Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [Review of TA540] [ID5084]

For showing onscreen, contains redacted information as [redacted]

Technology appraisal committee A [13 February 2023]

Chair: Radha Todd

Lead team: Peter Baker, Ana Duarte

External assessment group: KSR

Technical team: Catherine Spanswick, Joanna Richardson, Janet Robertson

Company: Merck Sharp & Dohme

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma

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

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Key to ICER impact: small  unclear 

Key issues

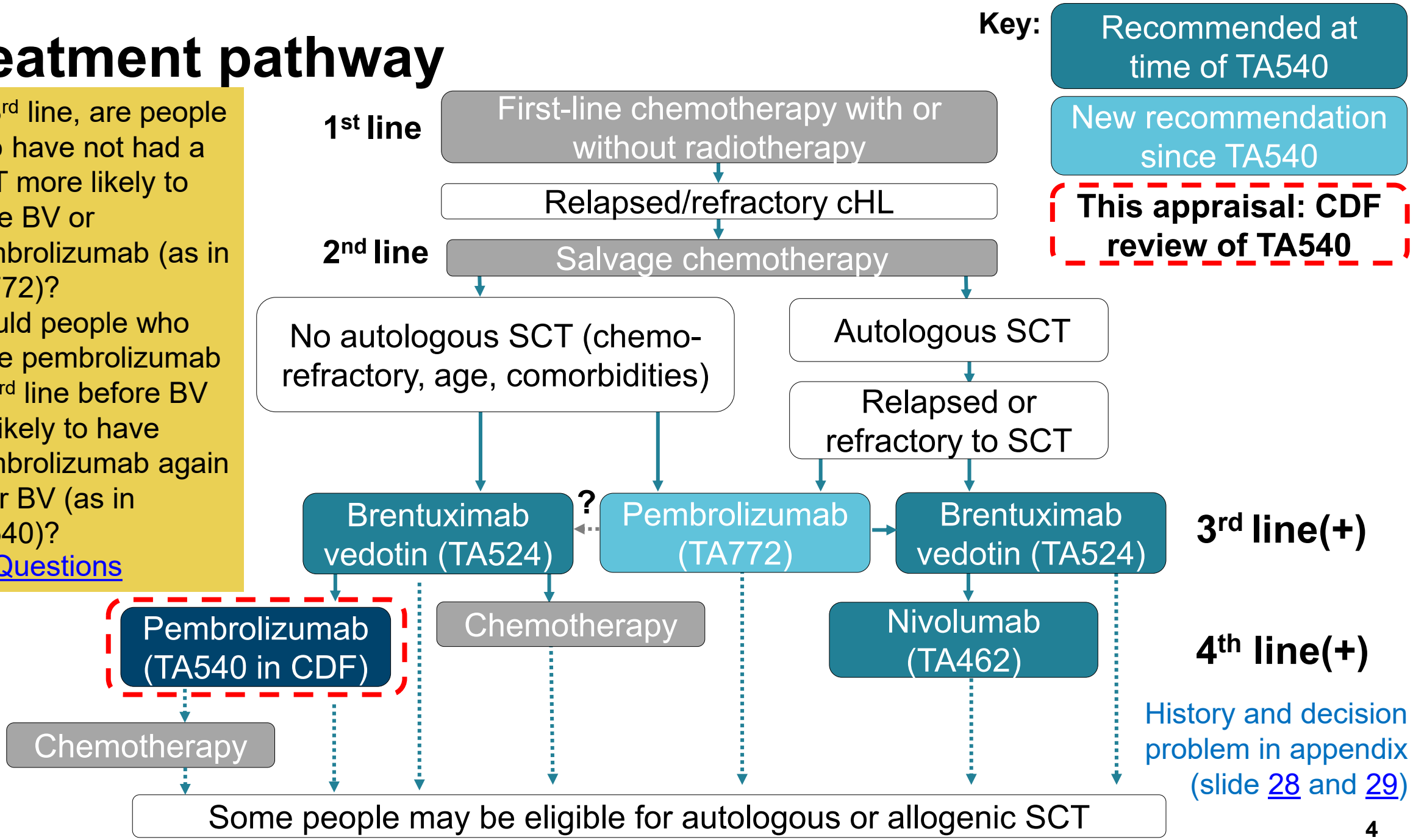
Key issues	Resolved?	ICER impact
1. Uncertainty in comparators and standard care	No, explored	Small
2. Major uncertainties in the ITC analyses (related to key issue 4)	No, explored	Unclear
3. Model structure inconsistent with good practice	No	Unclear
4. Uncertain comparative effectiveness including duration of treatment effect (partly related to key issue 2)	No, explored	Unclear/some small*
5. Utility values	No, explored	Small
Other issues		
Quality of the systematic literature review (see appendix slide 34)	No	Unclear
Misaligned outcomes from the SACT dataset (see appendix slide 35)	No	Unclear
Uncertainty in subsequent therapy assumptions (see appendix slide 43)	No, explored	Small

*See appendix for EAG scenario analysis (slide 45), where combined scenarios including no OS gain pre-landmark ('extreme' scenario) has a substantial impact increasing the ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy

Treatment pathway

At 3rd line, are people who have not had a SCT more likely to have BV or pembrolizumab (as in TA772)?
Would people who have pembrolizumab at 3rd line before BV be likely to have pembrolizumab again after BV (as in TA540)?
To Questions



History and decision problem in appendix (slide 28 and 29)

Abbreviations: BV, brentuximab vedotin; CDF, Cancer Drugs Fund; cHL, classical Hodgkin lymphoma; SCT, stem cell transplant

Patient and clinical perspectives

Current treatments and unmet need

- cHL and its treatment significantly affect patients' quality of life, with fatigue, nausea, vomiting and infections the most troublesome side effects
- There is a need for effective, less demanding treatments with fewer side effects that allow a better quality of life
- There is an unmet need for anti-PD1 therapy in patients who are not suitable for SCT because of disease progression despite salvage chemotherapy or brentuximab vedotin

Pembrolizumab potential advantages and disadvantages

- Patients feel that pembrolizumab has a more favourable side effect profile than most other treatments for relapsed and refractory Hodgkin lymphoma
- Anti-PD1 therapy is an important treatment in the management of cHL after failure of first-line therapy, salvage therapy, and brentuximab vedotin – can be used as a bridge to transplant

More detail in appendix (slide 30 to 32)

Abbreviations: cHL, classical Hodgkin lymphoma; PD1, programmed cell death protein 1; SCT, stem cell transplant

Pembrolizumab (Keytruda, Merck Sharp & Dohme)

Table: Technology details

Updated* marketing authorisation	Indicated as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma: • who have failed autologous stem cell transplant (ASCT) [TA722] or • **following at least two prior therapies when ASCT is not a treatment option** [TA540 in CDF → this evaluation] *Indication was in adults only (not paediatric patients) at time of TA540
Mechanism of action	• Humanised monoclonal antibody that blocks PD-1 to promote anti-tumour response • Anti-programmed cell death 1 (PD-1) antibody; blocks interaction with PD-L1 and PD-L2 ligands and reactivates T-cell anti-tumour activity
Administration	Intravenous administration • 200mg every 3 weeks† until disease progression, unacceptable toxicity or patient withdrawal • Maximum 35 cycles (~24 months)
Price	List price £2,630 (100mg vial); £5,260 per administration Company has agreed a confidential CAA with the Department of Health

†400mg every 6 weeks explored in a scenario analysis

Abbreviations: ASCT, autologous stem cell transplant; CAA, commercial access agreement; CDF, Cancer Drugs Fund; PD-1, programmed cell death protein 1

Small ICER impact

1. Key issue: Uncertainty in comparators and standard care

Comparator is standard care; treatment assumptions are uncertain

Background

- TA540: Cheah et al. (2016) and more recent UK study (Eyre et al. 2017) suitable data for standard care
- Comparators in company's decision problem differ from NICE scope. BSC (no active treatment) excluded

Company

For clinical effectiveness, as in TA540:

- Standard care from Cheah et al., adjusted to reflect practice at the time: 19% bendamustine, 39% chemotherapy, 43% investigational agents
- But 72% of patients had autologous SCT before BV so were not 'SCT naive'

For economic model, differs from TA540:

- Blended comparators of equal proportions because advisory board could not give confident estimates of proportions at 4L
- Proportions were varied in scenario and sensitivity analysis → only small ICER impact

Are the company's approaches for standard care reasonable, for proportions and no BSC?

