Fully redacted - contains **NO** ACIC

NICE National Institute for Health and Care Excellence

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies

2nd Appraisal Committee meeting

Chair presentation

Chair: Jane Adam

ERG: PenTAG, University of Exeter

Technical team: Albany Meikle, Mary Hughes, Janet Robertson

Company: MSD

2nd November 2021

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
- 2,145 new cases of HL in the UK in 2017
- Incidence peaks in young adults (20 to 24 years) and older adults (75 to 79 years)
- Incidence is higher in males (59%)

Pembrolizumab (KEYTRUDA)

Mechanism of action	Anti-programmed cell death 1 (PD-1) antibody; blocks interaction with PD-L1 and PD-L2 ligands and reactivates T-cell anti-tumour activity
Marketing authorisation	Indicated for people with relapsed or refractory cHL who have failed autologous stem cell transplant (autoSCT) or following at least two prior therapies when autoSCT is not a treatment option *Note: extension of licence previously held for treatment after at least 3 previous treatments*
Administration & dose	IV - 200mg every 3 weeks or 400 mg every 6 weeks
List price	£2,630 per 100mg Confidential PAS discount also in place

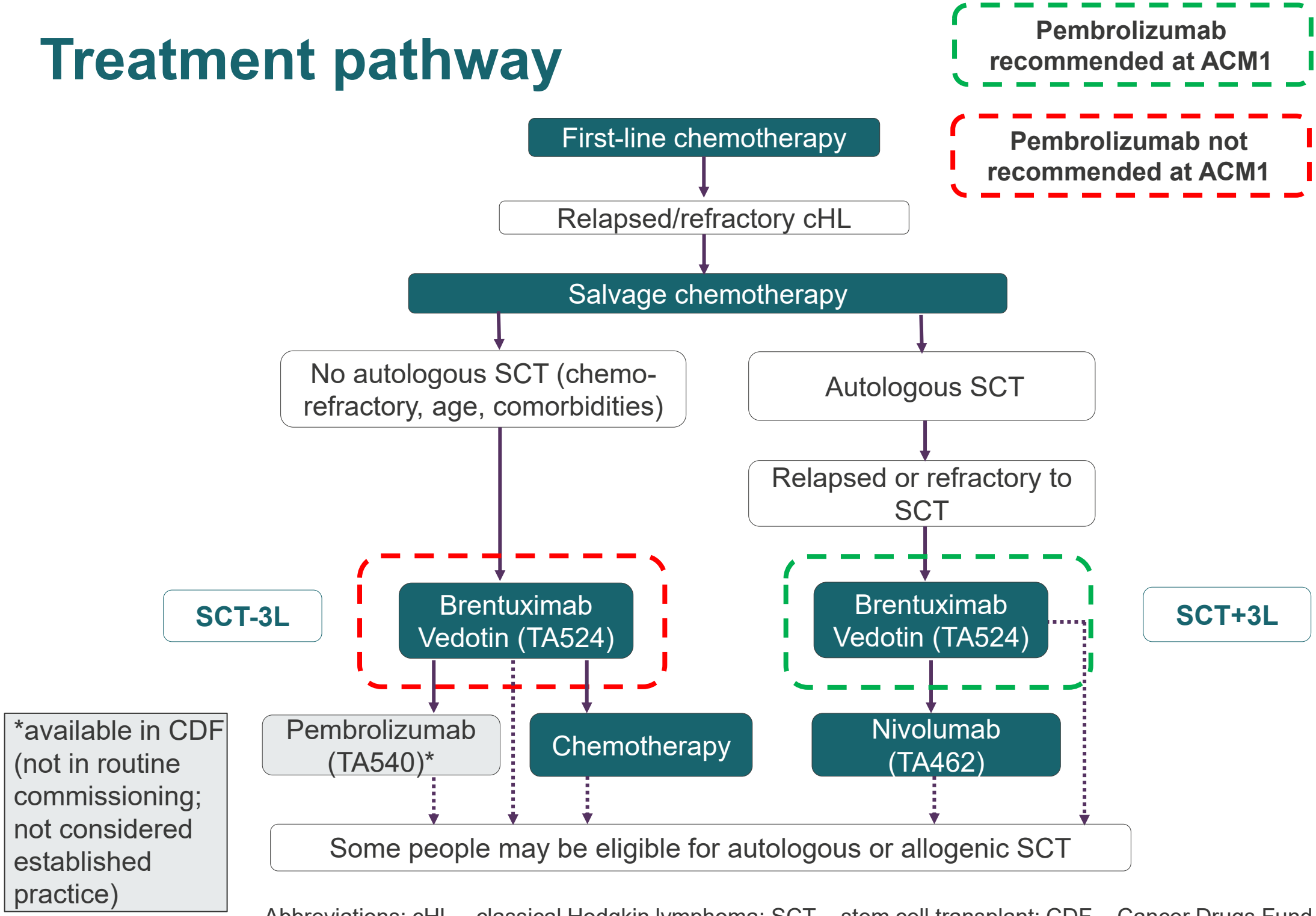
Abbreviations: cHL – classical Hodgkin lymphoma; IV – intravenous; PAS – patient access scheme

