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NICE National Institute for Health and Care Excellence

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 1 prior therapy

Lead team presentation

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Company: MSD

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Clinical key issues

- **Is the key clinical trial (KEYNOTE-204) generalisable to clinical practice?**
  - Company does not consider pembrolizumab a bridging therapy
  - Would pembrolizumab be considered as a bridge to stem cell transplant in clinical practice? Does this affect generalisability of KEYNOTE-204?
  - KEYNOTE-204 includes people with 2 or more previous treatments (3L+)
    - Pembrolizumab is compared with brentuximab vedotin, which is used 3rd line. Is KEYNOTE data generalisable to people who would currently have brentuximab vedotin in clinical practice?
- **Is the same relative benefit expected for all groups included in the marketing authorisation population?**
  - Pembrolizumab is indicated for people:
    - for whom an autologous SCT has failed
    - for whom an autologous stem cell treatment is not a treatment option and who have had 2 previous therapies
- **No overall survival data is available for pembrolizumab compared with brentuximab vedotin. What is the committee's view of the assumption of equal overall survival for the two treatments?**

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
- 5 to 10% don't respond to initial therapy (primary refractory) and 10 to 30% relapse after initial remission
- 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 in cHL, which was previously for adults with relapsed or refractory cHL who have failed autoSCT and brentuximab vedotin (not recommended in TA540) or are autoSCT ineligible and have failed brentuximab vedotin (recommended in CDF in TA540)*
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

Patient group perspectives

Patient group perspectives: living with the condition

Submission was received from Lymphoma Action

- Hodgkin lymphoma and its treatment significantly affect quality of life
- Fatigue is most common reported symptom, affecting around 3 in 4 people, and can persist for many years
  - "Fatigue is the most difficult to manage over the long term…my fatigue can be overwhelming"
- Around 1/3 of people experience depression, anxiety, isolation and loss of self-esteem; 40% report fear of lymphoma progression or relapse
- May have significant financial impact because affects ability to work
- Treatments and blood tests requires large time commitment and travel costs and logistics can be an issue. May leave people unable to care for children

Patient group perspectives: treatment options

Current treatments

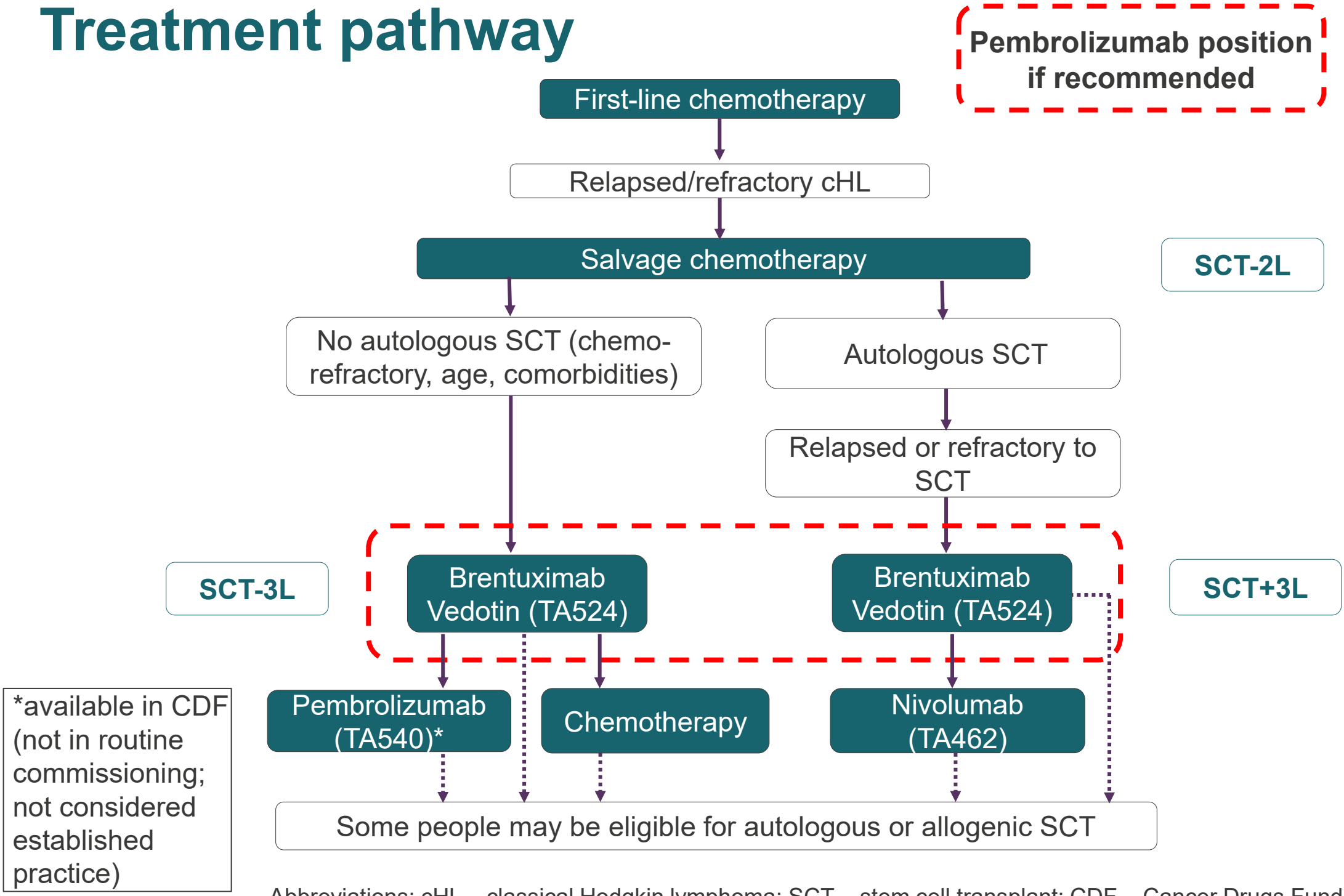
- Treatment is very intense and some people cannot tolerate current treatments
- Most people experience significant side effects, such as fatigue, nausea, pain and hair loss
- Stem cell transplant a dauting prospect
- Unmet need for effective, less demanding option with fewer side effects earlier in the treatment pathway
- Most important factors, in order, are: effectiveness, quality of life, tolerability

