Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma

For committee – Redacted

Technology Appraisal Committee C [5th November 2024]

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Company: Takeda

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine (A+AVD) for previously untreated late-stage classical Hodgkin lymphoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

A+AVD (intervention) and ABVD (comparator) combinations

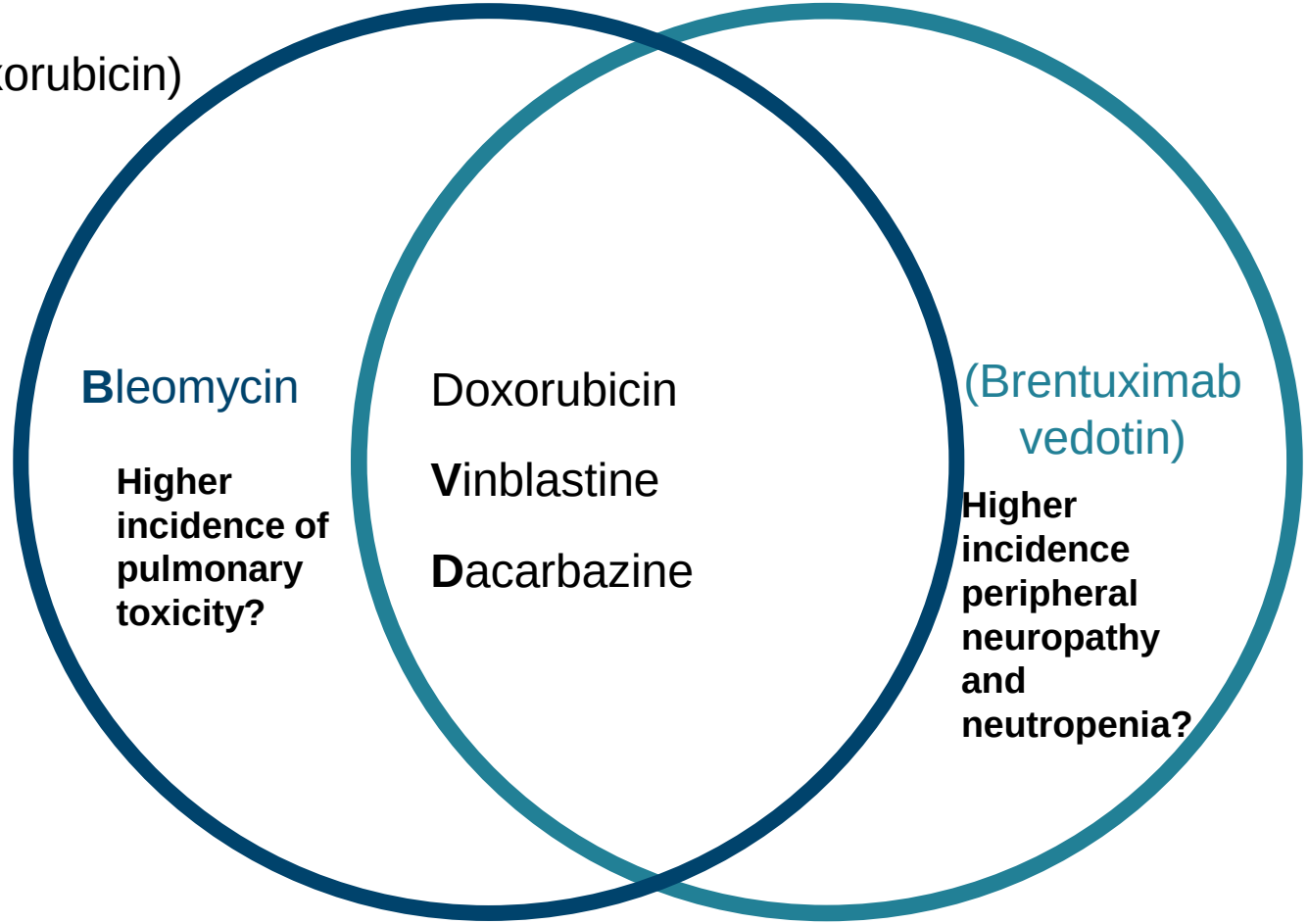
ABVD (B+AVD)

Adriamycin (=Doxorubicin)

Bleomycin

Vinblastine

Dacarbazine



A+AVD

A=Brentuximab vedotin (= **A**dcetris)

Adriamycin (=Doxorubicin)

Vinblastine

Dacarbazine

BEACOPP (Dac)
Bleomycin
Etoposide
Adriamycin (=doxorubicin)
Cyclophosphamide
Oncovin (=vincristine)
Procarbazine
Prednisolone
(**D**acarbazine)

Key issues

Issues for committee discussion	ICER impact
Generalisability of ABVD clinical data to practice	Unknown
Bimodal age patient population not adequately accounted for in model	Large
Use of one-knot spline model for OS survival modelling	Large
Use of different standardised mortality ratios for A+AVD and ABVD	Moderate
Life-long peripheral neuropathy not included in model	Large
Health-related quality of life/adverse event disutilities	Small
Other issues	
Subsequent treatment use	Small

Abbreviations: OS, overall survival

Background on classical Hodgkin lymphoma

Causes and epidemiology

- Cancer of the lymphatic system containing Hodgkin Reed-Sternberg (HRS) cells
- 1,861 new cases of HL in England in 2021 (822 cases stage 3 or 4)
- Classical HL (or CD30+ HL) is the most common type of HL (95% of cases)
- Highest incidence in young adults (20 to 24 years) and older adults (75 to 79 years)

Symptoms and prognosis

- Symptoms include lymph node swelling, fatigue, weight loss, high fevers and night sweats
- 3-year progression-free survival of 83% and 80% for stages 3 and 4 respectively
- Aim of first-line treatment for people with stage 3 or 4 HL is to cure without the need for additional therapy – with current standard of care, first-line cure rate is around 70%

Abbreviations: CD30, cell membrane receptor 30; HL, Hodgkin lymphoma

Patient perspectives: Submission from Lymphoma Action

Young people often face long-term side effects including infertility & require emotional support

Living with classical Hodgkin Lymphoma

- People often rely on family and friends while enduring long-term side effects like fatigue, fever, sweats, pain, swollen lymph nodes & frequent medical visits
- Fatigue is particularly troublesome and difficult to tolerate

Current treatment options and unmet need

- Current treatment options have significant side effects including nausea, vomiting, bowel changes, fatigue, lung and breathing problems
- Long-term post-treatment effects include lung damage and infertility
- Always need for more treatment options which are easy to administer and well tolerated
- Brentuximab vedotin adds a targeted cancer treatment to first-line treatment which is only currently available at later lines

"My husband has had to come to terms with the fact I can no longer have children and that we will go through rest of our lives together childless"

"We are currently going through the assisted fertility pathway, but there are no guarantees of children"

"It was decided that I would have AVD as bleomycin could cause lung damage and I only had one lung"

Clinical perspectives: Submissions from 2 clinical experts

Aim of treatment

- To cure the disease for most people with HL

Unmet need/current treatment options

- People who are not cured undergo intensive therapy including stem cell transplant which can have psychological and emotional impact on people and their families and is associated with significant long-term side effects

"The technology would allow the substitution of bleomycin (which causes lung toxicity and should be avoided in most patients over 60years) by brentuximab"

Brentuximab vedotin

- Would increase the chance of cure and overall survival which will improve the quality of life
- Expect A+AVD to replace ABVD and not BEACOPDac (both treatment choices in current care) - more impactful for older people who would otherwise get ABVD
- Minimal investment needed and may have a reduced impact on respiratory services (due to a decrease in lung side effects with bleomycin)
- Increased risk of peripheral neuropathy & sepsis - careful monitoring required with dose adjustments as required

Abbreviations: HL, Hodgkin lymphoma

Brentuximab vedotin (Adcetris, Takeda)

Marketing authorisation	In February 2019, brentuximab vedotin was granted marketing authorisation for: • 'Previously untreated CD30+ Stage 4 HL, in combination with AVD' In September 2024, brentuximab vedotin was granted a licence extension (relevant to this evaluation): • 'For the treatment of adult patients with previously untreated CD30+ **Stage 3 or** 4 HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD)'
Mechanism of action	• Anti-CD30 monoclonal antibody attached to a chemotherapeutic agent, monomethyl auristatin E (MMAE) • Targets CD30-expressing cancer cells
Administration	• 1.2 mg/kg administered as an IV infusion over 30 minutes on days 1 and 15 of each 28-day cycle for six cycles
Price	• List price: £2,500 per 50 mg vial • Cost per 28-day treatment cycle: £11,231 • Average cost per course of treatment (based on 5.5 cycles of brentuximab vedotin and 5.6 cycles of AVD): £61,793 • There is a confidential patient access scheme discount