EAG comments – uncertainty in standard care

- Preferred to reduce proportions of radiotherapy and gemcitabine based on Eyre et al. and increase bendamustine and mini-BEAM

Table: Base case assumptions for standard care

Treatment	Company	EAG
Bendamustine	14.3%[a]	23%
Mini-BEAM	14.3%[a–c]	23%
Gemcitabine-based	14.3%[c]	12%[b]
Radiotherapy	14.3%[b]	12%[b]
Chemotherapy, ICE, oral chemotherapy	14.3%[a–c] each	10% each

[a]Cheah et al.; [b]Eyre et al.; [c]expert opinion

To Questions

Abbreviations: 4L, 4th line; BSC, best supportive care; BV, brentuximab vedotin; ICE, ifosfamide, carboplatin, etoposide; ICER, incremental cost-effectiveness ratio; mini-BEAM, carmustine, etoposide, cytarabine, melphalan; SCT, stem cell transplant

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Key clinical trial – KEYNOTE-087

Table: Company pivotal trial for pembrolizumab

	KEYNOTE-087
Design	Phase II single arm, open label trial
Population	Adults with RRcHL†: • **Cohort 2 (n=81)** after salvage chemotherapy and BV (but did not have autoSCT); included 10 UK patients
Intervention	• Pembrolizumab 200mg as a 30 minute intravenous infusion every 3 weeks in an outpatient setting • On treatment for up to 2 years, or until unacceptable toxicity or progression
Outcomes	• Primary: Overall response rate (ORR) / Safety and tolerability • Secondary include ORR (investigator assessment), progression-free survival, duration of response and OS
Used in model?	Yes, for some parameters (pembrolizumab only): • baseline characteristics weight, body surface area • efficacy – KEYNOTE-087 OS data not used in base cases • adverse events

†Cohort 1 having autoSCT and BV are not the subject of this evaluation

EAG comments

- Considering the evidence base, EAG notes that company's systematic literature review was not updated from TA540 see appendix slide 33

Company

- No parallel RCTs have been done in 4L+ setting
- Model uses data from KEYNOTE-204, a phase 3 RCT of pembrolizumab and BV
- Subgroup of trial that had not had autoSCT were considered
- But pembrolizumab used at an earlier line of treatment (3L+) than in KEYNOTE-087

Abbreviations: 3L/4L, 3rd / 4th line; autoSCT, autologous stem cell transplant; BV: brentuximab vedotin; ORR, overall response rate; OS, overall survival; RCT, randomised controlled trial; RRcHL, relapsed or refractory classical Hodgkin lymphoma

KEYNOTE-087 and SACT data: overall survival and SCT

Median OS not reached in trial and real-world data; 30% had a SCT

Overall survival:

- Median OS not reached in KEYNOTE-087 and SACT†

Table: Overall survival results

Outcome	Cohort 2 of KEYNOTE-087 (N=81)	SACT dataset (N=215)
Events, n (%)	24 (30)	73 (34)
Median OS	Not reached	Not reached
Median follow-up	62.2 months	19.2 months
OS rate (%) at‡		
12 months	96	82 (76 to 87)
24 months	91	68 (61 to 75)
36 months	86	56 (47 to 64)
48 months	77	55 (46 to 63)
60 months	69	Not available

SCT after pembrolizumab:

- Cohort 2 of KEYNOTE-087
  - 24 (30%) patients had a SCT
  - Median time to SCT 30 months
- SACT dataset
  - 65 (30%) patients had a SCT
  - Median time to SCT 18 months‖

Company

- Consider SCT timing in SACT dataset to be more generalisable to clinical practice in England (clinical trial had fewer UK patients)

†Sensitivity analysis for ≥6 months follow up in SACT had similar result

‡KEYNOTE-087 OS rate from Kaplan–Meier method for censored data

‖In 132 people eligible for SCT

Abbreviations: autoSCT, autologous stem cell transplant; OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

More results in appendix (slide 35 to 39)

Company and EAG alternative indirect comparisons

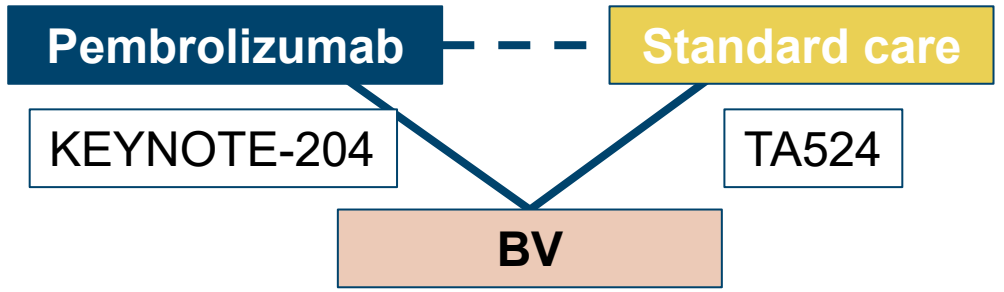
Several sources considered; neither selected approach used KEYNOTE-087 data

Table: Sources used in indirect comparisons

Study or dataset	Population
KEYNOTE-087 cohort 2	**Evaluation population**, single-arm trial of pembrolizumab at 4L
KEYNOTE-204 SCT naive group	3L trial of pembrolizumab vs BV, both arms had similar % of subsequent SCT
NICE TA524 of BV	Estimated HR for OS in patients with or without previous SCT, BV vs standard care in 3L setting
Eyre et al.	Retrospective study of 3L BV, SCT naive, 100% fit for transplant
Cheah et al.	Retrospective study of standard care after BV, 71% had prior SCT, 30% had investigational agents
SACT data	Evaluation population, real-world data on pembrolizumab

Company's preferred approach

- Unadjusted Bucher ITC using KEYNOTE-204:



- Estimated OS HR (95% CI): [redacted]

EAG's alternative approach

- Naive comparison using SACT data:

- Estimated OS HR (95% CI): 0.59 (0.40 to 0.86)

More ITC results in appendix (slide 40)

Is the committee satisfied the evidence base is complete? Have any key sources from the literature been missed?

To Questions

Abbreviations: 3L/4L, 3rd / 4th line; BV: brentuximab vedotin; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Unclear ICER impact

2. Key issue: Major uncertainties in the ITC analyses

EAG disagrees with comparators included in company's preferred ITC

Background

- TA540: Used data from KEYNOTE-087 and Cheah et al. (standard care) in indirect treatment comparisons

Company

- Did 3 types of analyses to compare pembrolizumab and standard care or BV, which gave HR estimates for OS from 0.21 to 0.66; all results favoured pembrolizumab and reached statistical significance
- The company's preferred analysis was an anchored Bucher ITC of:
  - KEYNOTE-204 – the only relevant randomised comparative trial of pembrolizumab (vs BV) and
  - NICE TA524 of BV – from which the Markov trace of BV vs standard care was used
    - Estimated HR for OS was [redacted], with the 95% CI not crossing the line of no effect
    - Considered conservative because BV has established clinical effectiveness vs standard care
- Acknowledged limitations in ITCs leads to uncertainty in the comparative effect estimates → Key issue 4

EAG comments

- Does not consider the company's preferred estimate to be the most appropriate due to KEYNOTE-204 and TA524 considering comparators that are not relevant to this evaluation, both including BV
- Considers the naïve-ITC of SACT versus Cheah et al. as most appropriate, albeit with limitations
- Cheah et al. reports outcomes for the most relevant comparators and at the most relevant line of therapy

Which of the comparisons presented by the company or EAG does the committee consider as a reasonable basis to inform comparative effect estimate for OS?

To Questions

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Abbreviations: BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matched adjusted indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy

More ITC results in appendix (slide 41)

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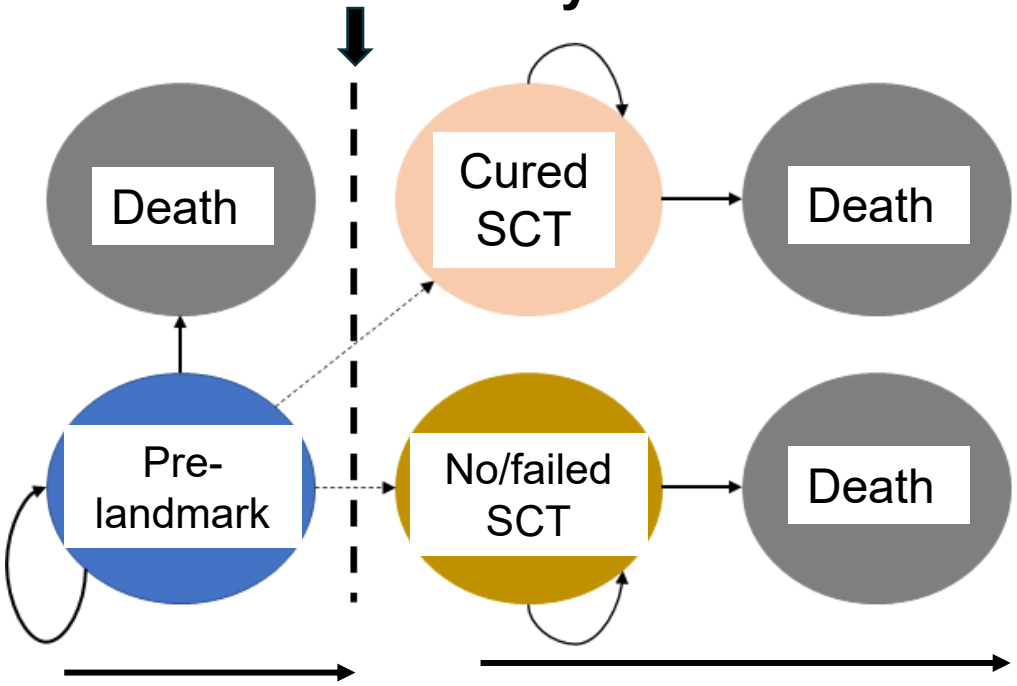
Company's model overview

How evidence incorporated in appendix (slide 42)

Model structure includes 3 Alive states, with a **landmark at 4 years**:



Pre-landmark:
1 Alive state.
Only OS modelled.
Both arms have same utilities, costs and transition probabilities

Post-landmark:
2 Alive states.
Arms independently modelled for OS, utilities, costs and transition probabilities

Model features:
Time horizon: 40 years
Cycle length: weekly
Treatment effect waning: not applied

Pembrolizumab affects costs vs standard care by:

- Increasing drug costs
- Increasing health state costs
- Savings in terminal care, AE, subsequent treatments

Pembrolizumab affects QALYs vs standard care by:

- Increasing QALYs by impacting HRQoL pre-landmark, when SCT cure, when not cured after SCT; and AE and SCT disutilities
- Increasing LYG especially post-landmark

