not the assumption of 8.2 cycles has been validated by clinical experts. The clinical expert at the TA478 committee meeting highlighted that real-world evidence suggests that the median number of cycles for BV is 5 to 6.
- **Technical team:** NICE provided the company with UK real-world evidence from the Systemic Anti-Cancer Therapy (SACT) dataset on the use of BV for patients with R/R sALCL, showing that the average number of cycles of BV monotherapy used for 2nd line sALCL was 6.

This issue is resolved.

Issue 6 – Choice of joint or stratified modelling

- **The company:** For both OS and PFS, the lines on the log-cumulative hazard plots are parallel, supporting the proportional hazards assumption. Hypothesis testing indicates that there is no evidence of a deviation from the proportional-hazards assumption. The company believes that the joint modelling approach is appropriate and represents the best use of available data.
- **ERG:** At technical engagement, asked whether the company had fully explored the appropriateness of a stratified modelling approach. The company reported results of the Schoenfeld test but these were for the ITT population only. The ERG considers that the joint modelling approach appropriate, based on the log-cumulative hazard plots.
- **Technical team:** The effect on the ICERs is marginal.

This issue is resolved.

Issue 7 – Grade 3 and 4 peripheral neuropathy management

- **The company:** In TA478 a cost to manage PN was included, but this assumption was based on feedback elicited over six years ago. Clinical input regarding the current management of PN in the UK has consistently been that clinicians would either dose reduce or dose delay BV, or in higher grades of PN (Grade 3 or 4) would stop treatment with BV. Clinical experts advised that no further interventions would be undertaken.
- **ERG:** Originally questioned whether there should be additional costs included in the model for grade 3 and 4 peripheral neuropathy (PN), as was the case in TA478. Following technical engagement, the ERG accept the company's justification.

This issue is resolved.

Cost effectiveness results

- Company's updated base-case (with PAS price)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CHOP	[redacted]	11.71	[redacted]	[redacted]	1.96	[redacted]	£21,192
BV+CHP	[redacted]	13.68	[redacted]				

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

The probabilistic ICER based on 5,000 Monte Carlo simulations was £20,694 per QALY

ERG scenario analysis – PFS

- PFS (OS = generalised gamma, with PAS price)

	Inc. costs (£)	Inc. QALYs	ICER
Generalised gamma	[redacted]	[redacted]	£22,074
Exponential	[redacted]	[redacted]	£18,386
Gompertz	[redacted]	[redacted]	£22,764
Log-logistic	[redacted]	[redacted]	£19,007
Lognormal	[redacted]	[redacted]	£19,258
Weibull	[redacted]	[redacted]	£17,899

ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma

ERG scenario analysis – Age at baseline

- Age at baseline (with PAS price)

Age at baseline (years)	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
52 (sALCL in ECHELON-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,047
55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,498
[redacted] (HMRN PTCL audit)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57.7 (UK sALCL in ECHELON-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,043
58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,233

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; HMRN = Haematologic Malignancy Research Network; ICER = incremental cost effectiveness ratio; incr. = incremental; PTCL = Peripheral T-cell lymphoma; sALCL = systemic anaplastic large cell lymphoma; UK = United Kingdom