Decision problem

	Company model
Population	People with relapsed or refractory cHL who have: • received 2 previous therapies and autologous SCT **(SCT+3L)** • received 2 previous therapies and not received SCT **(SCT-3L)**
Intervention	Pembrolizumab
Comparators	Brentuximab vedotin
Outcomes	• OS • PFS • Response rates • Proportion receiving subsequent stem cell transplant • Adverse effects of treatment • Health-related quality of life

Abbreviations: cHL – classical Hodgkin lymphoma; SCT – stem cell transplant; OS – overall survival; PFS – progression-free survival

Treatment pathway



Abbreviations: cHL – classical Hodgkin lymphoma; SCT – stem cell transplant; CDF – Cancer Drugs Fund

Recommendation at ACM1

Based on differences in the treatment pathway, 2 separate subgroups were considered for pembrolizumab as 3rd line treatment:

- People who have had 2 previous systemic treatments and **had** received autologous stem cell transplant which had not worked (SCT+3L) – recommended at ACM1
- People who have had 2 previous systemic treatments and **had not** received autologous stem cell transplant (SCT-3L) – recommended at ACM1 within Cancer Drugs Fund, but agreement between NHS England and company not reached resulting in negative recommendation in ACD

Pembrolizumab is recommended as an option for treating relapsed or refractory classical Hodgkin lymphoma in people aged 3 and older, **only if:**

- they **have had** an autologous stem cell transplant that has not worked
- they have not had brentuximab vedotin

Abbreviations: ACM – appraisal committee meeting; ACD – appraisal consultation document

Pivotal trial: KEYNOTE-204

Trial design	Randomised, open-label, phase 3 trial; multi-national including UK	
Population	• Relapsed/refractory cHL *SCT+3L+ and SCT-3L+ subgroups include people with or without previous stem cell transplant who are receiving **at least** 3rd line treatment*	
Intervention/ comparator	**Pembrolizumab** (Total n=151, SCT-3L+ n=[redacted]) 200mg IV every 3 weeks, up to 35 cycles	**Brentuximab vedotin** (Total n=153, SCT-3L+ n=[redacted]) 1.8mg/kg IV every 3 weeks, up to 35 cycles
Outcomes	• Includes: PFS and PFS2; OS data not yet available	

SCT+3L+ PFS based on BICR		
	Pembrolizumab (n=[redacted])	**BV (n=[redacted])**
Number of events (%)	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]
Estimated median PFS, weeks (95% CI)	[redacted]	[redacted]
SCT-3L+ PFS based on BICR		
	Pembrolizumab (n=[redacted])	**BV (n=[redacted])**
Number of events (%)	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]
Estimated median PFS, weeks (95% CI)	[redacted]	[redacted]

cHL - classical Hodgkin's lymphoma; SCT - stem cell transplant OS - overall survival; PFS - progression-free survival; PFS2 – time to progression on next treatment

Committee conclusions at ACM1

	Conclusions	ACD
Population	Appropriate to consider SCT- 3L+ and SCT+3L+ separately as subsequent treatments differ. Prognosis may be better for SCT+ than SCT-	3.9
Clinical effectiveness	Pembrolizumab: • improves progression-free survival in both subgroups • is more tolerable and convenient (does not need prolonged hospital stays) which is important to patients	 3.4 3.1
Overall survival	Highly uncertain. No KEYNOTE-204 data. Unknown if Balzarotti or Gopal appropriate. Assuming equal survival may be conservative.	3.11
Utility values	BV side effects may persist after stopping treatment but unlikely to persist for whole progression period. Preferred ERG approach, but conservative.	3.12