Company scenarios with greatest ICER impact:

- Removing standard care and subsequent treatment costs
- Using exponential OS curve after landmark
- Treatment waning effect on OS in no/failed SCT group

Abbreviations: AE, adverse event; HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; QALYs, quality-adjusted life years; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Unclear ICER impact

3. Key issue: Model structure inconsistent with good practice

EAG disagrees with model structure but does not change structure

Background: Company uses different modelling approach from TA540, with new structure and PFS omitted

Company

- Model allows for patients to have another round of chemotherapy after pembrolizumab, as a bridge to SCT – company's clinical experts considered PD-1 inhibitors can lead some patients to regain chemosensitivity
- PFS omitted as not recorded in SACT and not a reliable surrogate for OS or having a SCT; cure state added
- Having OS curves continue to 4-year landmark reflects the time taken to capture all SCT-related events

EAG comments – company's model structure is data driven

- **Structure:** pre-landmark is a single alive state including patients that had no, failed, and successful SCTs. Since SCT is a key mechanism by which pembrolizumab affects outcomes, within state heterogeneity could produce substantially biased results and lacks transparency. Also, 'time to SCT or death' SACT data not used.
- EAG uses model structure but proposes 3-health state alternative: no/failed SCT, successful SCT, and death
- **Treatment benefits:** Pembrolizumab used as a bridge to successful SCT. But company also assume it will improve OS and HRQoL for 4 years pre-landmark despite 2-year stopping rule; and in no/failed SCT group
- EAG prefers to assume no post-landmark benefits in no/failed SCT – as discussed in Key issues 4 and 5

Company response on model structure: Model structure minimises health states and transitions where data is lacking. Estimated data is needed for EAG proposed structure (e.g. KM for time-to-SCT or death for 'alive/no SCT' subgroup), which introduces uncertainty; time to SCT data only impacts pre-landmark period of model

Is the company's model structure acceptable for decision making?

Abbreviations: HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

To Questions

Unclear ICER impact

4. Key issue: Uncertain comparative effectiveness including duration of effect (1/2)

EAG explores alternative treatment effectiveness assumptions in SCT group

Background

- New OS evidence from SACT is less favourable for pembrolizumab than the KEYNOTE-087 evidence
- Despite this less favourable OS data for pembrolizumab, company's ICER is now lower than in TA540

Company

- SACT data provides largest source of real-world data for indication and is considered best source of evidence to reflect outcomes of patients on pembrolizumab in UK clinical practice
  - Preferred source for pembrolizumab arm of model → base case inputs for OS and SCT parameters
- New modelling approach includes a cure state and applying a severity modifier; treatment costs also differ

EAG comments

- Lower ICER in this evaluation also relates to Key issue 2 – ITC used for pre-landmark OS HR

<u>Company's treatment effectiveness assumptions:</u>

- General population mortality for cured post-SCT health state – EAG scenario explores 1.5x mortality ratio
- Probability of SCT and cure for patients in standard care arm based on expert elicitation – EAG scenario explores setting probability of these as equal for both arms in model

- Would people cured following a SCT be expected to have general population mortality (or higher)?
- Would probability of having a SCT and a curative SCT be expected to be different in people treated with pembrolizumab compared with standard care?

To Questions

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Unclear or small ICER impact

4. Key issue: Uncertain comparative effectiveness including duration of effect (2/2)

EAG removes assumption of any treatment effect in no/failed SCT group

Company continued

- No treatment effect waning assumed for pembrolizumab – previous NICE appraisals of pembrolizumab have assumed hazards equalise from 3 years after treatment stopping to 5 years
  - Applied at 3-5 years post cessation in sensitivity analysis in no/failed SCT arm → increased ICER
- Clinicians advising the company considered there would be a treatment effect for some years after stopping pembrolizumab but were unable to say how long this would last in the no/failed SCT group

EAG comments continued

- Pre-landmark period has long duration – in the absence of waning, EAG explores extreme scenario where it is assumed that pembrolizumab is solely a bridge to SCT with benefits in terms of HRQoL but no OS benefit, which removes 4-year treatment effect of pembrolizumab on OS prior to potential SCT
- Beyond 4-year landmark: **EAG base case removes treatment effect from 'no/failed SCT' group** (HR=1)

- Would any treatment effect of pembrolizumab be expected to be maintained after stopping treatment? If so, how long would this last for? Should a treatment waning effect be assumed?
- Before a potential SCT, would pembrolizumab be expected to have any OS benefit? Is the EAG's 'extreme' scenario assuming no OS benefit for pembrolizumab in 4 years pre-landmark reasonable?
- Would any treatment effect of pembrolizumab be expected in people who have no/failed SCT? Is the EAG's adjustment reasonable – to assume no treatment effect post-landmark in no/failed SCT group?

Abbreviations: HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; OS, overall survival; SCT, stem cell transplant

To Questions

Small ICER impact

5. Key issue: Utility values

Company and EAG differ in utilities assumed before and after landmark

Patient expert comments: Key aspects of HRQoL are toxicity and side effects of treatment and impact of hospital/clinic appointments on daily life. Eligibility for SCT is important to some, others prioritise ability to 'cope' in daily life. With or without a SCT, you will never have same HRQoL as someone who has not had cancer.

Company

- Comparative EQ-5D-3L data from KEYNOTE-204 are from 3L+, but ~37% of patients were treated at 4L+
- Values derived by simple naive means, although alternative mixed effect model explored at clarification

EAG comments – uses pre-landmark values derived from mixed effect model

Table: Utility values used in company and EAG base cases

Health state (Alive)	Base case	Pembrolizumab	Standard care	Difference
Pre-landmark (4 years)	Company	0.837	0.742	0.095
	EAG	0.816	0.730	0.085
No or failed SCT (beyond 4 years)	Company*	0.807	0.671	0.136
	EAG	As pre-landmark standard care (0.730)		0
Successful SCT (beyond 4 years)	Company	General population (0.864 at landmark)		0
	EAG	0.770 based on TA524		0

*Values based on 'progressed disease' state in trial, with data collected for up to 1 year only

Which utility values does the committee consider most reasonable? Would any utility benefit for pembrolizumab be expected in people who have had no/failed SCT?

To Questions

Abbreviations: 3L/4L, 3rd line / 4th line; EQ-5D, EuroQoL 5 Dimensions; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; SCT, stem cell transplant

Company and EAG base case assumptions

EAG

- Uses company model structure, but considers it inconsistent with good practice – see Key issue 3
- Areas of uncertainty in company's model are explored by EAG in scenario analyses

Table: Differences in assumptions between company and EAG bases cases (implemented)

Assumption	Company base case	EAG base case
Comparators	Proportions equal for all	Proportions amended, not equal for all
Pre-landmark OS HR (ITC)	Bucher ITC using KEYNOTE-204 and TA524	Naive comparison of SACT and Cheah et al.
No/failed SCT OS HR	HR from KEYNOTE-204 no-SCT subgroup applied to SACT	HR=1 so no benefit for pembrolizumab
Extrapolation of OS in no/failed SCT	Updated to use exponential at clarification	No extrapolation – see above (Agrees with company's exponential)
Pre-landmark utilities	KEYNOTE-204 naive data	KEYNOTE-204 modelled data
No/failed SCT utilities	KEYNOTE-204 naive data among trial patients with 'progressed disease'	Set equal to pre-landmark standard care arm (no HRQoL benefit)
Successful SCT utility	General population	Based on TA524

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Abbreviations: HR, hazard ratio; HRQoL, health-related quality of life; ITC, indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential discounted prices for pembrolizumab and some standard care components or subsequent treatments (including nivolumab in a small minority of patients after standard care)

Base case results accounting for all these discounts:

- Pembrolizumab versus standard care has an ICER below the range usually considered cost-effective – in both company and EAG base case, with severity modifier applied

In scenario analyses:

- Company: in single and combined scenarios, all ICERs below the range usually considered cost-effective
- EAG: in single and combined scenarios, ICERs within or below the range usually considered cost-effective…
  - …except when an 'extreme' scenario (removing all OS benefit of pembrolizumab pre-landmark) is added to the combined scenario, giving an ICER substantially above this range

More detail on the scenarios in appendix (slide 44 to 45)

Abbreviations: ICER, incremental cost-effective ratio; OS, overall survival

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- ❑ Summary

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Other considerations

- **No equality issues** were raised by the company, EAG or stakeholders during the appraisal process

- **Severity weighting:** company and EAG agree 1.2 weighting appropriate

Does the committee agree it is appropriate to apply a QALY weighting for severity? To Questions

- **Updated marketing authorisation** includes paediatric patients aged 3 years and older as well as adults

More detail on severity weighting in appendix (slide 46 to 47)

Abbreviations: QALY, quality-adjusted life year

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Key issues	Resolved?	ICER impact
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Other issues		
Quality of the systematic literature review (see appendix slide 34)	No	Unclear
Misaligned outcomes from the SACT dataset (see appendix slide 35)	No	Unclear
Uncertainty in subsequent therapy assumptions (see appendix slide 43)	No, explored	Small

*See appendix for EAG scenario analysis (slide 45), where combined scenarios including no OS gain pre-landmark ('extreme' scenario) has a substantial impact increasing the ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy

Recap of questions for the committee (1/2)