Pembrolizumab potential advantages and disadvantages

- High response rate to pembrolizumab, combined with tolerability offers significant advantage over other treatments
- More favourable side effect profile would have significant impact on quality of life
- Less time consuming and more convenient than other options, no prolonged hospital stays
- Many potential side effects are similar to lymphoma symptoms - it’s hard to feel reassured that treatment is working
- Uncertainty of long-term remission may be disadvantage, although off-set by high short-term response rate

Treatment pathway and decision problem

Treatment pathway



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

Pembrolizumab as bridge to transplant

- Company does not position pembrolizumab as a bridge to transplant
  - In key clinical trail, KEYNOTE-204, [redacted]% of participants had SCT before progression and subsequent treatment; average time to pre-progression SCT was [redacted]
- Rates of SCT modelled to be the same post-pembrolizumab or BV. Costs of SCT included, but not the impact of SCT on survival and quality of life
- Bridge to transplant included in previous Hodgkin lymphoma models (TA540 pembrolizumab, TA524 BV and TA462 nivolumab)

Clinical expert comments:

- Aim of treatment in younger/ fitter chemo-refractory people or people who fail autoSCT is to induce stable remission as a bridge to SCT
- For older people or people with co-morbidities who cannot have a transplant, aim is to induce a durable remission
- Expect pembrolizumab to be used as a bridge to SCT – used more in UK than in KEYNOTE-204
- PD-1 inhibition (e.g. pembrolizumab) can increase toxicity of alloSCT
- Benefit of autoSCT directly after 3L PD-1 inhibition (e.g. pembrolizumab) unclear

- **Would more patients achieve SCT with pembrolizumab than with BV?**

Abbreviations: SCT – stem cell transplant; BV – brentuximab vedotin; 3L – third line

Decision problem

Company updated the indication for pembrolizumab in its regulatory submission during technical engagement. A comparison is made with BV, which is a 3rd line treatment.

	Scope	Company model (post-technical engagement)
Population	People with relapsed or refractory cHL who have: • received autologous stem cell transplant (autoSCT) or • at least **1** prior therapy when autoSCT is not a treatment option *i.e. SCT-2L, SCT-3L+ and SCT+3L+*	People with relapsed or refractory cHL who have: • received autoSCT or • **at least 2** prior therapies when autoSCT is not a treatment option *MA narrower than original NICE scope *i.e. SCT-3L+ and SCT+3L+*
Intervention	Pembrolizumab	Pembrolizumab
Comparators	• Brentuximab vedotin • Chemotherapy for SCT-2L	Brentuximab vedotin
Outcomes	• Overall survival • Progression-free survival • Response rates • Proportion receiving subsequent stem cell transplant • Adverse effects of treatment • Health-related quality of life	• Same except response rates not included

Abbreviations: cHL – classical Hodgkin lymphoma; SCT – stem cell transplant; MA – marketing authorisation

Decision problem: subgroups

Company prefers to pool data for populations in scope, who have had different previous treatments

	Scope	Company model

Population	• Population of scope distinguishes people who have had:
	  • a SCT
	  • at least **2*** treatments when SCT is not a treatment option
	