Abbreviations: SCT - stem cell transplant

Key issues

- **Does pembrolizumab provide additional survival time compared with brentuximab vedotin?**
  - i.e. is there a survival benefit associated with pembrolizumab?
  - company updated model to include survival benefit (assumed no survival benefit at ACM1)
  - ERG: presence and magnitude of survival benefit is highly uncertain (no OS evidence from KEYNOTE-204 and other OS sources uncertain and/or in different lines of therapy)
  - if there is likely survival benefit, are the company's estimates plausible?
- **If there is no survival benefit, OS is assumed equal in both arms – what is the best source of estimating OS?**
  - if a survival benefit is assumed, the source of OS data has minimal impact on ICER
  - if there is no survival benefit assumed, the source of OS data has relatively large impact on ICER, (but less after comparator PAS are taken into account); ERG suggest using either Eyre et al. or Gopal et al.
- **Which utility values for progressed disease (PD) are most appropriate?**
  - company uses nivolumab trial PD utility data for pembrolizumab PD (less optimistic than ACM1)
  - ERG use brentuximab vedotin arm PD utility values for both arms in PD state
- **What percentage of people in each arm receive subsequent treatment following progression?**
  - company present analyses using proportion of subsequent treatments in each arm of KEYNOTE-204 ([redacted]% and [redacted]%), using proportion from BV arm for both arms ([redacted]%) and using proportion from pembrolizumab arm in both arms ([redacted]%)
  - ERG present analyses using proportion of subsequent treatments based on clinical expert opinion (30%)
  - **if assuming no survival benefit**, the proportion receiving subsequent treatments has large impact on ICER
- **Are there any equalities issues?**

ACD consultation responses

Responses received from:

- Company (MSD)
- Patient group (Lymphoma Action)
- Clinical experts
- Comparator company (Takeda)

Patient group responses

Lymphoma action:

- Recommendation excludes those with highest unmet need (without previous SCT)
- Treatment options are limited and aren't always tolerated
- Pembrolizumab has clear clinical benefits (improves progression-free survival and is generally better tolerated) and advantages over BV which would have a significant impact on QoL
- Pembrolizumab is an outpatient treatment with fewer hospital visits providing added convenience and lower chance of hospital acquired infection
- Recommendation will disproportionately impact older people who are less likely to be eligible for SCT

Abbreviations: SCT - stem cell transplant; BV – brentuximab vedotin; QoL – quality of life

Clinical expert responses

There is clinical need for pembrolizumab in people who haven't had a SCT:

- People who are unfit for transplant (due to age or comorbidities) have the greatest need for PD-1 inhibitors
- People who are chemo-refractory (and not eligible for SCT) have the highest risk of poor outcomes and pembrolizumab shows benefits for these people
- No biological reason PD-1 inhibitors should be less effective for people without previous SCT
- Current recommendation will mean people not eligible for SCT will be given a less effective treatment (BV) before becoming eligible for a more effective treatment (pembrolizumab 4th line in CDF)
- Response rates with PD-1 inhibitors are higher in Hodgkin's lymphoma than any other malignancy

Risk of discrimination:

- Basing recommendation on lack of SCT risks discrimination based on age (older people are less likely to be SCT eligible)

Inaccuracies in ACD:

- ACD misrepresented clinical expert comments on reduced effectiveness of SCT after pembrolizumab. Evidence that autologous SCT is highly effective in people who have responded to PD-1 inhibition - attractive to use pembrolizumab as bridge to transplant which will use fewer cycles (so will be cheaper) and increase the likelihood of cure
- ERG statement that time on treatment should be similar to PFS may not be true for some people who receive SCT and stop treatment before progression

Abbreviations: SCT - stem cell transplant; PD-1 programmed-cell death; CDF – Cancer Drugs Fund; PFS – progression-free survival

Comparator company responses

Takeda:

- Brentuximab vedotin (BV) can be used for up to 16 cycles according to its marketing authorisation – 12% of people treated with BV in KEYNOTE-204 received more than 16 cycles so this is not generalisable to the NHS
- Dispute clinical expert comment that people who have chemo-refractory disease may have poorer response to further chemotherapy, including BV. BV is a *targeted* chemotherapy with evidence of benefit in people with poor response to prior chemotherapy
- Evidence suggests a minimal difference in the number of people receiving SCT after pembrolizumab or BV; complete response is best indicator for SCT success and KEYNOTE-204 complete response rate was similar for pembrolizumab and BV arms
- Side effects more commonly associated with BV such as neuropathy can improve in time and rates of neuropathy are similar in both arms in KEYNOTE-204; pembrolizumab is also associated with severe immune-related adverse events for a minority of people

Abbreviations: SCT - stem cell transplant; BV – brentuximab vedotin

Company responses overview

- Pembrolizumab is recommended as 4th line treatment in the CDF (TA540). The real world budget impact of recommending pembrolizumab 3rd line is minimal as a positive recommendation would reverse the order of offering BV and pembrolizumab. The risk of decision error is small.