Background; Clinical effectiveness

- At 3rd line, are people who have not had a SCT more likely to have BV or pembrolizumab (as in TA772)?
- Would people who have pembrolizumab at 3rd line before BV be likely to have pembrolizumab again after BV (as in TA540)? (slide 4)
- Are the company's approaches for standard care reasonable, for proportions and no BSC? (#7)
- Is the committee satisfied the evidence base is complete? Have any key sources from the literature been missed? (#11)
- Which of the comparisons presented by the company [KEYNOTE-204 and TA524] or EAG [SACT and Cheah et al.] does the committee consider as a reasonable basis to inform comparative effect estimate for OS? (#12)

Modelling and cost effectiveness

- Is the company's model structure acceptable for decision making? (#15)
- Would people cured following a SCT be expected to have general population mortality (or higher)?
- Would probability of having a SCT and a curative SCT be expected to be different in people treated with pembrolizumab compared with standard care? (#16)

Abbreviations: BSC, best supportive care; BV, brentuximab vedotin; OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Recap of questions for the committee (2/2)

Modelling and cost effectiveness continued

- Would any treatment effect of pembrolizumab be expected to be maintained after stopping treatment? If so, how long would this last for? Should a treatment waning effect be assumed?
- Before a potential SCT, would pembrolizumab be expected to have any OS benefit? Is the EAG's 'extreme' scenario assuming no OS benefit for pembrolizumab in 4 years pre-landmark reasonable?
- Would any treatment effect of pembrolizumab be expected in people who have no/failed SCT? Is the EAG's adjustment reasonable – to assume no treatment effect post-landmark in no/failed SCT group? (#17)

- Which utility values does the committee consider most reasonable?
- Would any utility benefit for pembrolizumab be expected in people who have had no/failed SCT? (#18)

Other considerations

- Does the committee agree it is appropriate to apply a QALY weighting for severity? (#22)

Abbreviations: QALY, quality-adjusted life year; OS, overall survival; SCT, stem cell transplant

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Thank you.

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma

Supplementary appendix

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CDF recommendations of TA540

Optimised to people who cannot have an autologous SCT

TA540 published in September 2018 (optimised recommendation†):
Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory classical Hodgkin lymphoma in **adults who have had brentuximab vedotin and cannot have autologous stem cell transplant**, only if pembrolizumab is stopped after 2 years of treatment or earlier if the person has a stem cell transplant or the disease progresses

Further data collection in CDF, which may reduce the uncertainty in:

- timing of SCT (from first pembrolizumab treatment to SCT)
- proportion of people who have a SCT
- overall survival.

Real-world SACT data would be collected to help resolve these

CDF review February 2024

†Pembrolizumab was not recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous SCT and brentuximab vedotin

Go back to slide 4 in main deck

Abbreviations: CDF, cancer drugs fund; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Decision problem for evaluation of pembrolizumab

Table: Population, comparators and outcomes

	Final scope	Company submission	EAG comments
Population	People with relapsed or refractory cHL who have had BV and cannot have autoSCT	As per NICE scope, but considers only transplant naive†	Company narrows to adults
Comparators	Single or combination chemotherapy including drugs such as gemcitabine, vinblastine and cisplatin Best supportive care (BSC)	Standard care as per Cheah et al. (2016) [as in TA540]: • gemcitabine • bendamustine • other alkylatory • BV retreatment • platinum based • autoSCT • others	Cheah et al. includes multiple comparators – some are within scope, others are not. BSC is excluded To inform economic model, company uses blended comparators based on Cheah, Eyre et al. (2017) and expert option
Outcomes	• OS, PFS, RRs • Adverse effects • Health-related quality of life • Time to alloSCT	As per NICE scope, except: • Time to SCT (auto or allo)	Time to alloSCT no presented

†Pembrolizumab was not recommended in TA540 for treating RRcHL in people who had autoSCT and BV

Abbreviations: allo, allogenic; auto, autologous; BSC, best supportive care; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; RR, response rate; SCT, stem cell transplant

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Classical Hodgkin lymphoma: disease background

Lymphomas are cancers of the lymphatic system categorised as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma

HL further categorised as classical Hodgkin lymphoma (cHL) or nodular lymphocyte predominant Hodgkin lymphoma

- 20% of lymphomas are Hodgkin; 95% of HL are classical

Around 2,100 new cases of HL in the UK each year; >300 people die of HL each year

- 2 peaks in incidence, in young adults (20 to 24 years) and older adults (75 years or older)

5 to 10% of HL cases are refractory to initial therapy and 10 to 30% relapse after initial remission

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Abbreviations: (c)HL, (classical) Hodgkin lymphoma

Patient perspectives

Submission from Lymphoma Action

Living with classical Hodgkin Lymphoma

- cHL and its treatment significantly affect patients' quality of life, with fatigue, nausea, vomiting and infections the most troublesome side effects
- Fatigue affects around 3 in 4 people and can persist for many years, affecting work and physical and social activities

Current treatment options

- cHL generally responds very well to treatment and most people are cured
- People with relapsed / refractory cHL usually receive chemotherapy; a good response may result in the opportunity to have a stem cell transplant

Unmet need

- There is a need for effective, less demanding treatments with fewer side effects that allow a better quality of life
- Patients feel that pembrolizumab has a more favourable side effect profile than most other treatments for relapsed and refractory Hodgkin lymphoma

"Fatigue is the most difficult to manage over the long term… [that] and stress have often made it very difficult to contribute normally at work… my fatigue then can be overwhelming"

"Many of the options after failure of initial treatment do not have high success rates."

"I don't know how I would have managed my son's school years on other [non-targeted] treatments."

NICE

Abbreviations: cHL, classical Hodgkin lymphoma

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Clinical perspectives

Submissions from the Royal College of Pathologists

Current treatment options

- Initial chemotherapy and radiotherapy is curative in the majority of patients
- Patients who have relapse or recurrence after first line therapy, have subsequent salvage therapy, autologous SCT and brentuximab vedotin
    - Nivolumab is an option for patients who have had a SCT

Unmet need / current treatment

- There is an unmet need for anti-PD1 therapy in patients who are not suitable for SCT because of disease progression despite salvage chemotherapy or brentuximab vedotin
    - Use of anti-PD1 therapy here would be as a bridge to transplant

Side effects

- Patients who suffer debilitating side-effects with nivolumab and who may tolerate pembrolizumab [Note: nivolumab is recommended in a different populations: nivolumab – after failed autologous SCT

Anti-PD1 therapy is an important treatment in the management of cHL after failure of first-line therapy, salvage therapy, and brentuximab vedotin"

Nivolumab has been appraised previously (TA462) and is restricted to patients who have failed stem cell transplant

Some patients, due to progressive chemo-refractory disease, need anti-PD1 therapy as a bridge to transplant

NICE

Abbreviations: anti programmed cell death protein 1; cHL, classical Hodgkin lymphoma; anti PD-1, SCT, stem cell transplant

Go back to slide 5 in main deck

Other issue: Quality of the systematic literature review
SLR lacked sensitivity; no new evidence presented except SACT

Background

- SLR covered population who could not have autoSCT then had failure on BV, as per CDF recommendation
- No new evidence identified to inform company submission (except SACT dataset)

EAG comments – SLR may not have retrieved all relevant records

EAG comment at clarification	Company response at clarification
Conference proceedings excluded from Embase strategy (ASCO, EHA, ESMO)	Embase generates many irrelevant results from conference abstracts Additional searches done in Northern Light conference database (2021-2022) and by hand
Searches restricted to publications in English – against best practice	International conferences and journals publish in English Language of autoSCT eligibility not uniform – non-English difficult
Searches not re-run to take account of limitations above	Applying EAG's suggested changes not be expected to yield additional relevant studies

- Eligibility criteria should be reviewed, including to align comparators with NICE scope
- EAG re-ran the Embase search, which provided additional ~2,100 records from 2017 (not screened)
- SLR did not identify Cheah et al. (2016) and Eyre et al. (2017)

Is the company's SLR acceptable to inform the decision problem?

Abbreviations: ASCO, American Society of Clinical Oncology; BV, brentuximab vedotin CDF, Cancer Drugs Fund; EHA, European Haematology Association; ESMO, European Society for Medical Oncology; SACT, systemic anti-cancer therapy; SLR, systematic literature review

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Other issue: Misaligned outcomes from the SACT dataset

Similar proportion of SCT in trial and SACT, but more were alloSCT in SACT

Background

- TA540 recommended data collection related to outcome of 'subsequent alloSCT' after pembrolizumab
- **Tech team note:** NICE scope for current evaluation includes outcomes related to alloSCT, but should have been broader to capture those related autoSCT as well

Company

- **SCT types:** Company's experts considered there was a high number of alloSCT in SACT dataset that did not reflect UK clinical practice – patients older and less fit than in clinical trial

Table: SCT after pembrolizumab

SCT status	Cohort 2 of KEYNOTE-087	SACT dataset
Had SCT†, n (%)	**24 (30)**	**65 (30)**
• AutoSCT	14 (58)	23 (35)
• AlloSCT	9 (38)	42 (65)

†1 additional person in trial had both autoSCT and alloSCT

- **SCT outcomes:** SACT dataset does not differentiate between alloSCT and autoSCT for 'time to SCT' and 'OS'

EAG comments

- **SCT types:** Notable difference between clinical trial and SACT
  - Company's experts noted rates of autoSCT is increasing generally; alloSCT now used more after autoSCT failure
- **SCT outcomes:** Combining SCT types as an aggregate outcome distorts interpretation of the data

Is the committee satisfied that available data on SCT is suitable for informing the decision problem?