	* Updated after technical engagement
		• SCT+3L+ (people who had a previous SCT and at least 2 previous lines of treatment)
		• SCT-3L+ (people who did not have a previous stem cell transplant and had at least 2 previous lines of treatment)
		• *Company provides cost effectiveness results for these subgroups pre-technical engagement model only*
		• *After technical engagement company provided cost effectiveness results for whole 3L+ population only*
		• *ERG prefers to present results for subgroups separately*

Sub-groups (which could be considered if evidence allows)	• People who could have a subsequent stem cell transplant (autologous or allogenic) if they respond to treatment • People for whom stem cell transplant is contraindicated because of comorbidities	• Does not consider the outcomes for these groups separately

Abbreviations: SCT – stem cell transplant

Clinical effectiveness evidence

Pivotal trial: KEYNOTE-204

Trial design	Randomised, open-label, phase 3 trial; multi-national including UK	
Population	• Relapsed/refractory cHL • Received at least 1 prior multi-agent chemotherapy regimen: ▪ SCT-2L, SCT-3L+ and SCT+3L+ • ≥18 years (84% <65 years) • ECOG performance status 0 (61.2%), 1 ([redacted]) or 2 ([redacted])	
Intervention/ comparator	**Pembrolizumab** (n=151) 200mg IV every 3 weeks, up to 35 cycles	**Brentuximab vedotin** (n=153) 1.8mg/kg IV every 3 weeks, up to 35 cycles
Outcomes	• OS (primary outcome; data not yet available) • PFS (primary outcome) • PFS2 (progression-free survival on subsequent treatment) • Objective response rate • Complete remission rate • Safety and tolerability	
Stratification factors	• Prior autologous SCT status • Primary refractory or relapsed disease after 1st line treatment	

NICE Abbreviations: cHL - classical Hodgkin's lymphoma; IV - intravenous; SCT - stem cell transplant; OS - overall survival; PFS - progression-free survival

KEYNOTE-204 population of interest

- KEYNOTE-204 included people who had:
  - previous autologous SCT and 2 or more previous treatments (**SCT+3L+ subgroup**)
  - no previous autologous SCT and 2 or more previous treatments (**SCT-3L+ subgroup**)
- Company presents data for people who had 2 or more previous treatments, combining people with and without previous SCT (**3L+ subgroup**)
- ERG provides cost effectiveness results for **SCT+3L+** and **SCT-3L+ subgroups separately**
- Subgroups based on previous treatments defined post-hoc (not in statistical analysis plan)
- KEYNOTE-204 **3L+** population includes people with **2 or more** previous treatments; the comparator in this appraisal is current 3L practice [BV])

KEYNOTE ITT population previous treatments		
	Pembrolizumab (n=151)	**BV (n=153)**
SCT+3L+	56 (37.1%)	56 (36.6%)
SCT-3L+	68 (45.0%)	69 (45.1%)
Median number of previous lines of therapy (range)	2 (1 to 10)	3 (1 to 11)

- **Is the population of interest in KEYNOTE-204 representative of people currently having BV in clinical practice?**

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Abbreviations: SCT – stem cell transplant; ITT – intention to treat; BV – brentuximab vedotin

KEYNOTE-204 3L+ subgroup: progression-free survival

PFS based on BICR		
	Pembrolizumab (n=[redacted])	BV (n=[redacted])
Number of events (%)	[redacted]	[redacted]
Estimated median PFS, weeks (95% CI)	[redacted]	[redacted]
PFS based on investigator review		
Number of events (%)	[redacted]	[redacted]
Estimated median PFS, weeks (95% CI)	[redacted]	[redacted]

Comparison in cumulative hazard in BICR-assessed PFS over time between pembrolizumab and BV for 3L+ subgroup

Pembrolizumab increases PFS compared with BV

Abbreviations: ITT - intention to treat; BICR - blinded independent central review; BV - brentuximab vedotin; PFS - progression-free survival; CI - confidence interval

KEYNOTE-204 SCT-3L+ and SCT+3L+ subgroups: progression-free survival

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]

- Pembrolizumab more effective than BV in PFS in both SCT-3L+ and SCT+3L+ subgroups
- However, p-values or confidence intervals for between-arm differences not reported
- Prognosis for SCT-3L+ is poorer than SCT+3L+

- **Is the same relative benefit expected in both groups, despite poorer prognosis in SCT-3L+ subgroup?**

Abbreviations: SCT – stem cell transplant; BICR, blinded independent central review; BV, brentuximab vedotin; CI, confidence interval; PFS – progression-free survival