*NICE's position statement on products in the CDF states that these cannot be considered established practice, so pembrolizumab as 4th line treatment is **not** included in the model and does not come into the established clinical pathway relevant for decision making. TA540 CDF exit is due from July 2022.*

- Provided updated analyses and cost effectiveness results for the SCT-3L group
- Updated model to include overall survival benefit (not included previously), using separate external data sources for each treatment arm to model an indirect comparison
- Used alternative progressed disease utility values
- Used an alternative approach to accruing subsequent treatment costs
- Aligned PFS and time on treatment extrapolation break points in line with ERG preferred assumption
- Technical fixes to the model

Modelling overall survival benefit: data used

Company modelled median OS for pembrolizumab (using KN-087) vs BV arm (using Eyre et al.): [redacted] vs [redacted])

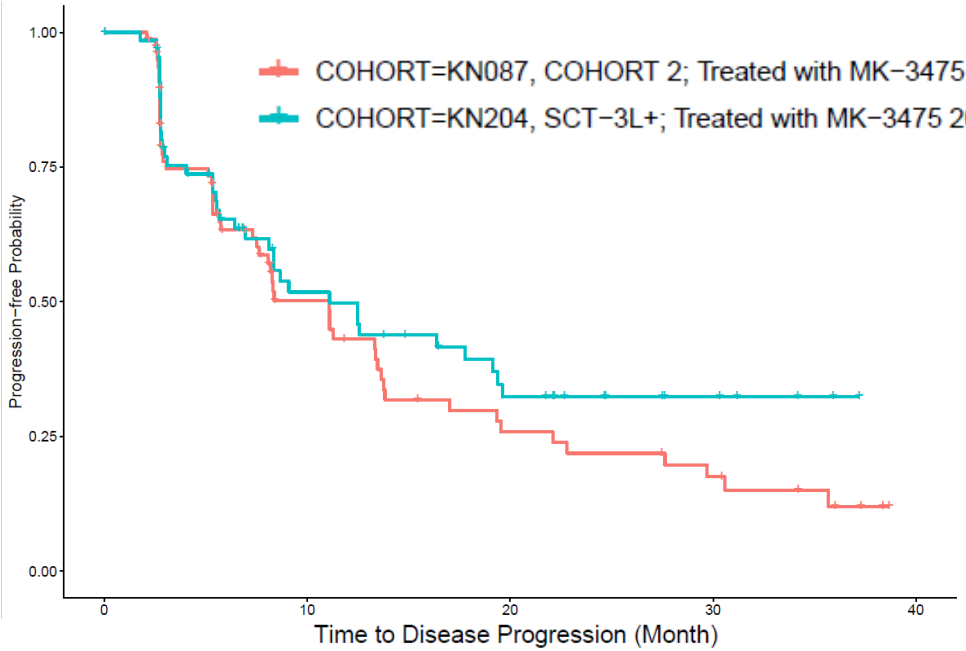
OS data source	Use in model	Company comments	Population characteristics compared with KN-204	ERG comments
KN-087 (n=81) • SCT-4L+	**Company:** Pembro arm base case	• only OS data available for pembro	• older population with more advanced disease • most other characteristics similar	• data are immature (median OS not reached) • later line of therapy
Eyre et al. (n=99) • SCT- • median 2 prior treatments	**Company:** BV arm base case **ERG:** Pembro and BV arms (equal OS) scenarios	• preferred in TA524 for BV OS • clinical expert at TE: reasonable source for SCT- group	• most characteristics similar • more people received SCT than in KN-204 BV arm • UK based	• median OS reached (37.2 months)
Gopal et al. (n=102) • SCT+ • median 2.5 prior treatments	**ERG:** Pembro and BV arms (equal OS) scenarios	• not reflective of SCT- group	• all received SCT	• used as OS source in company's previous analyses • median OS (40.5 months)

pembro – pembrolizumab; KN – KEYNOTE; OS – overall survival; BV - brentuximab vedotin; SCT - stem cell transplant; TE-technical engagement