Abbreviations: allo, allogenic; auto, autogenic; OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

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Public Health England SACT data for review of TA540

~50% of patients suitable had SCT, 50% were done within 18 months

215 eligible patients had pembrolizumab in CDF from 25 July 2018 to 30 September 2022

- Median treatment duration 5 months (95% CI 4.3, 6.2)
- Baseline characteristics: 60% male; 55% aged ≥50; most had PS of 0 or 1
- Median OS not reached

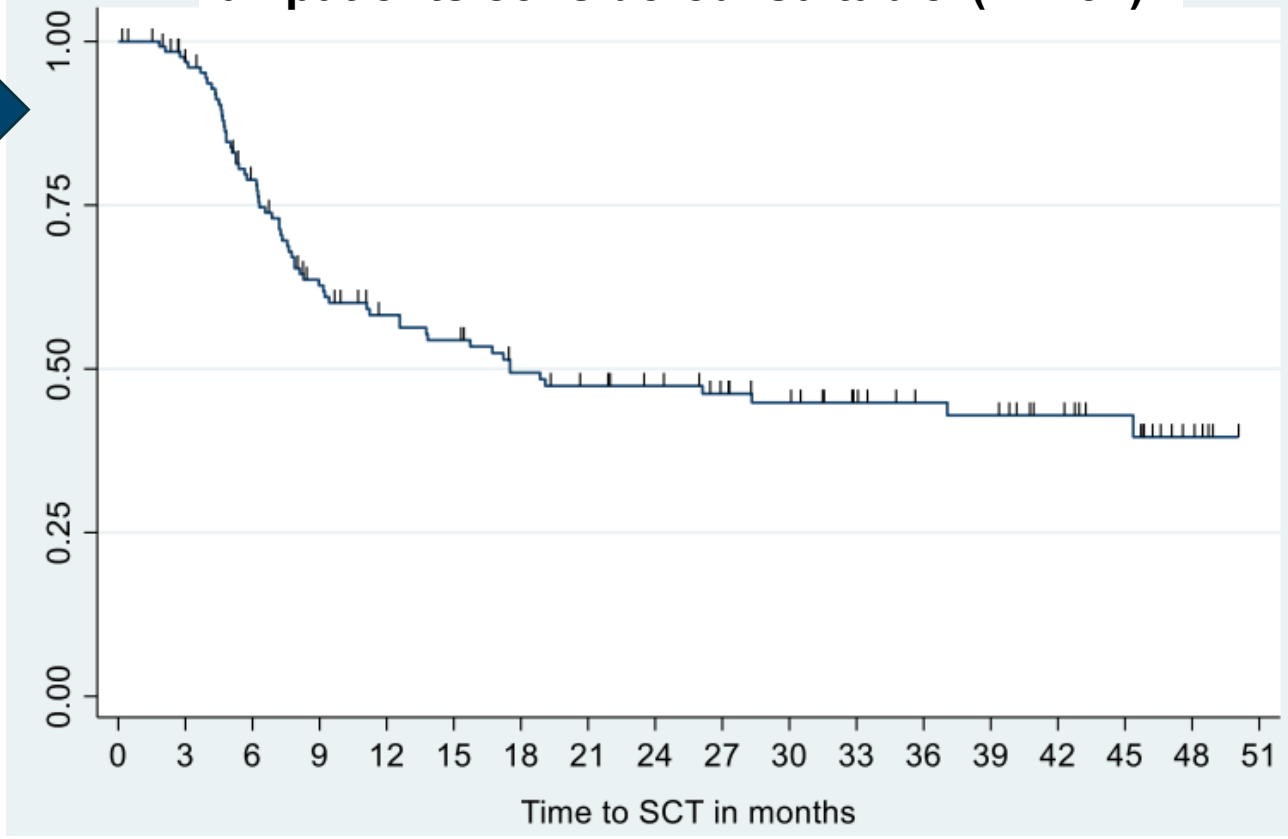
Stem cell transplant suitability:

- **132/215 patients 'suitable for SCT'** as identified in Blueteq
  65/132 had a SCT (49%) after pembro.
  - 42 allogenic transplant
  - 23 autologous transplant
- Most had another treatment before SCT

Timing of stem cell transplant (n=65):

- Median time to SCT 6.9 months from first pembrolizumab dose to having SCT (range 1.8 to 45.4 months)
- Median time by which 50% of those transplanted had SCT was 17.5 months

Kaplan-Meier estimate of time to SCT in all patients considered 'suitable' (N=132)



Abbreviations: CDF, cancer drugs fund; CI, confidence interval; OS, overall survival; PS, performance status; SACT, systematic anti-cancer therapy; SCT, stem cell transplant

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KEYNOTE-087 trial results: ORR (primary endpoint) and PFS

Cohort 2 of KEYNOTE-087 (N=81):

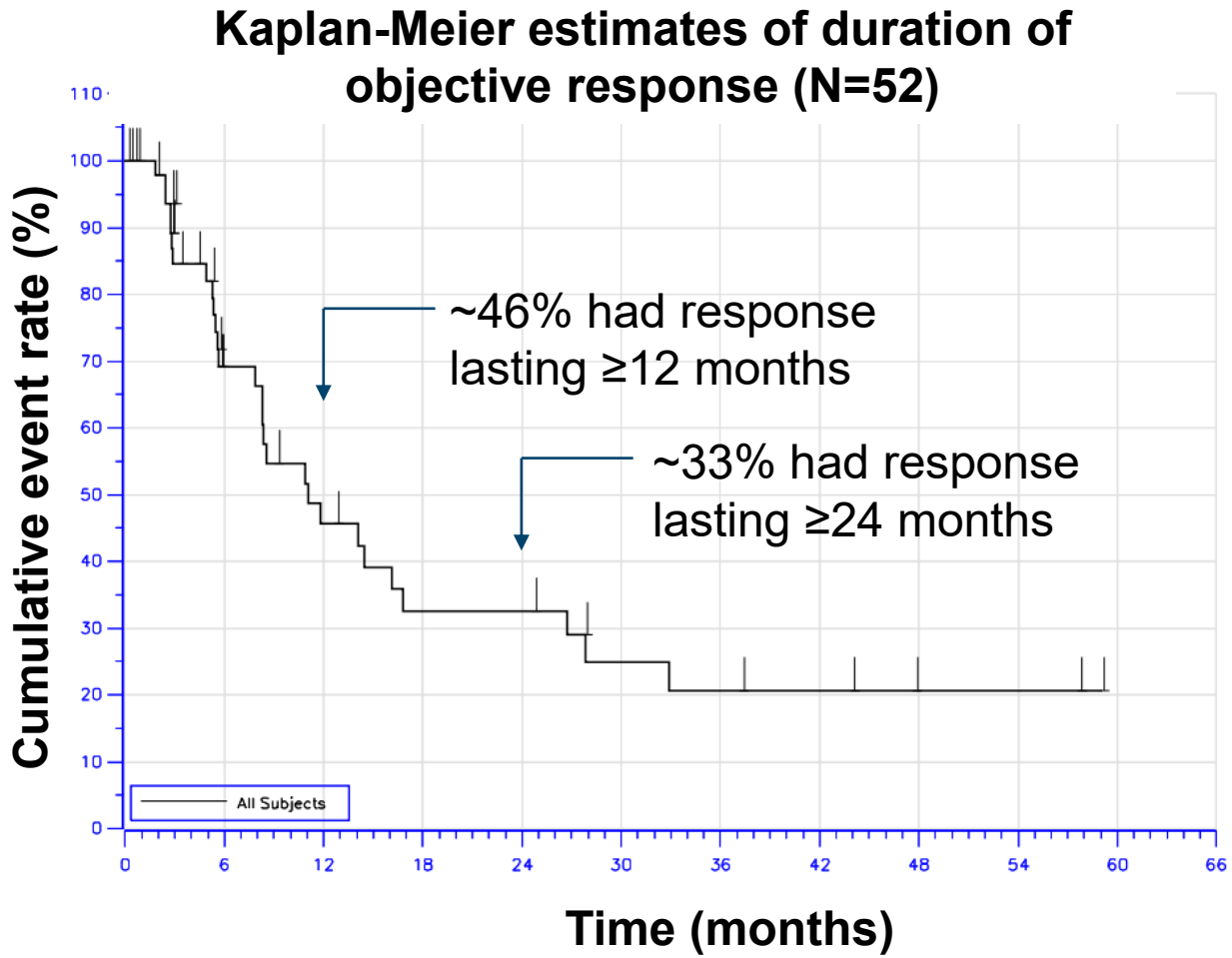
- Had salvage chemotherapy and BV followed by pembrolizumab
- Median 62 months follow-up

Table: Cohort 2 tumour response

Level of response†	% responders (N=81)
ORR (CR+PR)	**64**
CR	26
PR	38
SD	10
PD	24

†Blinded independent central review by IWG criteria (3% had no assessment)

- Median duration of OR 11 months (0 to 59)



Progression-free survival: median 11 months (8 to 14); 45%, 25% and 17% at 1, 2 and 3 years

NICE

Abbreviations: autoSCT, autologous stem cell transplant; BV, brentuximab vedotin; CR, complete response; IWG, International Working Group; OR(R) objective response (rate); PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease

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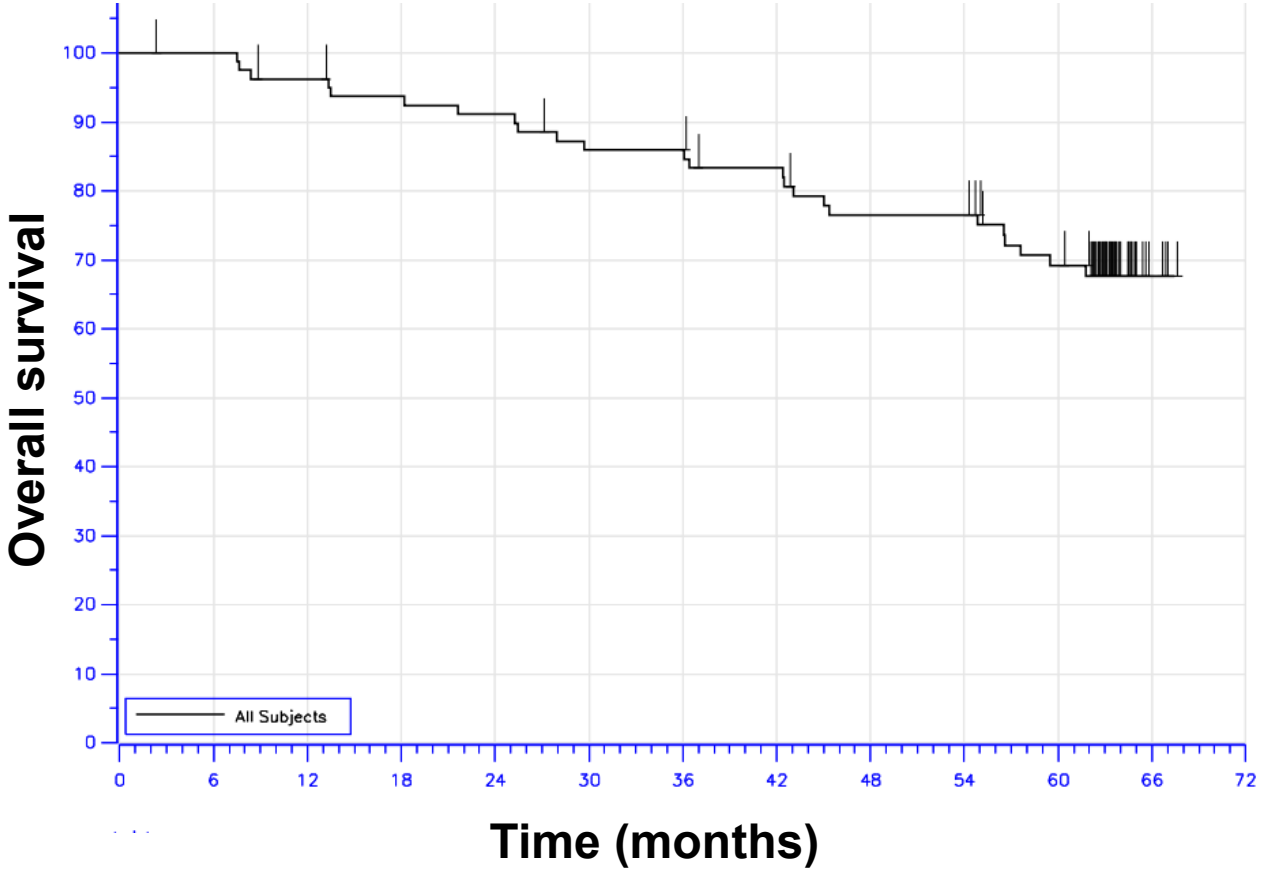
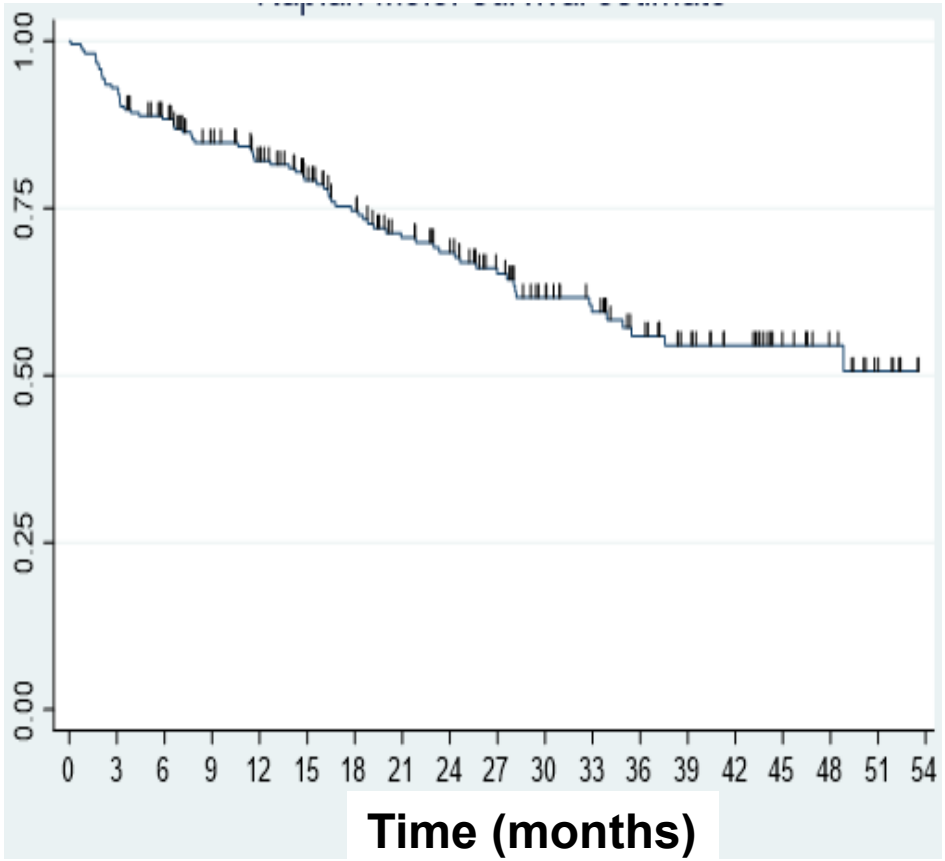
KEYNOTE-087 and SACT: overall survival with pembrolizumab
OS worse for SACT population than Cohort 2 of clinical trial

Figure: Kaplan–Meier estimates of OS for **Cohort 2 of KEYNOTE-087**† (N=81):



- 91% alive at 24 months, 77% at 48 months

Figure: Kaplan–Meier estimates of OS for the **SACT dataset** (N=215):



- 68% alive at 24 months, 55% at 48 months

NICE Abbreviations: OS, overall survival; SACT, systemic anti-cancer therapy

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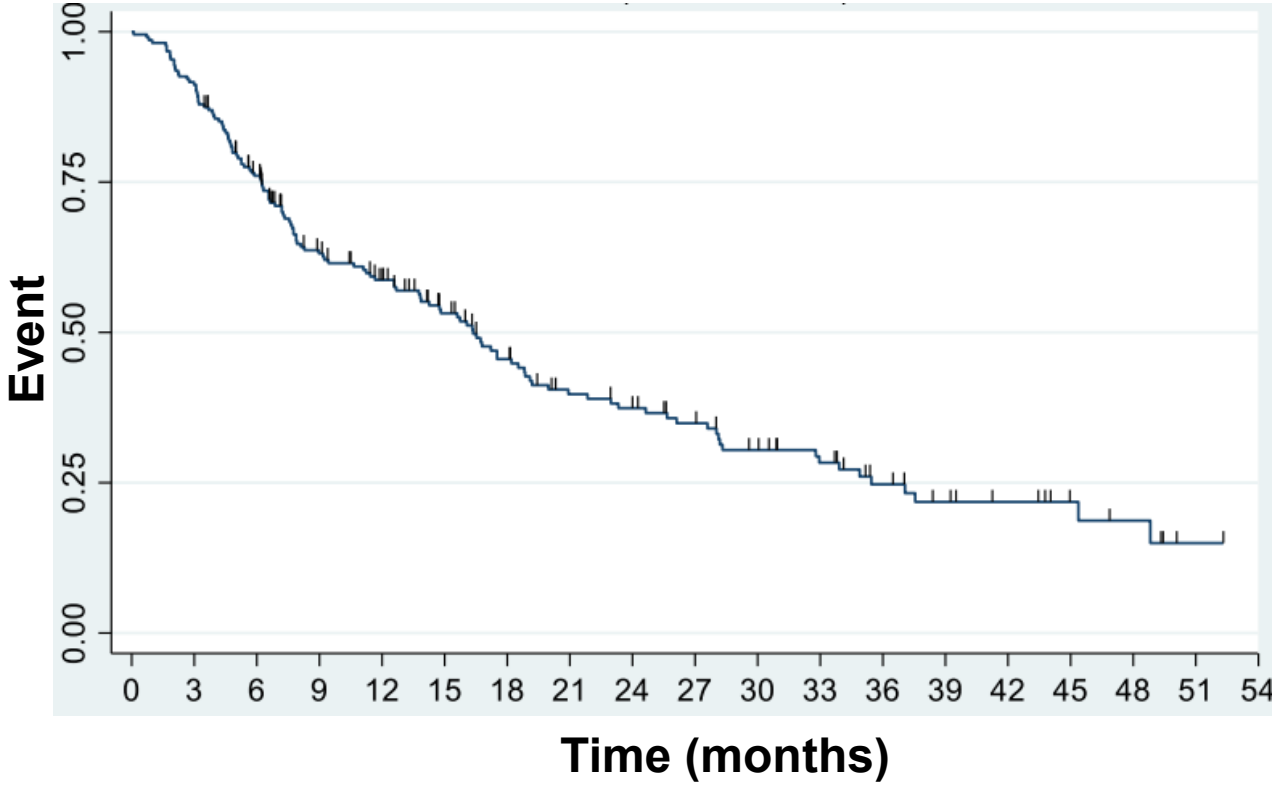
SCT-dependent outcome results from SACT
Kaplan–Meier estimates of time to SCT or death and OS without SCT