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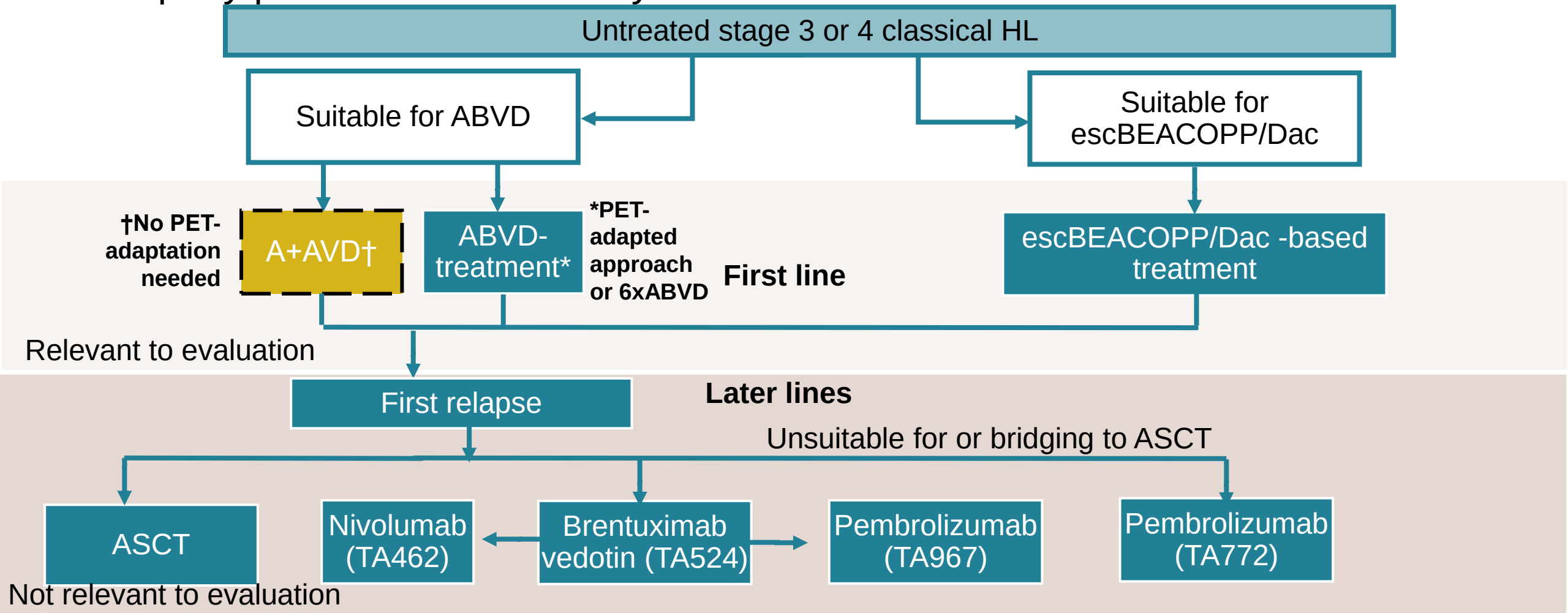
Abbreviation; CD30, cell membrane receptor 30; HL, Hodgkin lymphoma

Treatment pathway: untreated Stage 3 or 4 CD30+ HL

Company positioned A+AVD only when ABVD is suitable



- Would brentuximab vedotin replace use of ABVD only?

Does the treatment pathway accurately represent standard care for people with untreated stage 3 or 4 disease?

Proposed position

Supplementary slide

Abbreviations: ASCT, Autologous stem cell transplantation; HL, Hodgkin lymphoma; PET, Positron emission tomography TA, technology appraisal

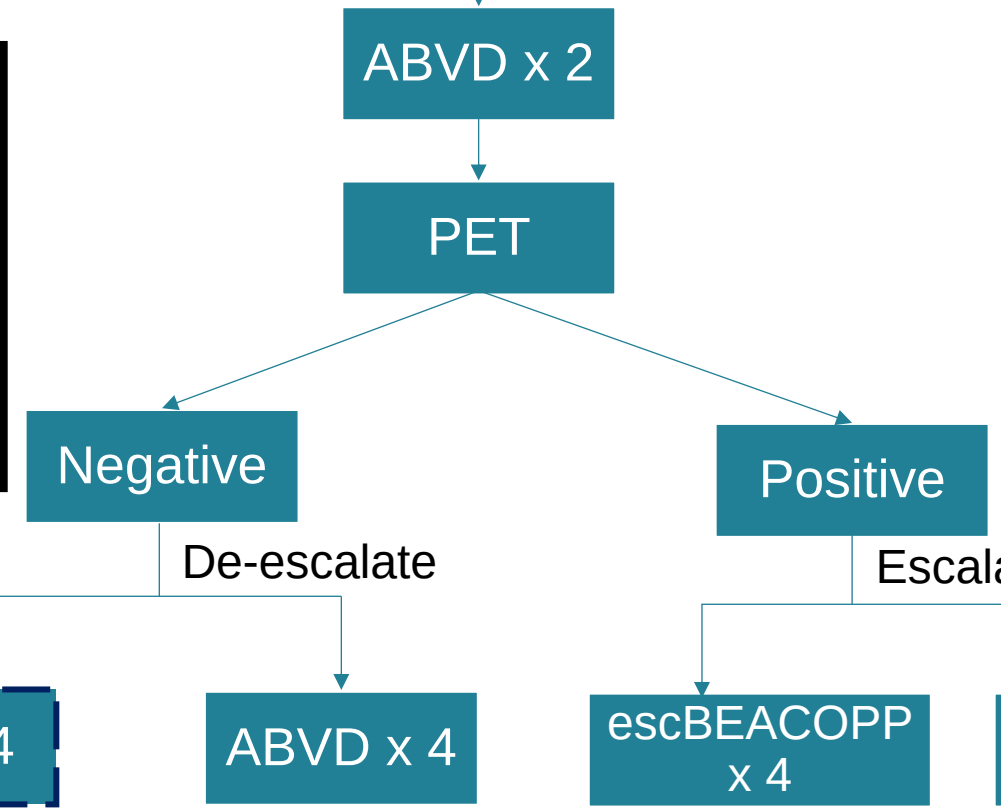
RATHL trial approach

EAG:

- PET-adapted ABVD approach recommended in UK clinical practice (which includes escalation or de-escalation based on PET)

Company

- Not all UK centres use a PET-adapted approach, some use 6-cycles of ABVD
- Used weighted average of ABVD treatment for 6-cycles (10%) and PET-adapted (90%) in model



UK clinical practice

- Is PET-adapted ABVD the main comparator for A+AVD?
- Is the efficacy of 6-cycles of ABVD without PET adaptation equal to PET-adapted ABVD?
- Is the assumed UK standard of care for PET-escalation or de-escalation treatments correct?