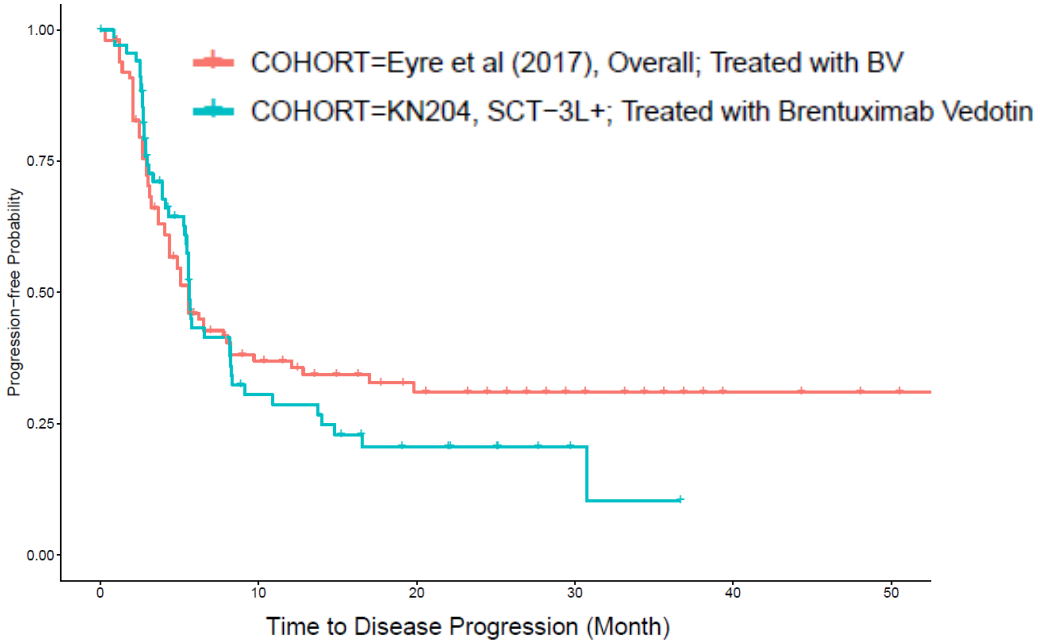
Modelling overall survival benefit: comparison of PFS in KN-204 and external sources of OS

KEYNOTE-204 PFS hazard ratio = [redacted]

Pembrolizumab PFS in KN-087 and KN-204



BV PFS in Eyre et al. and KN-204



Company's interpretation of comparison of PFS results and what this suggests about OS estimates using these data sources:

- PFS time is similar for around 60% (pembrolizumab) and 70% (BV) of participants
- PFS data indicates that Eyre et al. may overestimate OS and KN-087 may underestimate OS that will be seen in KN-204

Abbreviations: PFS – progression-free survival; KN – KEYNOTE; BV - brentuximab vedotin; SCT - stem cell transplant; OS – overall survival

Modelling overall survival benefit: ERG comments

ERG:

- Company's original approach assumed no survival benefit - no robust evidence to change this assumption
- Pembrolizumab OS estimates are highly uncertain in absence of any KEYNOTE-204 data
- No data to support that KEYNOTE-087 underestimates OS because population were older and sicker (4th line) than in KEYNOTE-204
- Magnitude of company's modelled median OS for pembrolizumab vs BV is implausible according to clinical experts; OS for pembrolizumab estimated to be [redacted] compared to [redacted] for BV
- If OS benefit it assumed, results are not sensitive to company sensitivity analysis using alternative parametric functions or data sources

Abbreviations: OS – overall survival; BV – brentuximab vedotin

Progressed disease utility values

	ACM1 PD utility assumptions
Company	• Utilities from pooled SCT- and SCT+ 3L+ KEYNOTE-204 population
ERG	• Pembrolizumab PD utilities = BV PD utilities • KN-204 utilities are uncertain, lack face validity and are likely to be overestimated

ACM1 committee conclusion:
- BV associated with more side effects in PD state but difficult to quantify difference in HRQoL
- Preferred ERG's assumption which might be conservative

	ACM2 PD utility assumptions
Company	• Pembrolizumab values from nivolumab trial data (CheckMate205); higher than BV but lower than pembrolizumab utilities in KEYNOTE-204
ERG	• Same as ACM1 ERG assumption, in line with committee conclusion • Acknowledge nivolumab PD utility may be a helpful scenario

	KN-204 pooled 3L+ PF utilities	KN-204 pooled 3L+ PD utilities	Company updated PD utilities	ERG preferred PD utilities
Pembrolizumab	[redacted]	[redacted]	0.715*	[redacted]
BV	[redacted]	[redacted]	[redacted]	[redacted]

- *CheckMate205 cohort all have had previous SCT and majority (74%) previous BV treatment
  (source: TA524 company submission)

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Abbreviations: PD – progressed disease; BV - brentuximab vedotin; SCT - stem cell transplant; HRQoL – health related quality of life