Time to SCT or death:

- Median time to event 16 months
- Median follow-up 11 months

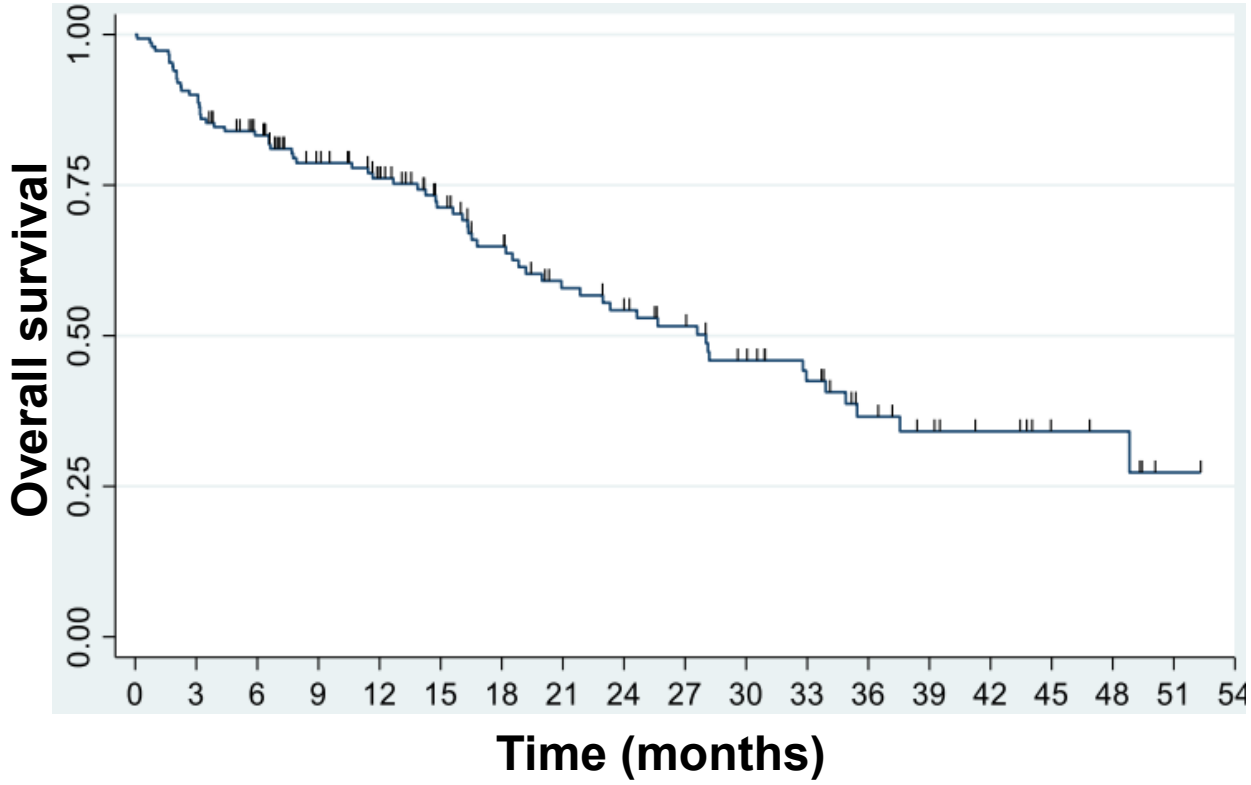
Figure. Kaplan–Meier estimates of time to event (SCT or death) from SACT (N=215):



OS in patients who did not have a SCT:

- Median OS 28 months
- Median follow-up 15 months

Figure. Kaplan–Meier estimates of OS from SACT in patients who did not have a SCT (N=150):



NICE Abbreviations: OS, overall survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

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Company's indirect comparisons

The company presented a series of indirect comparisons

Table. Summary of OS HR estimates from the company's indirect comparisons

Company ranking	Comparison type	Sources	HR (95% CI)	
1	Bucher ITC	KEYNOTE-204† (pembrolizumab vs BV) and TA524 (BV vs standard care)	[redacted]	← Company preferred
2	Within trial	KEYNOTE-204†	[redacted]	
3	Bucher ITC	SACT (pembrolizumab) vs Eyre et al. (BV) and TA524	0.41 (0.22 to 0.77)	
4	Naive	SACT vs Eyre et al.	0.66 (0.44 to 0.98)	
5	Naive	SACT vs Cheah et al. (standard care)	0.59 (0.40 to 0.86)	← EAG alternative
6	MAIC	KEYNOTE-087 cohort 2 (pembrolizumab) vs Eyre et al.	0.21 (0.12 to 0.37)‡	
7	MAIC	KEYNOTE-087 cohort 2 vs Cheah et al.	0.24 (0.14 to 0.40)	← EAG scenario analysis

†SCT naive subgroup

‡After matching

Abbreviations: BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matched adjusted indirect treatment comparison; OS, overall survival; SACT, systemic anti-cancer therapy

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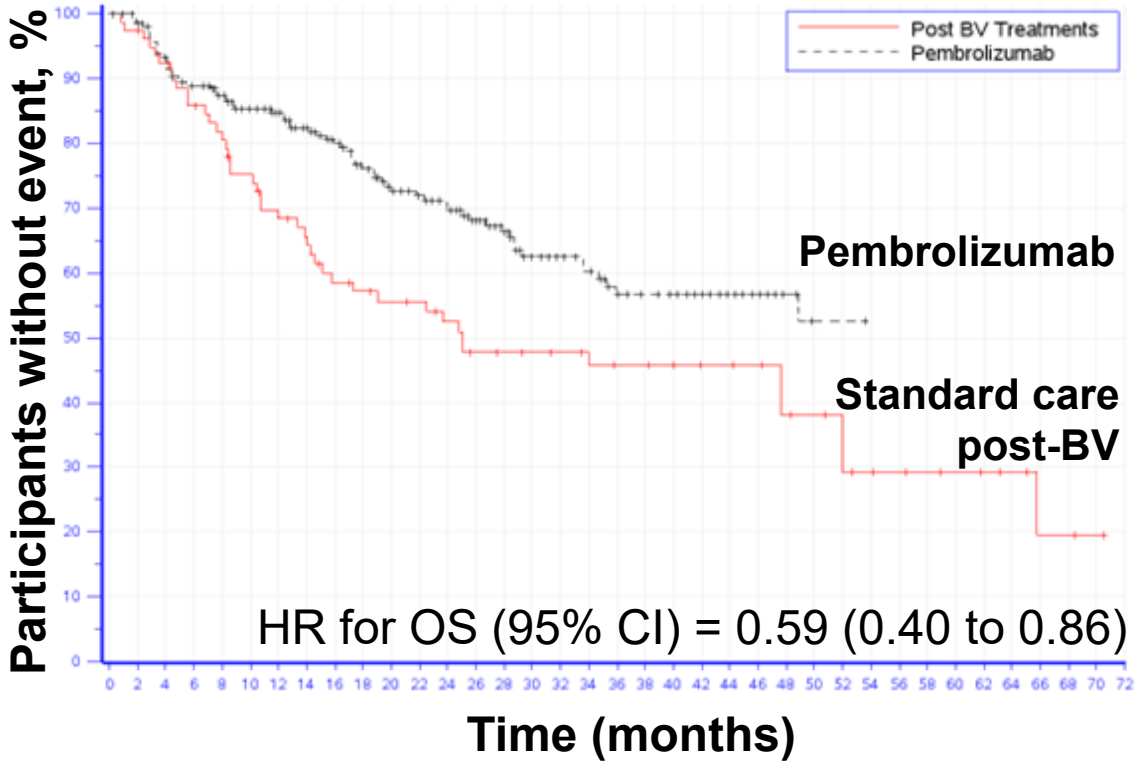
2. Key issue: Major uncertainties in the ITC analyses continued
EAG selected to use SACT data over trial data for pembrolizumab

EAG comments

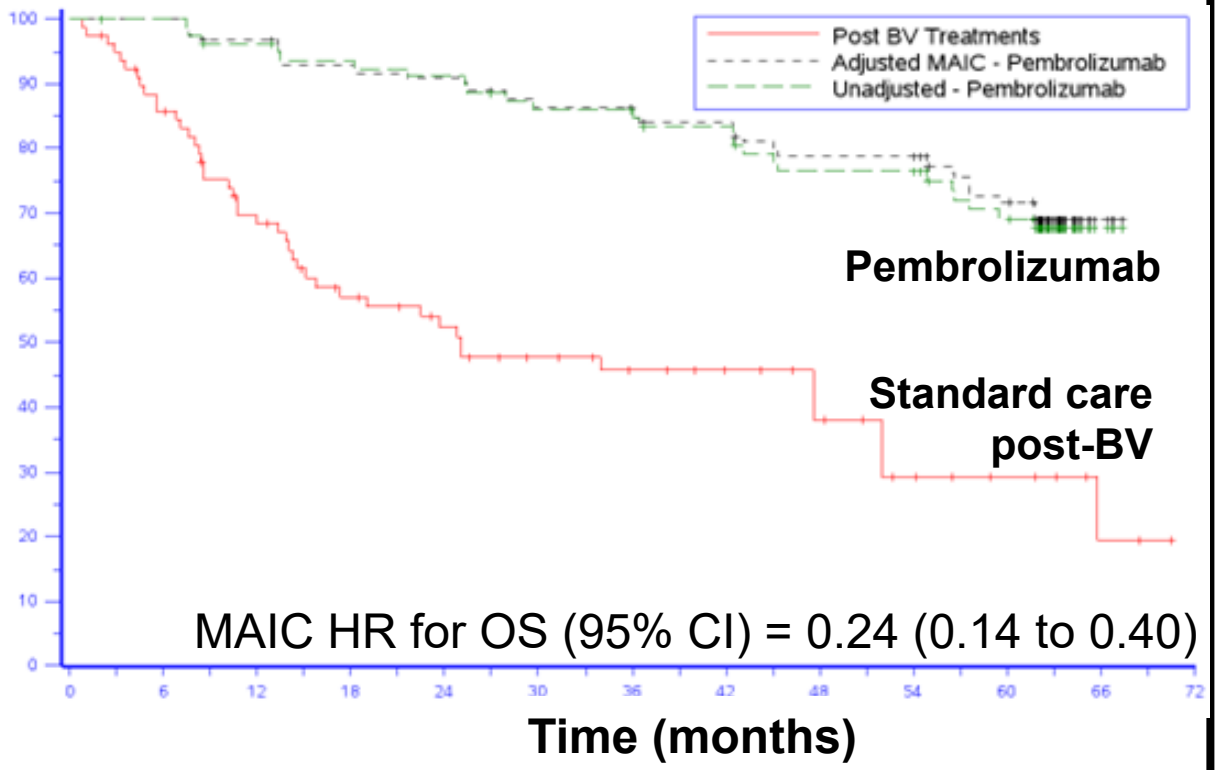
- Comparison used in EAG base case (naive):