Abbreviations; HL, Hodgkin lymphoma; PET, Positron emission tomography; RATHL - Response-Adapted Therapy for advanced Hodgkin Lymphoma

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Key clinical trial – ECHELON-1 (NCT01712490)

Clinical trial designs and outcomes

	ECHELON-1
Design	Open label, randomised, controlled two-arm phase 3 trial
Population	Treatment-naïve adult patients (≥18 years old) with histologically confirmed CD30+ Stage 3 or 4 HL (based on Ann Arbor staging)
Intervention	A+AVD: brentuximab vedotin (A) plus doxorubicin (A; also called Adriamycin), vinblastine (V), and dacarbazine (D)
Comparator	ABVD: doxorubicin (A), bleomycin (B), vinblastine (V), and dacarbazine (D)
Duration	Median PFS follow-up: 89.2 months (95% CI: 86.4–90.1) Median OS follow-up: 89.3 months (95% CI: 87.0–90.2)
Primary outcome	Modified PFS per IRF
Key secondary outcomes	OS, PFS per INV, ORR, TEAEs, QoL
Locations	218 sites, 21 countries including the UK and EU
Used in model?	Yes

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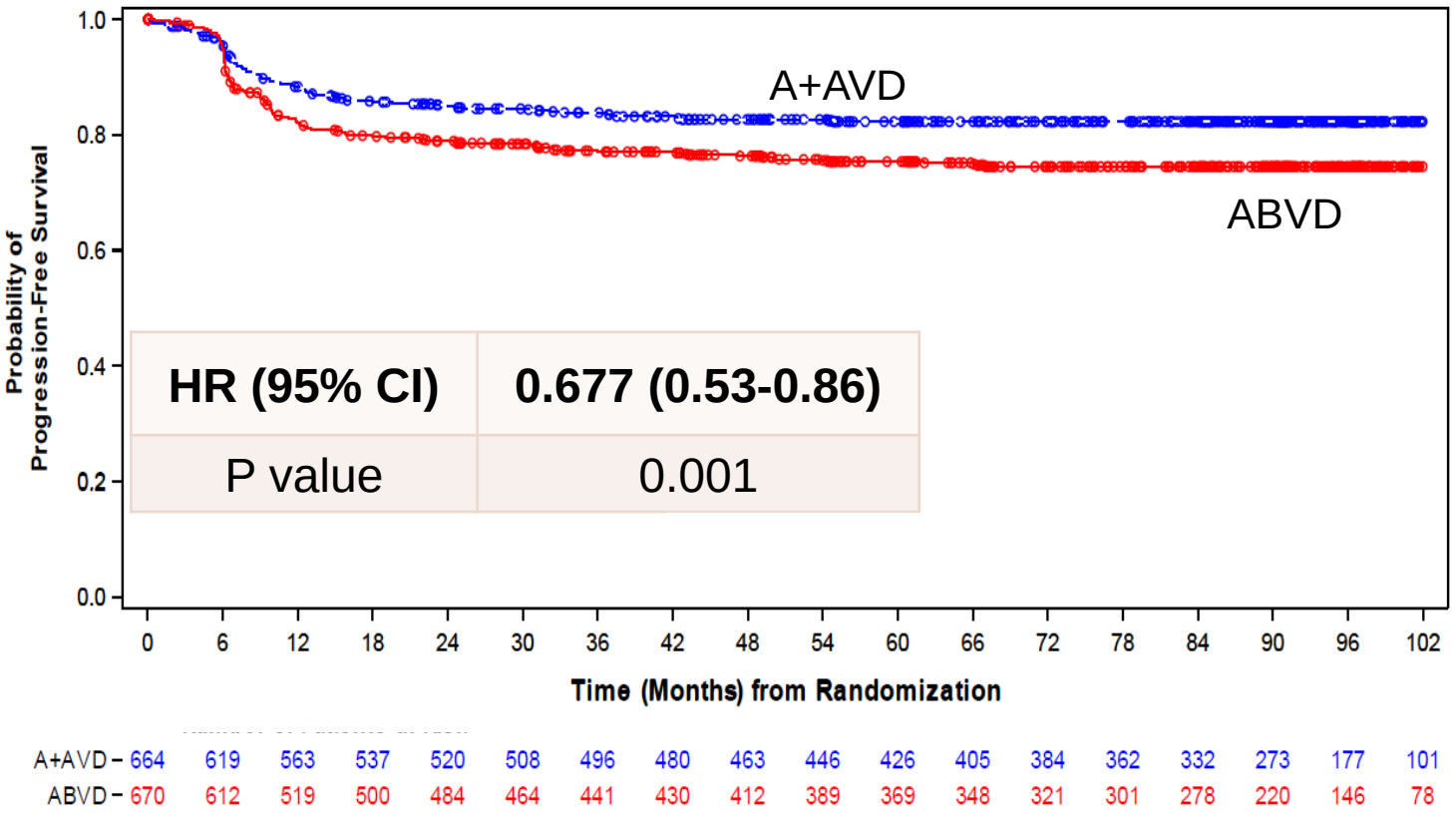
Abbreviations:CD30, cell membrane receptor 30; CI, confidence intervals; INV, investigator; IRF, independent review facility; ORR, overall response rate; QoL, quality of life

ECHELON-1: Progression-free survival

Statistically significant improvement in PFS-INV for A+AVD compared with ABVD
Median PFS not estimable

Figure: Kaplan-Meier plot for PFS for ECHELON-1 (Mar 2023 DCO)



PFS probability timepoints	A+AVD (n=664)	ABVD (n=670)
12 months (95% CI)	88.3 (85.6 to 90.6)	82.1 (78.9 to 84.8)
48 months (95% CI)	82.7 (79.5 to 85.4)	76.3 (72.8 to 79.4)
84 months (95% CI)	82.3 (79.1 to 85.0)	74.5 (70.8 to 77.7)
102 months (95% CI)	82.3 (79.1 to 85.0),	74.5 (70.8 to 77.7)

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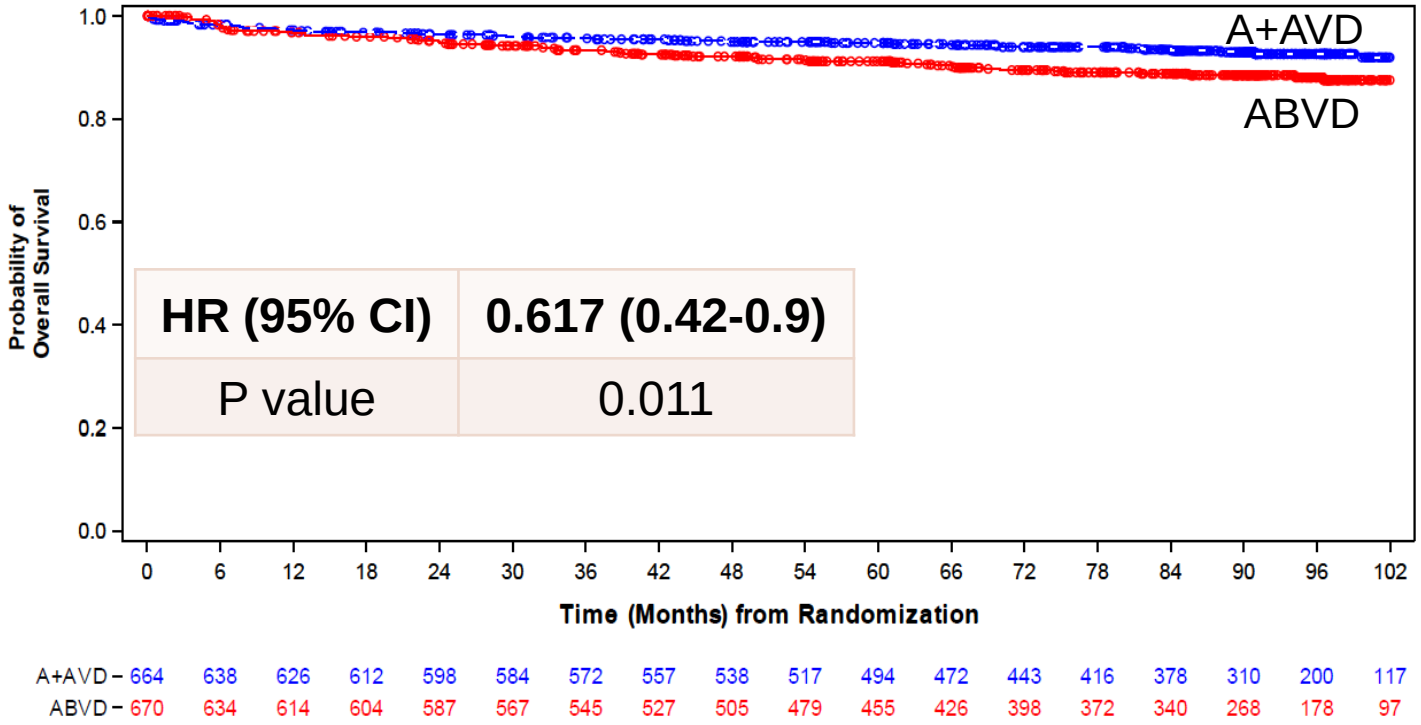
Abbreviations: CI, confidence intervals; INV, investigator; DCO, data cutoff

ECHELON-1: Overall survival

Statistically significant improvement in OS for A+AVD compared with ABVD
Median OS not estimable

Figure: Kaplan-Meier plot for OS for ECHELON-1 (Mar 2023 DCO)