Subsequent treatments

Company and ERG presented analyses using different **proportions** of progressed disease state receiving subsequent treatment - drives ICER when **no overall survival benefit assumed:**

- when **OS benefit is included**, time spent in PD state in pembro arm is longer compared to BV arm; cost of BV as subsequent treatment following pembrolizumab is offset by large life year and QALY gain; subsequent treatment proportions do not have a major impact on ICER
- when **no OS benefit is included**, time spent in PD state in pembro arm is shorter compared to BV arm; the incremental QALY gain associated with pembrolizumab is no longer large enough to offset the increase in costs from subsequent treatment; subsequent treatment proportions have a large impact on ICER (higher proportion = higher ICER)

Abbreviations: BV – brentuximab vedotin; OS – overall survival; PD – progressed disease; ICER – incremental cost effectiveness ratio; QALY – quality-adjusted life year

	Assume equal OS using Eyre	Assume equal OS using Gopal	Assume OS benefit using KN-087 (pembrolizumab) and Eyre (BV)
Relative time in PD state	Longer for BV than pembrolizumab	Longer for BV than pembrolizumab; both arms also have longer time in PD because Gopal OS estimates longer than Eyre	Longer for pembrolizumab than BV
OS estimate for pembrolizumab	Shortest →		Longest

[redacted]

Changes to company model assumptions

	Company assumptions at ACM1	Company assumptions at ACM2
Pembrolizumab OS	Gopal et al. (for pooled SCT- and SCT+ 3L population): equal to BV OS	Unadjusted KN-087 SCT- cohort data with log-logistic extrapolation
BV OS	Gopal et al. (for pooled SCT- and SCT+ 3L population)	Eyre et al. 2017 data with log-logistic extrapolation
Utility in pembro PD state	KEYNOTE-204 3L+ population EQ-5D data	0.715 (nivolumab CheckMate205 SCT+ population)
Subsequent treatment proportions	100%	KEYNOTE-204 data from each arm
Subsequent treatment accrual	Based on PD entry	Based on PFS exit (accounting for deaths)
Subsequent treatment following BV	Bendamustine	Weighted average of multi-agent chemotherapy
PFS break point	52 weeks	26 weeks
Time on treatment break point	80 weeks	26 weeks

Greatest impact on ICER

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Abbreviations: PFS – progression-free survival; OS – overall survival; KN – KEYNOTE; BV - brentuximab vedotin

Cost effectiveness results overview

Includes patient access scheme for pembrolizumab but not BV or other treatments in pathway (results including these will be presented in Part 2)

SCT-3L+ population	Treatment	Total LYs	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)
Company deterministic base case	Pembrolizumab	10.39	[redacted]	[redacted]	-	-	-
	BV	4.36	[redacted]	[redacted]	[redacted]	[redacted]	10,133
Company probabilistic base case (95% CI)	Pembrolizumab	10.31	[redacted]	[redacted]	-	-	-
	BV	4.43	[redacted]	[redacted]	[redacted]	[redacted]	10,065 (6,156 to 18,768)

The ERG did not present a base case post-ACD but provided a range of scenario analyses

Abbreviations: LY – life years; QALY – quality adjusted life year; BV – brentuximab vedotin; CI – confidence interval

Company scenario analyses overview

Company scenario analyses did not significantly impact the ICER, including:

- Changing source of OS data for pembrolizumab, BV or changing OS extrapolations
- Assuming equal pembrolizumab and BV PD utility values
- Proportion receiving subsequent treatments (limited impact because OS benefit included)

Company base case ICER £10,133

Company scenario	Impact on ICER
Changing source of OS data for pembrolizumab to adjusted KN-087 or SACT	£9,499 to £10,114 / QALY
Changing source of OS data for BV to Walewski	£10,262 / QALY
Changing extrapolation curve for OS	£9,932 to £11,626 / QALY
Assume pembrolizumab PD utility equal to BV PD utility	£10,515 / QALY
Subsequent treatments based on % receiving subsequent treatment from pembro arm in KN-204 ([redacted]%), BV arm ([redacted]%) or 100% based on PFS exit approach	£10,311 to £13,119 / QALY
Subsequent treatments based on PD entry approach	£8,547 to £10,787 / QALY
Including treatment waning between 5 and 7 years	£10,282 / QALY

Abbreviations: QALY – quality adjusted life year; BV – brentuximab vedotin; OS – overall survival; PD – progressed disease

ERG combined scenario analyses – using Eyre et al. in both arms (equal OS)