KEYNOTE-204 overall survival data not available

- KEYNOTE-204 OS data not available - [redacted]
- Company model uses external data and assumes equal OS in both arms
- Company:
  - PFS2 data suggests OS may be increased with pembrolizumab vs BV
  - PFS2 significantly higher for pembrolizumab than BV at 24 months ([redacted] versus [redacted])
- ERG:
  - median PFS2 [redacted] – substantial limitation for use as alternative end point
  - PFS2 data not implementable in model

Clinical key issues

- **Is the key clinical trial (KEYNOTE-204) generalisable to clinical practice?**
  - Company does not consider pembrolizumab a bridging therapy
  - Would pembrolizumab be considered as a bridge to stem cell transplant in clinical practice? Does this affect generalisability of KEYNOTE-204?
  - KEYNOTE-204 includes people with 2 or more previous treatments (3L+)
    - Pembrolizumab is compared with brentuximab vedotin, which is used 3rd line. Is KEYNOTE data generalisable to people who would currently have brentuximab vedotin in clinical practice?
- **Is the same relative benefit expected for all groups included in the marketing authorisation population?**
  - Pembrolizumab is indicated for people:
    - for whom an autologous SCT has failed
    - for whom an autologous stem cell treatment is not a treatment option and who have had 2 previous therapies
- **No overall survival data is available for pembrolizumab compared with brentuximab vedotin. What is the committee's view of the assumption of equal overall survival for the two treatments?**

Cost effectiveness

Cost key issues

Major impact on ICER

- **Is it appropriate to use a pooled 3L population or separate subgroups based on previous stem cell transplant?**
  - The company provide cost effectiveness results for the whole population having a 3rd line treatment regardless of stem cell transplant history; ERG prefer to use subgroups based on previous stem cell transplant
- **Subsequent treatments are uncertain**
  - Company and ERG use different assumptions - which reflect clinical practice?
- **Overall survival is assumed to be equal for pembrolizumab and brentuximab vedotin**
  - What is the most appropriate source of overall survival data for the whole population or subgroups?
- **Utility values for progressed disease health state for pembrolizumab in KEYNOTE-204 are uncertain**
  - Is a maintained benefit in utility after progression on pembrolizumab plausible?
  - Or is the ERG's assumption of equal post-progression utilities appropriate?

Appropriate population(s) to consider: pooled 3L+ or SCT-/+ subgroups

Company base case uses **3L+ population** – pooled KEYNOTE-204 data from SCT-3L+ and SCT+3L+ subgroups for PFS and ToT

ERG prefers **SCT-3L+** and **SCT+3L+** subgroups modelled separately because these groups have different subsequent treatment options and consider different estimates of overall survival

Stakeholder comments (comparator company):

- Appropriate to consider subgroups separately:
  - outcomes worse in autoSCT ineligible patients
  - different treatment pathways for each subgroup
  - BV appraisal (TA524) considered subgroups separately and made distinct recommendations

- **Is it appropriate to use the pooled 3L+ analyses or SCT-3L+ and SCT+3L+ subgroup analyses?**

Abbreviations: PFS – progression-free survival; ToT – time on treatment; BV - brentuximab vedotin; SCT - stem cell transplant

TA524 & 540 considered subgroups separately

Technology	Marketing authorisation	Recommendation	Recommendation (after CDF)
BV	Adults with relapsed or refractory CD30- positive Hodgkin lymphoma: • after autoSCT or • after ≥2 prior therapies when autoSCT or multi-agent chemotherapy not a treatment option	TA446: recommended after autoSCT	TA524: recommended
		TA446: recommended through CDF after ≥2 previous therapies and cannot have autoSCT or multi-agent therapy	TA524: recommended
Pembrolizumab	*At time of TA540* Adults with relapsed or refractory cHL who: • have failed autoSCT and BV or • are SCT ineligible and have failed BV	TA540: not recommended for adults who have had autoSCT and BV	n/a
		TA540: recommended through CDF for adults who have had BV and cannot have autoSCT	TBC
Nivolumab	Adults with relapsed or refractory cHL after autoSCT and BV	TA462: recommended	n/a

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

Cost effectiveness results – overview

- Includes patient access scheme for pembrolizumab but not BV and nivolumab (results including these patient access schemes will be presented in Part 2)
- Pembrolizumab less costly and more effective (dominant) apart from in ERG base case SCT-3L+

		Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case 3L+ (deterministic)	Pembrolizumab	[redacted]	4.13	-	-	
	BV	[redacted]	3.54	-11,872	0.59	Dominant
ERG base case 3L+	Pembrolizumab	[redacted]	3.92	-	-	-
	BV	[redacted]	3.52	-5,587	0.41	Dominant
ERG base case SCT-3L+	Pembrolizumab	[redacted]	4.67	-	-	-
	BV	[redacted]	4.32	15,572	0.35	44,725
Company assumptions SCT-3L+*	Pembrolizumab	[redacted]	4.12	-	-	-
	BV	[redacted]	3.52	-18,213	0.61	Dominant
ERG base case SCT+3L+	Pembrolizumab	[redacted]	3.98	-	-	-
	BV	[redacted]	3.52	-23,248	0.46	Dominant
Company assumptions SCT+3L+*	Pembrolizumab	[redacted]	4.14	-	-	-
	BV	[redacted]	3.58	-47,629	0.56	Dominant

*produced by ERG at request of NICE

Abbreviations: QALY – quality adjusted life year; BV – brentuximab vedotin

Company's cost effectiveness model – post-technical engagement

Model type	3-state partitioned survival model: • progression-free • progressed-disease • death
Time horizon	50 years*
Model cycle	1 week
Discount rates	3.5%
Population	KEYNOTE-204 3L+* population†
Intervention	Pembrolizumab
Comparators	Brentuximab vedotin*

*Updated by company during technical engagement
† KEYNOTE-204 did not include children but only data from KEYNOTE-204 included in model. Data from KEYNOTE 051 (single arm study of pembrolizumab in children) not included. Company states this was because NHS England policy is to fund requests for medicines for children within a specialised service that are approved in adults by a NICE TA.

Company's cost effectiveness model – post-technical engagement: data sources and key assumptions

Outcomes	PFS: KEYNOTE-204 KM data and log-normal extrapolation after week 52 OS: Gopal et al. 2015, log-normal extrapolation (same OS assumed for both treatment arms)
Utility values	KEYNOTE-204 3L+ population EQ-5D data
Time on treatment	KEYNOTE-204 KM data and extrapolation after week 80, up to maximum 35 cycles (105 weeks) for pembrolizumab or 16 cycles for BV*
Resource use	Higher resource use (monitoring) assumed in PD state, based on clinical opinion, as per ERG preferred assumption*
SCT rates	KEYNOTE-204 3L+ data; pembrolizumab arm rates applied to both arms
Subsequent treatments	Pembrolizumab arm – 100% BV BV arm – 55.2% bendamustine; 44.8% nivolumab*

* Updated by company in response to technical engagement

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

ERG's preferred modelling assumptions in separate SCT-3L+ and SCT+3L+ subgroups

	Parameter/ assumption	ERG SCT-3L+ subgroup	ERG SCT+3L+ subgroup
ERG uses different assumptions in each subgroup Also differs from company assumptions	OS data	Balzarotti et al. applied to both arms	Gopal et al. applied to both arms
	PFS data	KEYNOTE-204 SCT-3L+ KM	KEYNOTE-204 SCT+3L+ KM
	Subsequent treatments	Pembrolizumab failure → 100% BV BV failure → 100% bendamustine	Pembrolizumab failure → 100% nivolumab BV failure → 100% nivolumab
ERG uses same assumptions in each subgroup but different assumptions to company	Utility values	KEYNOTE- 204 3L+ EQ-5D data with BV PD utility value applied to both treatment arms	
	Methods for extrapolating time on treatment	KEYNOTE-204 3L+ KM data to 26-week cut-point	
	Dose intensity	100% in both treatment arms	

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PFS – progression-free survival; KM – Kaplan Meier; BV – brentuximab vedotin; PD – progressed disease; ToT – time on treatment

Subsequent treatment assumptions (1)

Major driver of ICER

- ERG base case (3L+ pooled) same as company base case but ERG notes considerable uncertainty
- Company scenario uses most expensive chemotherapy after BV
- ERG SCT-3L+ subgroup models bendamustine after BV; company SCT-3L+ subgroup analyses (provided by ERG at NICE request) models pembrolizumab after BV
- Pembrolizumab after BV in SCT-3L+ group is recommended in CDF – not considered routine clinical practice (pre-TE company assumption presented as no updated base case for subgroups provided)

Model	Modelled population	Modelled first treatment	Follow on treatment	
			SCT-3L+	SCT+3L+
Company base case	Pooled 3L+ 55.2% had SCT-3L+ treatments 44.8% had SCT+3L+ treatments Modelled based on distribution of these groups	**Pembrolizumab**	BV	BV
		BV	bendamustine	nivolumab
ERG base case (3L+ pooled)		**Pembrolizumab**	BV	BV
		BV	bendamustine	nivolumab
Company scenario		**Pembrolizumab**	BV	BV
		BV	most expensive chemotherapy	nivolumab
ERG base case (SCT-3L+ and SCT+3L+ subgroups)	Separate SCT-3L+ and SCT+3L+ population	**Pembrolizumab**	BV	nivolumab
		BV	bendamustine	nivolumab
Company SCT-3L+ and SCT+3L+ subgroups*	Separate SCT-3L+ and SCT+3L+ population	**Pembrolizumab**	BV	BV
		BV	pembrolizumab	nivolumab