OS probability timepoints	A+AVD (n=664)	ABVD (n=670)
12 months (95% CI)	97.2 (95.7–98.3)	96.7 (95.1–97.9)
48 months (95% CI)	94.9 (92.9 to 96.4)	92.1 (89.7–94.0)
84 months (95% CI)	93.5 (91.1 to 95.2)	88.8 (85.8–91.1)
102 months (95% CI)	91.9 (89.0–94.1)	87.5 (84.2–90.2)

Clinical experts

- Survival data effectively highlights the benefit: consider remarkable for this population

NICE

Abbreviations: CI, confidence intervals; HR, hazard ratio, DCO, data cutoff; INV, investigator; OS, overall survival

ECHELON-1: Safety

More grade ≥3 drug-related TEAEs and peripheral neuropathy for A+AVD

	A+AVD (n=662)	ABVD (n=659)
Drug-related TEAEs with at least one grade ≥3, n (%)	528 (80)	393 (60)
Neutropenia	344 (51.96)	242 (36.72)
Febrile neutropenia	120 (18.13)	46 (6.98)
Neutrophil count decreased	81 (12.24)	64 (9.71)
Anaemia	46 (6.95)	18 (2.73)
People with ≥1 treatment-emergent grade ≥3 PN event, n (%)	68 (10)	11 (2)
Peripheral sensory neuropathy	32(5)	3 (<1)
Neuropathy peripheral	28 (4)	6 (<1)
Peripheral motor neuropathy	13(2)	0
Muscular weakness	2 (<1)	1 (<1)
Others (hypoesthesia, neuralgia, polyneuropathy, autonomic neuropathy)	3 (<1)	2 (<1)

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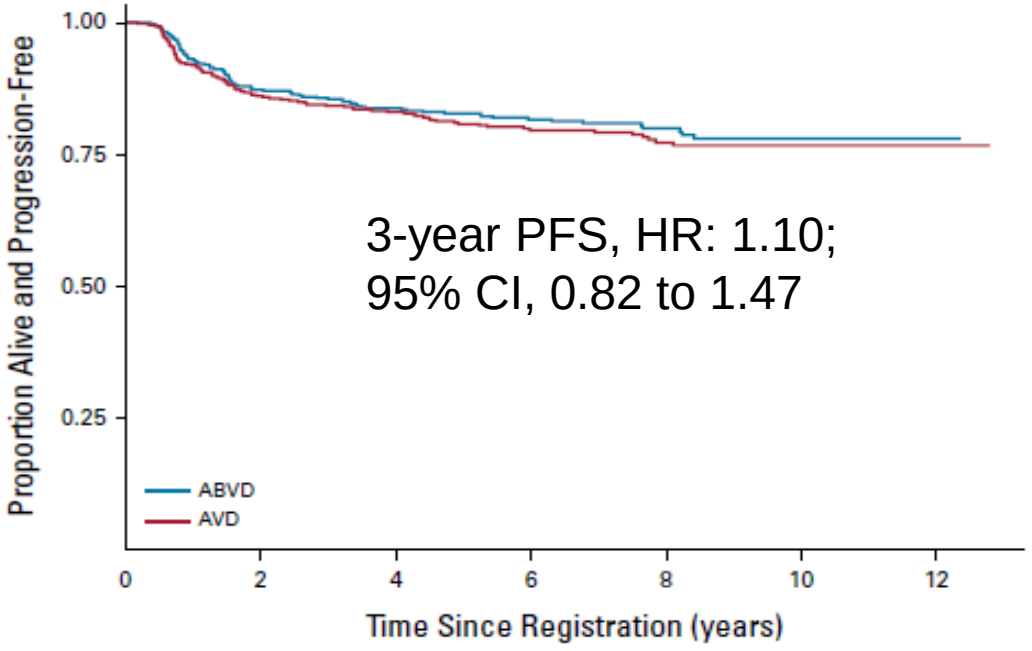
Abbreviations; G-CSF, granulocyte-colony-stimulating factor; TEAE, treatment-emergent adverse event

RATHL results: survival outcomes (PFS and OS)

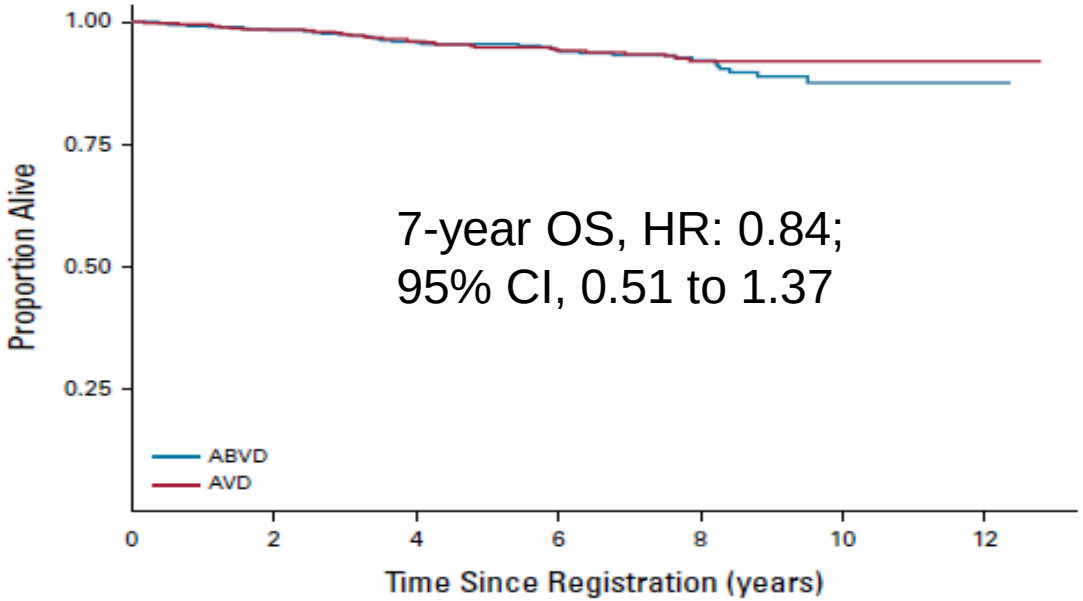
PFS of PET2-negative who received ABVD or AVD



3-year PFS, HR: 1.10;
95% CI, 0.82 to 1.47

No. at risk:							
ABVD	469	396	339	256	141	33	3
AVD	464	380	336	249	144	40	1

OS of PET2-negative who received ABVD or AVD



7-year OS, HR: 0.84;
95% CI, 0.51 to 1.37

No. at risk:							
ABVD	469	446	392	295	166	42	3
AVD	464	432	386	294	167	46	1

- RATHL trial results show no significant difference in outcomes between ABVD or AVD for people who de-escalate treatment after a negative PET scan after cycle 2
- 86% ABVD arm PET-2 negative in ECHELON-1 – would be de-escalated from ABVD to AVD in clinical practice
- 9% ABVD arm PET-2 positive in ECHELON-1 – would be escalated to escBEACOPDac in clinical practice
- But, 6 cycle ABVD used for all participants in ABVD arm in ECHELON-1 regardless of PET-2 status – so, no head-to-head evidence for A+AVD vs PET-adapted ABVD

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Abbreviations: CI, confidence intervals; HR, hazard ratio; OS, overall survival; PET, positron emission tomography PFS, progression-free survival

Key issues: Generalisability of ABVD clinical data to practice

Unknown Impact ?

Company

- Assumed equal efficacy between 6-cycle and PET-adapted ABVD
- Equal efficacy supported by unanchored MAIC informed by RATHL trial outcomes, reflective of PET-adapted ABVD in UK (includes PET+ve escalation and PET-ve de-escalation)
- Results of unanchored MAIC driven by age, as RATHL population younger than ECHELON-1; when adjusting for age, residual differences in MAIC outcome may be due to differences in treatment practices across regions - conducted further MAIC removing adjustment for age but still adjusted for all other variables

EAG

- Insufficient justification for removal of age from MAICs
- Proportional hazards assumption not shown to hold for fully adjusted MAICs – reported HRs should be interpreted with caution; also concerns around face validity of results from MAICs
- Agrees most robust source of evidence for A+AVD vs ABVD is ECHELON-1 - but raises concerns around use of 6-cycle ABVD in ECHELON-1 when PET-adapted ABVD is clinical practice and equivalence not proven

ABVDx6 vs PET-adapted ABVD MAIC results: OS	HR (95% CI)
Fully adjusted (age, IPS, ECOG, stage, sex, B-symptoms, bulky disease and presence of extra-nodal sites)	0.59 (0.40 to 0.85), p=0.005
Adjusted for all variables, but age	0.88 (0.61 to 1.27), p=0.490

Indicates 6xABVD better OS than PET-ABVD

Abbreviations: CI, confidence intervals; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPS, international prognostic score MAIC, matched adjusted indirect comparison; PET, positron emission tomography

Supplementary slide

Is assuming 6-cycle ABVD equivalent to PET-adapted ABVD reasonable?