Figure. KM curve for OS for pembrolizumab using SACT dataset vs standard care from Cheah et al.



- Comparison used in EAG scenario analysis (MAIC):

Figure. KM curve for OS for pembrolizumab using KEYNOTE-087 vs standard care from Cheah et al.



Abbreviations: BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; OS, overall survival; SACT, systemic anti-cancer therapy

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How company incorporated evidence into model

Table: Model inputs and evidence sources

Input	Assumption and evidence source
Baseline characteristics	SACT and KEYNOTE-087
Pembrolizumab efficacy	**Pre-landmark OS:** SACT data. **Post-landmark OS with no/failed SCT:** SACT data
Comparator efficacy	**Pre-landmark OS:** HR from ITC applied to pembrolizumab (see Key issue 2) **Post-landmark OS with no/failed SCT:** HR from KEYNOTE-204 no-SCT subgroup applied to pembrolizumab (validated by expert elicitation at 4+ years)
SCT outcomes	Probability of SCT: SACT (pembrolizumab) and expert elicitation (standard care) Probability of curative SCT: expert elicitation **Post-landmark OS when cured with SCT:** general population mortality
Time on treatment	SACT (pembrolizumab); various studies (standard care)
Treatment effect waning	Not applied (3-5 years post cessation applied in sensitivity analysis in no/failed SCT only)
Utilities	KEYNOTE-204 from EQ-5D-3L (KEYNOTE-087 used in sensitivity analysis) Adverse event-related disutility from literature (not collected in KEYNOTE-087)
Adverse events	KEYNOTE-087 (pembrolizumab); various studies (standard care)
SCT complications	QALY decrement applied at cycle 0 to all having SCT by landmark, 2 year cap
Costs	PSSRU, NHS Reference costs (2021/22) including for SCT, eMIT, BNF
Resource use	National schedule of NHS Costs and clinical expert opinion

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; EQ-5D, EuroQoL 5 Dimensions; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life years; SACT, systemic anti-cancer therapy; SCT, stem cell transplant

Other issue: Uncertainty in subsequent therapy assumptions

Subsequent therapy proportions influence costs and are uncertain

Background

- After pembrolizumab, patients may have subsequent therapy, and this may be before having a SCT

Company

- Based on SCT-naive subpopulation of KEYNOTE-204, it was assumed fewer patients in pembrolizumab arm had subsequent therapy (51%; £1,625 total cost) than in BV arm as standard care (69%; £2,230 total cost). Proportions were:

Table: Subsequent therapy proportions used to calculate weighted costs

Subsequent therapies	Pembrolizumab arm	Standard care arm
Bendamustine	36%	48%
Gemcitabine monotherapy, DHAP, CHOP, IVAC, PMitCEBO	2.5% each	3.3% each
Radiotherapy	2.5%	3.3%
Nivolumab	0	<0.1%
No active treatment	49%	32%

- In KEYNOTE-204, both arms went on to have a similar proportion of SCT

EAG comments

- Uncertain whether these proportions are suitable for informing model
- Scenario assuming £0 subsequent therapy costs → small ICER increase

Are the company's subsequent therapy assumptions reasonable?

Abbreviations: BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, prednisolone, vincristine; DHAP, dexamethasone, cytarabine, cisplatin; ICER, incremental cost-effectiveness ratio; IVAC, cytrabine, etoposide, ifosfamide, mesna; PMitCEBO, bleomycin, cyclophosphamide, etoposide, mitoxantrone, prednisolone, vincristine; SCT, stem cell transplant

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Company deterministic base case and scenario analysis

All ICERs <£20,000; severity modifier applied

No.	Selected scenarios	Incremental costs (£) versus SC	Incremental QALYs versus SC	ICER (£/QALY) versus SC
-	**Company original base case**	See part 2	See part 2	**Below £20,000**

- The Company explored 25 single scenarios including the 6 alternative HRs for OS derived from the different indirect comparisons – in all the ICER remained below £20,000
- When a combinatorial analysis was performed:
  1. A more conservative pre-landmark OS HR was used (Bucher of Eyre and TA524) +
  2. Exponential post-landmark transitions for No/Failed SCT* +
  3. Treatment effect waning 3–5 years applied +
  4. Standardised mortality ratio of 1.2 for patients cured by SCT +
  5. Standard care comprised 100% bendamustine (an inexpensive option) +
  6. Equal utility assumed for 2 arms post-landmark **1–6→ ICER below £20,000**

  *The company implemented this scenario as a change to its base case at the clarification stage (using the exponential curve for post-landmark transitions) → this is the updated base case presented in Part 2

Results do not include confidential commercial discounts for comparators

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; SC, standard care; SCT, stem cell transplant

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EAG deterministic base case and scenario analysis

Combinatorial analyses produce ICERs above £20,000; severity modifier applied

No.	Selected scenarios	Incremental costs (£) versus SC	Incremental QALYs versus SC	ICER (£/QALY) versus SC
-	**EAG base case**	See part 2	See part 2	**Below £20,000**

- The EAG explored 9 single scenarios – in all the ICERs were below or close to £20,000
- When combinatorial analyses were performed:
  1. Subsequent treatment costs set to £0 +
  2. Both arms had equal probability of SCT and being cured by SCT +
  3. Standardised mortality ratio of 1.5 applied for patients cured by SCT +
  4. QALY decrement of 0.3 applied for SCT +
  5. Equal AE rates on standard care +
  6. Exponential curve selected for pre-landmark OS +
  7. Landmark of 2 years + **1–7 → ICER above £20,000**
  8. No OS gain pre-landmark ('extreme' scenario) **1–8 → ICER substantially above £30,000**

Results do not include confidential commercial discounts for comparators

NICE

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; SC, standard care; SCT, stem cell transplant

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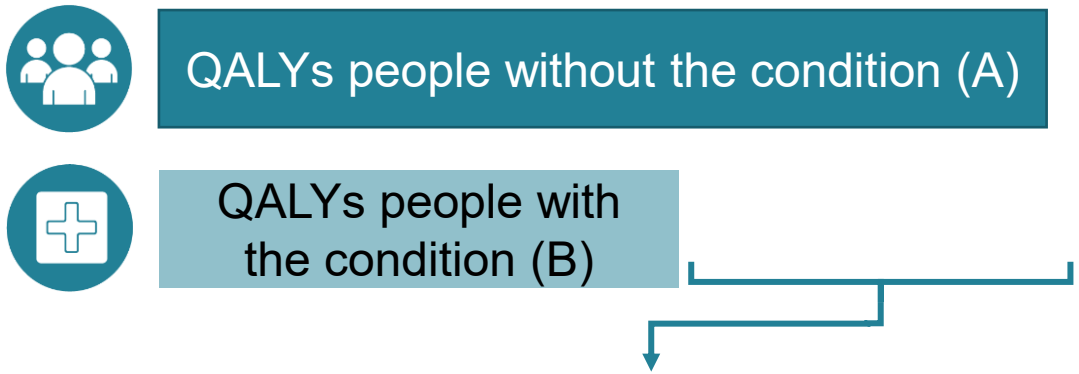
QALY weightings for severity (1/2)

New severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

NICE

Abbreviations: QALY, quality-adjusted life year

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QALY weightings for severity (2/2)

Background

- Company concluded patients with RRcHL, who receive BV but are ineligible for autoSCT qualify for a 1.2 severity modifier
- Calculated using the ScHARR QALY Shortfall calculator tool:
  - Patient population characteristics: 40% female, 51 years mean starting age
  - Utilities for people with the condition: 1.31
- A severity modifier of 1.2 was also suggested by the EAG analysis
- Cost-effectiveness results are presented with QALY weighting of 1.2 applied

	QALYs of the general population	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**
Company base case	15.6	1.31	14.29	0.92

EAG comments

- EAG replicated the company's analysis and agree 1.2x weighting applies

Abbreviations: auto, autologous; BV, brentuximab vedotin; QALY, quality-adjusted life year; RRcHL, relapse or refractory classical Hodgkin lymphoma; ScHARR, Sheffield Centre for Health and Related Research; SCT, stem cell transplant

NICE

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NICE National Institute for Health and Care Excellence