Significant impact to ICER when assuming equal OS using Eyre et al. **combined** with [redacted]% receiving subsequent treatment in each arm and/or equal PD utilities

All scenarios other than company base case use Eyre et al. as source of OS data in both arms (assuming equal OS)

Scenario	Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	10,133
OS from Eyre et al. for both arms, only	[redacted]	[redacted]	[redacted]	[redacted]	11,455
Equal PD utilities in both arms [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,469
[redacted]% receiving subsequent treatment (% in KN-204 pembro arm)	[redacted]	[redacted]	[redacted]	[redacted]	13,556
[redacted]% receiving subsequent treatment (% in KN-204 BV arm)	[redacted]	[redacted]	[redacted]	[redacted]	34,960
[redacted]% receiving subsequent treatment (% in KN-204 BV arm) + equal PD utilities in both arms [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,052

Abbreviations: QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; KN – KEYNOTE; OS – overall survival; BV – brentuximab vedotin; PD – progressed disease

ERG combined scenario analyses – using Gopal et al. in both arms (equal OS)

Impact to ICER when assuming equal OS using Gopal et al.
Significant impact to ICER when assuming equal OS using Gopal et al. **combined** with [redacted]% receiving subsequent treatment in each arm and/or equal PD utilities

All scenarios other than company base case use Gopal et al. as source of OS data in both arms (assuming equal OS)

Scenario	Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	10,133
OS from Gopal et al. for both arms, only	[redacted]	[redacted]	[redacted]	[redacted]	21,963
Equal PD utilities in both arms [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,728
[redacted] receiving subsequent treatment (% in KN-204 pembro arm)	[redacted]	[redacted]	[redacted]	[redacted]	23,968
[redacted] receiving subsequent treatment (% in KN-204 BV arm)	[redacted]	[redacted]	[redacted]	[redacted]	47,798
[redacted] receiving subsequent treatment (% in KN-204 BV arm) + equal PD utilities in both arms [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,814

Abbreviations: QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; KN – KEYNOTE; OS – overall survival; BV – brentuximab vedotin; PD – progressed disease

ERG scenario analyses – using 30% subsequent treatment in each arm

Assuming a lower proportion of people receiving subsequent treatment in each arm decreases the ICER

ERG clinical experts advised that approx. 30% of people in pembrolizumab and BV arms would receive subsequent treatment

Scenario uses company base case with assumption of 30% subsequent treatment

Scenario	Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	10,133
Subsequent treatment proportion of 30% for both arms	[redacted]	[redacted]	[redacted]	[redacted]	6,434

Abbreviations: QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Impact of combining overall survival and subsequent treatment proportion scenarios

Company base case ICER £10,133

	OS benefit – using KN-087 (pembro) and Eyre (BV)	Equal OS – using Eyre (both arms)	Equal OS - using Gopal (both arms)
30% in both arms have subsequent treatment (ERG scenario)	6,434	-	-
[redacted] in both arms receiving subsequent treatment (% in KN-204 pembro arm)	8,661	13,556	23,968
[redacted] (pembro arm) and [redacted] (BV arm) receiving subsequent treatment (KN-204 data)	10,133	11,455	21,963
[redacted] in both arms receiving subsequent treatment (% in KN-204 BV arm)	10,236	34,960	47,798
Equal PD utilities in both arms [redacted]	10,515	12,469	24,728
[redacted] in both arms receiving subsequent treatment (KN-204 BV arm) + equal PD utilities in both arms	-	38,052	53,814

Key issues

- **Does pembrolizumab provide additional survival time compared with brentuximab vedotin?**
  - i.e. is there a survival benefit associated with pembrolizumab?
  - company updated model to include survival benefit (assumed no survival benefit at ACM1)
  - ERG: presence and magnitude of survival benefit is highly uncertain (no OS evidence from KEYNOTE-204 and other OS sources uncertain and/or in different lines of therapy)
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- **If there is no survival benefit, OS is assumed equal in both arms – what is the best source of estimating OS?**
  - if a survival benefit is assumed, the source of OS data has minimal impact on ICER
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- **Which utility values for progressed disease (PD) are most appropriate?**
  - company uses nivolumab trial PD utility data for pembrolizumab PD (less optimistic than ACM1)
  - ERG use brentuximab vedotin arm PD utility values for both arms in PD state
- **What percentage of people in each arm receive subsequent treatment following progression?**
  - company present analyses using proportion of subsequent treatments in each arm of KEYNOTE-204 ([redacted]% and [redacted]%), using proportion from BV arm for both arms ([redacted]%) and using proportion from pembrolizumab arm in both arms ([redacted]%)
  - ERG present analyses using proportion of subsequent treatments based on clinical expert opinion (30%)
  - **if assuming no survival benefit**, the proportion receiving subsequent treatments has large impact on ICER
- **Are there any equalities issues?**