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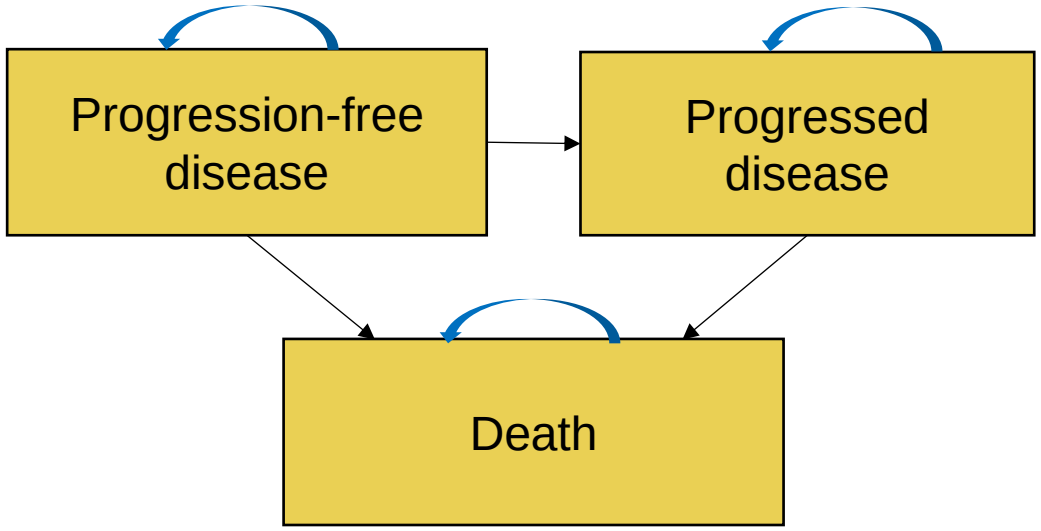
Company's model overview



Affects **QALYs** by:
- Decreasing the probability of disease progression
- Increasing rate of survival and probability of adverse events

Affects **costs** by:
- More costly and more people requiring adverse event treatments
- Fewer people require subsequent treatments, treatment administration, monitoring and follow-up care

Assumptions with greatest ICER effect:
- Weighting ICER based on age groups
- SMR applied to A+AVD and ABVD
- Choice of OS extrapolation model and curve
- Inclusion of people with lifelong peripheral neuropathy

EAG
- 3 health states, with relapsed and refractory PD people included within a single health state
- Previous TAs modelled 5 health with relapsed and refractory being considered separately

Company
- Previous TAs informed by short data (24.9 months vs 89.3 months), so in absence of mature data higher health states more appropriate

Is the company's model structure appropriate?

Abbreviations: PD, progressed disease; ICER, Incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life years; SMR, standardised mortality rate; TA, technology appraisal

Supplementary slide

Key issues: Late-stage cHL affects the population bimodally

Figure: Distribution of ECHELON-1 ages

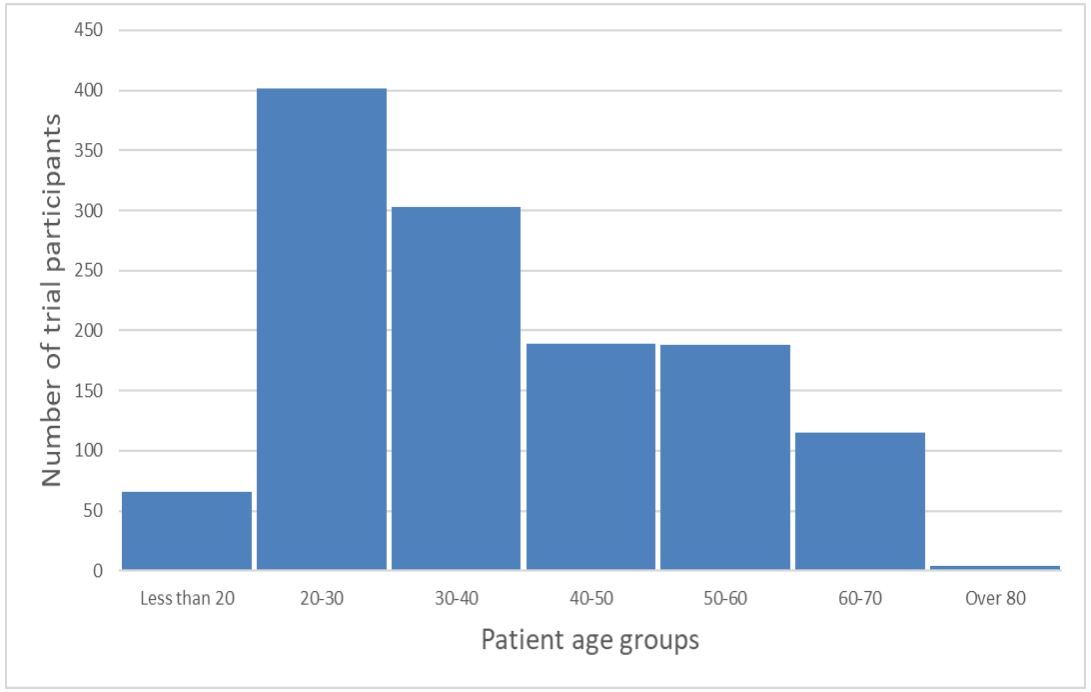
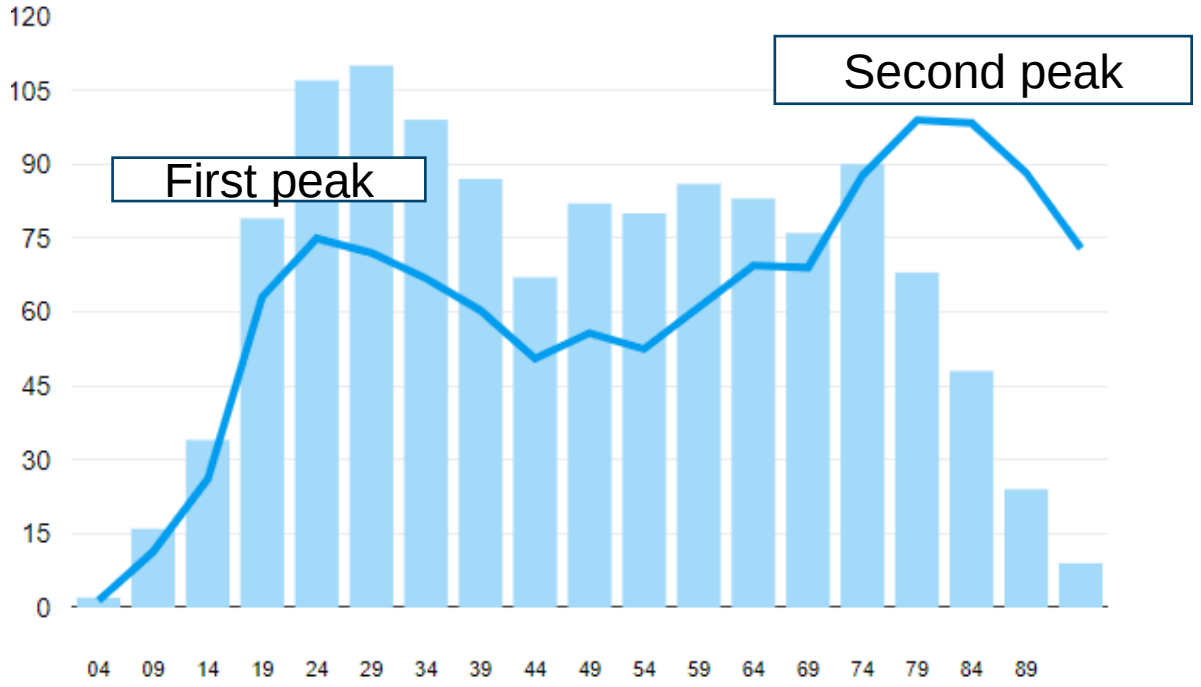


Figure: Age at diagnosis Cancer Research UK (2017-2019)



- Age-specific incidence rates rise sharply during childhood and peak around age 20-29 with a second peak between age 75-84
- Highest rates are in the 20 to 24 age group for females and the 75 to 79 age group for males

Is age a treatment effect modifier?