*produced by ERG at request of NICE

Abbreviations: BV – brentuximab vedotin; CDF – Cancer Drugs Fund

Subsequent treatment assumptions (2)

Company comments:

- SCT-3L+:
  - no standard of care - not all people will receive bendamustine after BV
  - assuming 100% bendamustine after BV is not representative as this is least expensive option
  - mix of options should be considered
  - company scenario analysis assumes 100% use of most expensive chemo option after BV
- SCT+3L+:
  - inappropriate to assume nivolumab given after pembrolizumab (as in ERG base case); BV more appropriate
- SCT ineligible group have high unmet need and having BV as option at 4th line is highly desirable

ERG comments:

- Considerable uncertainty around subsequent treatments
- Agree multiple chemotherapy options following BV used in practice – bendamustine included in ERG base case on clinical advice
- Company scenario analysis using most expensive chemotherapy resulted in minor increase in incremental costs for BV, but did not impact overall results

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

Subsequent treatment assumptions (3)

Clinical expert comments:

- Nivolumab is not valid treatment option after pembrolizumab – would not use a 2nd PD-1 inhibitor
- Pembrolizumab is standard of care after BV for SCT-3L+ *(in CDF, not considered routine practice by NICE)*

Stakeholder comments (comparator company):

- Subsequent treatment pathway after pembrolizumab in SCT+3L+ pathway should be fully considered:
  - BV, followed by nivolumab (supported by NICE TA524 and TA462)
- Including just BV or nivolumab as subsequent treatment does not fully capture the treatment costs

- **What are the most appropriate subsequent treatments?**
- **Should BV and nivolumab both be considered subsequent treatments for SCT+3L+ subgroup?**

Abbreviations: BV – brentuximab vedotin; SCT – stem cell transplant; CDF – Cancer Drugs Fund

Company: assuming equal overall survival with pembrolizumab and BV is conservative

Company comments

- Company clinical expert opinion that immunotherapies have large impact on OS in cHL in later lines of therapy - same expected at this point
- KEYNOTE-204 PFS benefit indicates a likely OS benefit, mainly in people ineligible for SCT
- PFS2 highlighted by EMA as reliable endpoint when OS data not available – median PFS2 [redacted]; ITT HR [redacted]
- KEYNOTE-087 provides longer-term evidence of OS for pembrolizumab:
  - Median follow-up 39.5 months (range 1.0 to 44.8 months)
  - Median OS not reached
  - 12 month OS [redacted] and 24 month OS [redacted] (compared with model: 87.1% and 69.4% respectively)
  - KEYNOTE-204 1 line earlier – might have improved OS benefit

KEYNOTE-087:

- Single arm study of pembrolizumab in cHL
- Included:
  - R/R to autoSCT and BV
  - R/R to salvage chemotherapy (no autoSCT) plus R/R to BV
  - R/R to autoSCT and not received BV

- ERG: Agree assuming equal OS in pembrolizumab and BV arms may be conservative

OS – overall survival; cHL – classical Hodgkin lymphoma; PFS – progression-free survival; BV – brentuximab vedotin; PFS2 – 2nd progression-free survival; EMA – European Medicines Agency; ITT – intention to treat; HR – hazard ratio; R/R – relapsed/refractory

Data used to model overall survival

All models assume same overall survival in pembrolizumab and BV treatment arms*

Source	How used in model	Intervention	Median number previous treatments (range)	Previous SCT?	Median OS	5-year survival estimated by model
Gopal et al. 2015	• Company base case (3L pooled) • ERG analyses using company assumptions (SCT-3L+ and SCT+3L+ subgroups) • ERG base case (SCT+3L+)	BV	3.5 (1 to 13)	Yes	40.5 months	37.4%
KEYNOTE-087 (single arm study)	Company scenario 1 (3L population)	Pembrolizumab	4 (1 to 12)	39% previous SCT	not reached median follow up of 39.5 months	[redacted]
Balzarotti et al. 2016	ERG base case (SCT-3L+ only)	IGEV	1 (1 to 1)	No	Not reported	48%

*Exception: Company additional scenario using OS to PFS ratio from Gopal et al. applied to pembrolizumab and BV PFS curves from KEYNOTE-204

OS – overall survival; PFS- progression-free survival; BV – brentuximab vedotin; SCT – stem cell transplant; IGEV - ifosfamide, vinorelbine, and gemcitabine

Generalisability of Gopal et al. to people who have not had a SCT (1)

ERG comments:

- Concerns around generalisability of Gopal et al. to SCT-3L+ subgroup
- OS may differ according to subgroup