Back up slides

Scenario analyses – impact of different overall survival extrapolation curves and data sources

Company base case

Scenario			Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
Extrapolation	OS data source						
	Pembrolizumab	BV					
Log-logistic	KN-087	Eyre	[redacted]	[redacted]	[redacted]	[redacted]	10,133
Weibull	KN-087	Eyre	[redacted]	[redacted]	[redacted]	[redacted]	10,187
Log-normal	KN-087	Eyre	[redacted]	[redacted]	[redacted]	[redacted]	10,057
Log-logistic	SACT	Eyre	[redacted]	[redacted]	[redacted]	[redacted]	9,499
Log-logistic	KN-087	Walewski	[redacted]	[redacted]	[redacted]	[redacted]	10,262
Log-normal	Adjusted KN-087	Eyre	[redacted]	[redacted]	[redacted]	[redacted]	10,114

- Minimal difference in ICER using alternative extrapolation curves in different data sources (e.g. changing extrapolation for arms using SACT data)

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Abbreviations: QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; KN – KEYNOTE; SACT – systemic anti-cancer therapies

Scenario analyses – impact of using alternative utility value for progressed disease state

Company base case

Scenario	Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
Pembrolizumab PD utility based on nivolumab utility in CheckMate205 SCT+4L+ subgroup	[redacted]	[redacted]	[redacted]	[redacted]	10,133
Pembrolizumab PD utility equal to BV PD utility	[redacted]	[redacted]	[redacted]	[redacted]	10,515

Abbreviations: PD – progressed disease; BV – brentuximab vedotin; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Scenario analyses – different subsequent treatment approaches

Company base case

Non-death PFS event: company's updated approach
PD entry: company's approach at ACM1

Scenario		Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
Non-death PFS event or PD entry approach	**% having subsequent treatment**					
Non-death PFS event	% receiving subsequent treatment from each arm in KN-204	[redacted]	[redacted]	[redacted]	[redacted]	10,133
Non-death PFS event	100%	[redacted]	[redacted]	[redacted]	[redacted]	13,119
Non-death PFS event	% receiving subsequent treatment from pembro arm of KN-204	[redacted]	[redacted]	[redacted]	[redacted]	8,661
Non-death PFS event	% receiving subsequent treatment from BV arm of KN-204	[redacted]	[redacted]	[redacted]	[redacted]	10,236
PD entry	% receiving subsequent treatment from each arm in KN-204	[redacted]	[redacted]	[redacted]	[redacted]	8,547
PD entry	100%	[redacted]	[redacted]	[redacted]	[redacted]	10,787

PFS – progression-free survival; PD – progressed disease; BV – brentuximab vedotin

Scenario analyses – impact of assuming treatment waning

Company base case

Scenario	Pembro total costs (£)	BV total costs (£)	Pembro total QALYs	BV total QALYs	ICER (£/QALY)
No treatment waning	[redacted]	[redacted]	[redacted]	[redacted]	10,133
Treatment waning between 5 and 7 years	[redacted]	[redacted]	[redacted]	[redacted]	10,282

Abbreviations: PD – progressed disease; BV – brentuximab vedotin; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Modelling assumptions at ACM1

3-state partitioned survival model

	Company	ERG
Population	KEYNOTE-204 pooled 3rd line population	KEYNOTE-204 SCT-3L and SCT+3L modelled separately
Progression-free survival	KEYNOTE-204 KM data extrapolated from week 52	KEYNOTE-204 KM data extrapolated from week 26
Overall survival	Assumed same in both arms. External data from Gopal et al. for pooled 3rd line population	Assumed same in both arms. SCT-3L: Balzarotti et al. SCT+ 3L: Gopal et al.
Utility values	PF: KEYNOTE-204 PD: KEYNOTE-204 (30 days follow up)	PF: KEYNOTE-204 PD: KEYNOTE-204 BV values applied to both arms
Time on treatment	KEYNOTE-204 KM data extrapolated from week 80	KEYNOTE-204 KM data extrapolated from week 26
Subsequent treatment after BV in SCT-3L	Bendamustine	Bendamustine

Abbreviations: SCT - stem cell transplant; KM – Kaplan Meier; BV – brentuximab vedotin; PF – progression free; PD – progressed disease