Abbreviations; cHL, classical Hodgkin lymphoma

Key issues: Late-stage cHL affects the population bimodally

Large impact

Background

- Company used mean age from ECHELON-1 in model (39.53 years)
- EAG prefer age-weighted ICER using mean age in subgroups <60 and ≥60 years

Company

- Age-weighted ICER not appropriate: age would not impact how the disease is treated
- Subgroup data breaks randomisation and a smaller population informs subgroup analyses vs ITT (≥60 subgroup: A+AVD n=84, ABVD n=102 vs. ITT: A+AVD n=664, ABVD n=670)
- May lead to population subgroups being considered separately and does not fully characterise uncertainty as specified in NICE manual (only provides deterministic ICER): previous TAs have not modelled based on age
- Provided probabilistic analysis randomly sampling age from ECHELON-1 IPD to account for bimodal age

EAG

- Crucial to account for the age bimodal population to allow generalisability to clinical practice
- Uncertainty introduced by breaking randomisation and assessing subgroups outweighed by benefits of accounting for subgroups; can be effectively managed to produce reliable probabilistic outcomes
- Age distribution in ECHELON-1 is not bimodal - company's probabilistic analysis sampling from trial will not account for age bimodal population
- EAG's probabilistic ICER uses weighted samples from both subgroups – can be considered probabilistic

Abbreviations; cHL, classical Hodgkin lymphoma; ICER, Incremental cost-effectiveness ratio; IPD, individual patient data; ITT, intent-to-treat;

Supplementary slide

Is the company or the EAG's approach accounting for bimodal age appropriate?

Key Issue: Use of a spline model for OS modelling

Large impact

Background

- Company extrapolated A+AVD and ABVD PFS KM survival data using MCM based on trial results, literature and clinical opinion but used one-knot spline model to extrapolate OS data
- EAG consider no clear reason not to use MCM for OS, so used MCM for OS extrapolation in its base case

Company

- Proportional hazard assumption violated
- Flexible parametric modelling appropriate, so used one-knot spline model to extrapolate OS in base case
- In probabilistic analysis MCM leads to implausible estimated cure rates due to wide CI
- Gompertz MCM produced implausible probabilistic cure fractions; exponential MCM CIs were narrower than Gompertz, but led to ABVD cure fraction exceeding that of A+AVD - clinically implausible

[redacted]

[redacted]

Abbreviations: CI, confidence interval; KM, Kaplan-Meier, MCM, mixed cure model, OS, overall survival, PFS, progression-free survival

Supplementary slide

Key Issue: Use of a spline model for OS modelling

EAG

- Cure fraction not estimated by spline model but spline modelled around assumed cure fraction, leading to bias and potential overfitting of model to KM data: so consider MCM more appropriate – supported by mature data and cure fraction well established in literature and supported by ECHELON-1 data
- Company's arguments to dismiss exponential MCM lack evidence:
  - deterministic A+AVD mean cure fraction >ABVD, probabilistic variance reflects uncertainty of treatment effect in trial
  - exponential curve aligns with clinical opinion: 70%-80% achieve cure
  - although poor statistical fit to A+AVD, provides clinically plausible extrapolation and robust probabilistic cure fractions
- EAG used exponential-MCM for both arms in <60 years subgroup and ABVD arm in ≥60 years subgroup; used lognormal for A+AVD arm in ≥60 years subgroup due to no curve being a good visual fit, but providing most optimistic long-term survival

[redacted]

[redacted]

Abbreviations: KM; Kaplan-Meier ;MCM, mixed sure model; OS, overall survival

Which model is more appropriate for modelling OS?

Key issue: Use of different SMR for A+AVD and ABVD

Moderate impact

Background

- Higher SMR rates applied to ABVD (1.1) than A+AVD (1.05) based on clinical opinion to company
- EAG applied equal SMR rates to both ABVD and A+AVD (1.05)

Company

- ABVD bleomycin-containing treatment associated with increased pulmonary toxicity, second malignancies, higher rates of disease progression and subsequent treatment toxicity than A+AVD
- Due to a lack of evidence, it applied SMR to mortality rates based on clinical opinion and in line with previous TAs
- Conducted a rapid review to explore alternative SMRs on EAG's request

Table: Second malignancies & pulmonary toxicity ECHELON-1 and RATHL

Treatment	A+AVD	6-cycle ABVD	PET-ABVD
%Second malignancies	4.98%	5.92%	4.58%
Pulmonary toxicity	5 (<1%)*	21 (3%)*	17 (3.6%)**
Grade ≥3 drug-related TEAE	80%	60%	-

* Grade≥ 3 (DCO 2017); **Grade≥ 3 RATHL

Abbreviations: SMR, standard mortality ratio; TA, technology appraisal

EAG

- Same SMR should be applied to both arms
- Second malignancies broadly similar between treatments and A+AVD arm recorded more grade ≥3 adverse events compared to ABVD in ECHELON-1
- 4 relevant publications identified by company's targeted review, only study by Glimelius et al 2015 considered relevant to decision problem of SMR
- Glumelius et al measured a 1.05 rate of mortality after 15 years compared to the Swedish general population
- EAG clinical opinion considers mortality of cured individuals similar to general population with SMR of 1.05 and different SMR in each arm not clinically plausible

Supplementary slide

Which SMR rates are appropriate for decision making?

Key issue: Treatment-related lifelong peripheral neuropathy

Large impact

Background

- Proportion of people with lifelong peripheral neuropathy (PN) not accounted for in company base case

Company

- Consider proportion of people with lifelong PN overestimated by EAG; without long-term follow-up & have limited data on duration of PN because of loss to follow-up or people withdrawing
- Only people alive with >3 years grade ≥3 PN at the last follow-up should be considered to have lifelong PN
- EAG's disutility for PN (-0.33, Swinburn et al), remaining constant for life lacks face validity (greater than disutility for progression; may improve over time) and sourced from vignette study
- Conducted multivariate utility analysis of ECHELON-1 and identified -0.0836 grade ≥3 PN specific disutility
- Validated calculated disutility values against literature from Hirose et al. 2020 showing sensory PN reduced utility by -0.06 but had limitations (Japanese population with multiple diseases with lymphoma only 6.7%)
- PN was included in previous TAs using Swinburn et al disutility but did not include lifelong PN

	A+AVD (n=662)	ABVD (n=659)
Grade ≥3 PN at last follow-up, n (%)	16 (2.4%)	4 (0.6%)
Grade ≥3 PN, alive at end of follow-up, n (%)	13 (2.0%)	2 (0.3%)
Grade ≥3 PN, alive at end of follow-up and had grade ≥3 PN for at least 3 years prior to their last follow-up date	[redacted]	[redacted]

Company | EAG

Abbreviations: PN , peripheral neuropathy

Key Issue: Treatment-related lifelong peripheral neuropathy

EAG

- People with ongoing grade ≥3 PN at last follow-up should be considered to have lifelong PN; only including those alive would exclude people with chronic PN who died before the end of the study; only including if >3 years prior PN excludes people who progress within 3 years of end of study
- Trial length was 2—3 years in previous TAs, compared to ECHELON-1 (~13 years); longer study duration safety data indicates a proportion of people have lifelong PN that might not be seen in shorter studies
- Company's original regression analysis lacked face validity and underestimated PN disutility – raising concerns around validity of company's regression and its outcomes
- Hirose et al not relevant to grade ≥3 PN: included only 36 Japanese people with grade ≥2 PN, not providing disutility by grade or proportion of people with each grade and only included sensory PN
- Swinburn et al most appropriate in the absence of alternative sources

How should lifelong PN be included:

- appropriate proportion of people
- appropriate disutility associated with PN?

Abbreviations; AEs, adverse events; PN, peripheral neuropathy TA, technology appraisal

Health-related quality of life

Small impact

Company

- Used with duration derived by taking the mean of a regression model to derive health state utility values for different health states and applied them to everyone except the cured population
- Applied one-off disutility to cover all AEs using a regression model relevant AEs from previous TAs

EAG

- Utility values lack face validity: lower in progression-free, on-treatment health states than progressed disease with worse disease
- A+AVD shows lower rate of disease progression than ABVD, high utility value for progressed disease reduces incremental QALYs for A+AVD compared with ABVD
- Disutilities sourced from previous TAs incorrect
- Used disutilities from literature as allows decrement of AEs to be applied individually rather than weighted—results in larger one-off QALY decrement for AEs

Health state	Mean utilities at baseline
Progression-free, on treatment	0.781
Progression-free, off treatment	0.861
Progressed disease	0.791

Grade ≥3 AEs	Disutility				
	Company			EAG	
	Base case*	Literature**	Source	Literature	Source
Anaemia	-0.03	-0.17	TA (641 & 874)	-0.069	Doyle et al
Febrile neutropenia	-0.03	-0.12		-0.115	Lloyd et al
Neutropenia	-0.03	-0.09		-0.048	Nafees et al
Neutrophil count decrease	-0.03	-0.05		-0.048	

Which approach to derive disutility values is more appropriate?

Abbreviations; AE, adverse events; QALY, quality-adjusted life years; TAs technology appraisal

*regression ** scenario

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- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Equality considerations and severity: no issues identified

- **Severity**: company submission notes no severity modifier should be applied given the calculated QALY shortfall
- **Equality:** no equality issues were identified relevant to the access of brentuximab vedotin
- **Managed access:** company has not submitted a managed access proposal for brentuximab vedotin with doxorubicin, dacarbazine and vinblastine:
    - May not be appropriate since ECHELON-1 has over 7 years follow-up

Abbreviations; QALY, quality-adjusted life years

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine (A+AVD) for previously untreated late-stage classical Hodgkin lymphoma

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Summary of company and EAG base case assumptions

Assumption	Company preferred assumptions	EAG preferred assumptions
Bimodal age	• Mean-age based ICER	• Age-weighted ICER
OS modelling	• One-knot spline model	• Mixed cure model • Separate survival curves were fit to <60 and ≥60-year-old OS data

SMR	• Separate for both treatments
	  ○ A+AVD= 1.05
	  ○ ABVD = 1.10
		• Same SMR for both treatment arms = 1.05

Utility values	• Utility regression analysis	• Literature-based approach to calculate adverse event disutility
Adverse events		• Applying treatment specific mean time to PN resolution • Accounting for people with lifelong PN
Subsequent treatment	• Based on ECHELON-1	• Company clinical expert opinions • 5% of people with progressed disease will require radiation therapy

Abbreviations: OS, overall survival; PN, peripheral neuropathy; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate

Key issues and questions for committee

Issues for committee discussion		Slide
Clinical evidence	• Is the clinical data for ABVD from ECHELON-1 generalisable to clinical practice?	See slide
Cost-effectiveness	• Is the company or the EAG's approach accounting for bimodal age appropriate?	See slide
	• Which model is more appropriate for modelling OS?	See slide
	• Which SMR rates are more appropriate for decision-making?	See slide

	• How should lifelong PN be included:
	  ○ appropriate proportion of people
	  ○ appropriate disutility associated with PN?
		See slide

	• Which approach to deriving disutility values is more appropriate?	See slide
	• Is the EAG's approach to subsequent treatment estimates appropriate?	See slide

Abbreviations: OS, overall survival; PN, peripheral neuropathy; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential prices for other treatments in the pathway:

Analyses to be presented include:

- Company and EAG base cases
  - Company base suggests A+ AVD is more effective and more expensive than ABVD (ICER above £30,000/QALY gained)
  - EAG base case suggests A+AVD is more effective and more expensive than ABVD (ICER above £30,000/QALY gained)
- EAG scenario analyses

Abbreviations; ICER, incremental cost-effectiveness; QALY, quality-adjusted life years

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Thank you.

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine (A+AVD) for previously untreated late-stage classical Hodgkin lymphoma

Supplementary appendix

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Abbreviations

- **A+AVD** - brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine
- **ABVD** - doxorubicin, bleomycin, vinblastine, dacarbazine
- **BEACOPDac** - Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, dacarbazine
- **BEACOPP** - bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone
- **BEACOPP-14** - 14-day bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone regimen
- **G-CSF**- Granulocyte-colony-stimulating factor
- **HL-** Hodgkin lymphoma
- **HR**- Hazard ratio
- **ICER** - Incremental cost-effectiveness ratio
- **MAIC** - Matched adjusted indirect comparison
- **MCM** - Mixture cure model
- **OS** - Overall survival
- **PET** - Positron emission tomography
- **PFS** - Progression-free survival
- **PN** - Peripheral neuropathy
- **QALY** - Quality-adjusted life year
- **RATHL** - Response-Adapted Therapy for advanced Hodgkin Lymphoma
- **TEAE** - Treatment-emergent adverse event

Decision problem

Abbreviations; CD30, cell membrane receptor 30HL, HRQoL, heath- related quality of life; MA, marketing authorisation; NA, not applicable; PET - Positron emission tomography

	Final scope	Company	EAG	Clinical experts
Population	People with previously untreated late-stage classical Hodgkin lymphoma	Adults previously untreated CD30+ Stage 3 or 4 Hodgkin lymphoma Adjusted in line with MA	Narrow to those eligible for ABVD	A+AVD likely to replace ABVD
Intervention	Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine	As in scope	Appropriate	NA
Comparators	Single or combination chemotherapy including but not limited to drugs such as doxorubicin, bleomycin, dacarbazine and vinblastine	Combination chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD-based regimens) • In line with proposed positioning (previously untreated patients with CD30+ Stage 3 or 4 HL who would otherwise be suitable for treatment with ABVD) • Weighted average use of PET-adapted ABVD (90%) and ABVDx6 cycles (10%)	Agreed with comparator ABVD-based regimen but PET- adapted approach is widely used in clinical practice – 100% PET-adapted ABVD appropriate	PET adapted RATHL widely used in clinical practice
Outcomes	OS, PFS, response rate, adverse effects of treatment, HRQoL	As in scope	Appropriate but final data cut-off not provided in clinical-effectiveness	NA

Baseline characteristics- ECHELON-1 & RATHL

EAG

- Stage 3 and 4 RATHL subgroups are potentially more representative than ECHELON-1 who are likely to be eligible for A + AVD
- Similar proportion of people aged <60 years and ≥60 years in ECHELON and stage 3 and 4 RATHL trial

Baseline characteristics		ECHELON-1			RATHL Stage 3 &4
		A+AVD (n=664)	ABVD (n=670)	Total (n=1,334)	
Sex,n (%)	Female	378 (56.9)	398 (59.4)	776 (58.2)	[redacted]
	Male	286 (43.1)	272 (40.6)	558 (41.8)	[redacted]
Mean age – years (SD; range)		38.8 (15.8)	40.2 (16.1)	39.5 (15.9)	[redacted]
Age group (years) – n (%)	≤60	585 (88.1)	579 (86.4)	1,164 (87.3)	[redacted]
	>60	79 (11.9)	91 (13.6)	170 (12.7)	[redacted]
Cancer stage n (%)	Stage 3	237 (35.8)	246 (36.9)	483 (36.3)	[redacted]
	Stage 4	425 (64.2)	421 (63.1)	846 (63.7)	[redacted]

*Median

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Abbreviations: CI, confidence intervals; ORR, Overall response rate; RATHL - Response-Adapted Therapy for advanced Hodgkin Lymphoma; SD, standard deviation; QoL, quality of life

ECHELON-1: PET status after Cycle 2

Higher rate of PET2 negative people in A+AVD arm

Stage 4 had greatest difference* between A+AVD vs. ABVD

		A+AVD (n=664)	ABVD (n=670)
ITT population	PET2 negative	588 (89)	577 (86)
	PET2 positive	47 (7)	58 (9)
	Missing PET at Cycle 2	29 (4)	35 (5)
PET2 negative status relative risk (95% CI)		1.028 (0.99 to 1.07)	
Stage 3	PET2 negative	209 (88)	219 (89)
	PET2 positive	13 (5)	15 (6)
	Missing PET at cycle 2	15 (6)	12 (5)
PET2 negative status relative risk (95% CI)		0.991 (0.93 to 1.06)	
Stage 4	PET2 negative	379 (89)	358 (85)
	PET2 positive	34 (8)	42 (10)
	Missing PET at Cycle 2	12 (3)	21 (5)
PET2 negative status relative risk (95% CI)		1.049 (1.00 to1.10)	

*Not adequately powered to demonstrate statistically significant differences

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Abbreviations: CI, confidence interval; ITT, intent-to-treat; PET, positron emission tomography

How company incorporated evidence into model

Table: Summary of evidence used to inform the company's model

		Assumptions and evidence source
Model Structure		• Partition survival model
Baseline characteristics		• ECHELON-1 (mean age:39.53)
Time horizon **Cycle length**		• Lifetime (60 years) • 7 days
Treatment effectiveness	**PFS**	• Mixture cure model to extrapolate PFS
	OS	• One-knot splines to extrapolate OS
Utilities		• ECHELON-1
Mortality		• SMRs of 1.05 and 1.10 are applied to background mortality in A+AVD and ABVD respectively
Cost		• eMIT, BNF, NHS Reference Costs, published literature for second malignancy costs, previous NICE appraisals (TA462, TA478, and TA524) for subsequent therapy costs
Perspective		• NHS and PSS

Abbreviations: ICER, incremental cost-effectiveness ratio; BNF, British National Formulary; eMIT; electronic Market Information Tool; OS - overall survival; PFS, progression-free survival; SMR, standardised mortality; TA, technology appraisal

Source: EAG report, table 21

Main slide

Key issues: Generalisability of ABVD clinical data to practice (2)

Background

- SmPC recommends using G-CSF primary prophylaxis for all previously untreated Hodgkin lymphoma from cycle 1 but only 13% of people in A+AVD arm of ECHELON-1 had G-CSF primary prophylaxis from cycle 1
- AE data from RATHL used in model to capture AEs related to PET-adapted ABVD

EAG

- G-CSF used in ECHLEON-1 does not align with UK clinical practice, and may have resulted in more neutrophil-related AEs with A+AVD than expected
- 81% people in A+AVD arm had G-CSF in trial at anytime
- Large discrepancies in grade ≥3 AE incidences for ABVD in ECHELON-1 vs PET-adapted ABVD from RATHL
- AE data from RATHL used in model uses all (rather than drug-related) TEAEs; escalation treatment used in RATHL (escBEACOPP) doesn't align with escalation treatment used in clinical practice (escBEACOPDac)
- Overall, difficult to predict the direction of resulting bias in AE data used in the model

Outcome	G-CSF primary prophylaxis	No G-CSF primary prophylaxis
Neutropenia	35%	73%
Febrile neutropenia	11%	21%
Grade ≥3 neutropenia	29%	70%

Main slide

Unknown Impact ?

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Abbreviations: AE, adverse events; G-CSF, granulocyte-colony-stimulating factor; RATHL - Response-Adapted Therapy for advanced Hodgkin Lymphoma

Key Issue: Use of a spline model for OS modelling

Large impact

EAG

- ≥60 years old ABVD OS MCM curves show minimal variation and aligned with KM data, with exponential curve providing best fit; so preferred to use in its base case

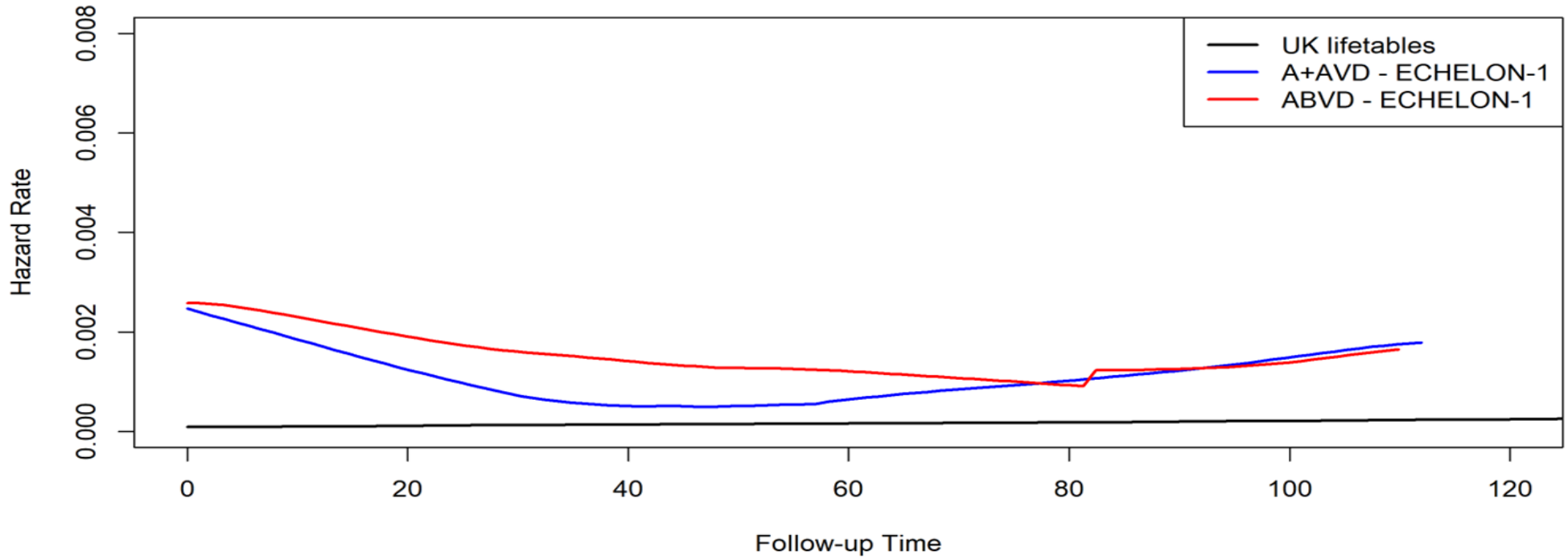
Figure: OS age subgroup survival modelling using MCMs and EAG preferred extrapolation

Abbreviations; MCM, mixed cure model; KM, Kaplan Meier; OS, overall survival

Main slide

Key issue: Use of different SMR for A+AVD and ABVD

Figure: comparison of observed hazards for OS in ECHELON-1 with UK lifetables



Abbreviations: OS, overall survival; SMR, standardised mortality rate;

Main slide

Key issue: Use of different SMR for A+AVD and ABVD

Publication	Population and disease setting	SMR
Glimelius et al. 2015[39]	1,947 Swedish HL patients diagnosed between 1992-2009, aged 18-59 years old	1.01 for relapse free patients at five years and 1.05 at 15 years
Núñez-García et al. 2023[40]	338 HL Spanish patients with up to 45 years of follow-up	Overall SMR was 3.57. The SMR of those diagnosed after 2000 was 2.73 when excluding HL as the cause of death
Dores et al. 2016[41]	20,007 US patients aged 20 to 74 years old with HL diagnosed between 2001 and 2009	2.4 for advanced HL when excluding cancer related mortalities
Perez-Callejo et al. 2018[42]	595 Spanish patients diagnosed with HL between 1966 and 2014	Excluding the primary tumour as the cause of death, the SMR obtained was 2,266

Abbreviations: HL, Hodgkin lymphoma; SMR, standardised mortality rate

Subsequent treatments

Small impact

EAG

- Used proportion of people having subsequent treatment based on company's clinical expert's opinion to reflect clinical practice
- Proportion of people who have radiotherapy would be higher than 0% suggested by company's clinical experts; EAG assumed 5% receive radiotherapy after progression

Proportion receiving each treatment

Treatment	A+AVD (ECHELON-1)	ABVD (ECHELON-1)	A+AVD (clinical opinion)	ABVD (clinical opinion)
ASCT	31.25%	33.96%	57.9%	60.08%
Pembrolizumab	1.55%	3.65%	65.85%	52.04%
Nivolumab	13.16%	14.59%	8.05%	8.24%
Brentuximab vedotin monotherapy	8.09%	44.03%	23.53%	47.88%
alloSCT or donor lymphocyte infusion	7.72%	14.47%	3.13%	3.82%
Multiagent chemotherapy	78.68%	87.42%	106.59%	108.26%
Radiation	8.58%	9.1%	0%	0%

Abbreviations: alloSCT: allogenic stem cell transplant; ASCT: autologous stem cell transplant