ERG base case:

- Used data from Balzarotti et al. 2016 to estimate OS for SCT-3L+ subgroup and Gopal et al. for SCT+3L+ subgroup

Balzarotti et al. 2016

- People with HL relapsed/refractory to first-line chemotherapy

ERG scenario analysis

1. Used KEYNOTE-087 OS ITT data as alternative source of OS data for pembrolizumab and BV arms (SCT-3L+ and SCT+3L+ subgroups)
2. Used Balzarotti et al. to estimate OS in SCT-3L+ subgroup AND used alternative log-logistic fit to model OS
3. Used log-logistic parametric OS model from Gopal et al. data (SCT-3L+ and SCT+3L+ subgroups)

Abbreviations: OS – overall survival; ITT – intention to treat; BV – brentuximab vedotin; HL – Hodgkin's lymphoma; SCT – stem cell transplant

Generalisability of Gopal et al. to people who have not had a SCT (2)

Company comments:

- Balzarotti et al. population not comparable to the SCT-3L+ subgroup in KEYNOTE-204
- Balzarotti et al.:
  - SCT-2L population
  - Intervention was chemotherapy, not BV
  - Assume most eligible for SCT: excluded people with inadequate organ function and people aged 65+; at least 81% went onto transplant (lower than in KEYNOTE-204 SCT-3L+ group)

Clinical expert comments:

- Gopal et al. reasonable source for SCT+3L+ subgroup
- Gopal et al. less good for SCT ineligible – OS in SCT ineligible likely lower than in Gopal et al.
- Eyre et al. 2017 another reasonable source for SCT naïve (although fit for SCT)

- **What is the most appropriate source of OS data?**

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Abbreviations: OS – overall survival; BV – brentuximab vedotin; SCT – stem cell transplant

Utility values used in the progressed disease health state for pembrolizumab (1)

Background

- Utility values from KEYNOTE-204 3L+ population used in company base case
- EQ-5D-3L questionnaires used for 1 year or until progression; patient reported outcomes were obtained at discontinuation and at the 30-day safety follow up

EQ-5D health utility scores 3L+ population in KEYNOTE-204

Treatment	Progression Free utility	Progressed Disease utility
Pembrolizumab	[redacted]	[redacted]
BV	[redacted]	[redacted]
Pooled utilities	[redacted]	[redacted]

ERG comments

- KEYNOTE-204 QoL data uncertain:
  - 30-day follow-up to estimate PD utility is short and unlikely to capture changes in QoL
  - Small participant numbers for estimating PD utility ([redacted] pembrolizumab and [redacted] BV)
- PD utility value for pembrolizumab lacks face validity (ERG clinical expert), highly uncertain and likely to be overestimated
- Prefers assuming pembrolizumab PD = company's BV PD

NICE comments

- Committee's preferred PD utility values in previous appraisals:
  - TA540 - pembrolizumab after BV and SCT ineligible: between ([redacted]) and ([redacted])
  - TA462 - nivolumab after BV, following SCT: [redacted] (same utility across all treatments)

Abbreviations: QoL – quality of life; PD, progressed disease; BV, brentuximab vedotin; PF, progression-free; ITT – intention to treat

Utility values used in the progressed disease health state for pembrolizumab (2)

Company comments

- Reasonable that PD utility values lower in BV arm – BV associated with neuropathy; side effects continue following discontinuation; pembrolizumab side effects are more manageable and less debilitating on average
- PFS on pembrolizumab longer and time to relapse is prognostic factor - therefore poorer QoL expected for people on BV who are likely to relapse sooner than people on pembrolizumab
- Checkmate-205 (nivolumab trial) reported 4L population (failed BV) utility value of 0.715 for PD
  - not plausible that QoL at 3L is worse than at 4L – expect to be at least as high

Clinical expert comments

- Progression associated with extreme psychological distress
- Pembrolizumab relapse associated with slightly better QoL than BV relapse:
  - BV associated with worse QoL with higher rates of side effects, including neuropathy
  - pembrolizumab generally slightly better tolerated
- Immune-related side effects cause significant morbidity for minority (~5%) on pembrolizumab

- **Are the utility values reported in KEYNOTE-204 plausible?**
- **What is the most appropriate method to model utility values?**

Abbreviations: PD, progressed disease; BV, brentuximab vedotin; PFS, progression-free survival; QoL, quality of life; 4L, 4th line; 3L, 3rd line;

Cost effectiveness results – overview reminder

- Includes patient access scheme for pembrolizumab but not BV and nivolumab (results including these patient access schemes will be presented in Part 2)
- Pembrolizumab less costly and more effective (dominant) apart from in ERG base case SCT-3L+

		Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case 3L+ (deterministic)	Pembrolizumab	[redacted]	4.13	-	-	
	BV	[redacted]	3.54	-11,872	0.59	Dominant
ERG base case 3L+	Pembrolizumab	[redacted]	3.92	-	-	-
	BV	[redacted]	3.52	-5,587	0.41	Dominant
ERG base case SCT-3L+	Pembrolizumab	[redacted]	4.67	-	-	-
	BV	[redacted]	4.32	15,572	0.35	44,725
Company assumptions SCT-3L+*	Pembrolizumab	[redacted]	4.12	-	-	-
	BV	[redacted]	3.52	-18,213	0.61	Dominant
ERG base case SCT+3L+	Pembrolizumab	[redacted]	3.98	-	-	-
	BV	[redacted]	3.52	-23,248	0.46	Dominant
Company assumptions SCT+ 3L+*	Pembrolizumab	[redacted]	4.14	-	-	-
	BV	[redacted]	3.58	-47,629	0.56	Dominant

*produced by ERG at request of NICE

Abbreviations: QALY – quality adjusted life year; BV – brentuximab vedotin

Company's cost effectiveness results – scenario analyses (pooled 3L+ group)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	-11,872	0.59	Dominant
Utility same in both arms in PD state [redacted] (BV PD utility)	-11,872	0.40	Dominant
OS based on KEYNOTE-087	-7,854	1.51	Dominant
PFS piecewise week 26 cut-point	-13,016	0.61	Dominant
Subsequent treatment – most expensive chemo post-BV in SCT-3L+ subgroup	-12,416	0.59	Dominant

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

ERG scenario analyses SCT-3L+ and SCT+3L+ subgroups

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	+/-
SCT-3L+				
Company base case SCT-3L+	-18,213	0.61	Dominant	-
Utility same in both arms in PD state [redacted] (BV PD utility)	-18,213	0.39	Dominant	-55%
26-week cut-point for modelling ToT	-10,174	0.61	Dominant	44%
Subsequent treatment – BV > 100% bendamustine; pembrolizumab > 100% BV	8,597	0.61	14,154	147%
Balzarotti et al. for OS data	-17,501	0.77	Dominant	24%
KEYNOTE-087 used for OS data	-16,036	1.52	Dominant	65%
SCT+3L+				
Company base case SCT+3L+	-47,629	0.56	Dominant	-
Utility same in both arms in PD state [redacted] (BV PD utility)	-47,629	0.39	Dominant	-44%
Subsequent treatment – BV > 100% nivolumab; pembrolizumab > 100% nivolumab	-31,810	0.56	Dominant	33%
KEYNOTE-087 used for OS data	-50,631	1.47	Dominant	60%
Generalised gamma curve for PFS	-41,558	0.61	Dominant	20%

Abbreviations: TE – technical engagement; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PD – progressed disease; BV – brentuximab vedotin; OS – overall survival; PFS – progression-free survival; ToT – time on treatment

Equality considerations and innovation

Equalities issues

- No issues identified

Innovation

- Company comments:
  - Pembrolizumab is a step-change in management of relapsed/refractory cHL
  - Currently limited treatment options for people ineligible for SCT
  - Granted Breakthrough Therapy Designation in 2013 (FDA) – continued to be recognised for innovation within numerous tumour types including cHL

- **Are there any equality issues to consider?**
- **Is pembrolizumab a 'step change' in treatment?**
- **Are there benefits not included in the model?**

Abbreviations: cHL – classical Hodgkin lymphoma; SCT – stem cell transplant; FDA – Food and Drug Administration

Cost key issues

Major impact on ICER

- **Is it appropriate to use a pooled 3L population or separate subgroups based on previous stem cell transplant?**
  - The company provide cost effectiveness results for the whole population having a 3rd line treatment regardless of stem cell transplant history; ERG prefer to use subgroups based on previous stem cell transplant
- **Subsequent treatments are uncertain**
  - Company and ERG use different assumptions - which reflect clinical practice?
- **Overall survival is assumed to be equal for pembrolizumab and brentuximab vedotin**
  - What is the most appropriate source of overall survival data for the whole population or subgroups?
- **Utility values for progressed disease health state for pembrolizumab in KEYNOTE-204 are uncertain**
  - Is a maintained benefit in utility after progression on pembrolizumab plausible?
  - Or is the ERG's assumption of equal post-progression utilities appropriate?

Back-up slides

Company and ERG's preferred modelling assumptions in 3L+ population

ERG also provided pooled 3L model

Parameter/assumption	Company	ERG
OS data	Gopal et al. applied to both arms	Same as company
PFS data	KEYNOTE-204 3L+ KM data to week 52-week cut-point, with log-normal distribution extrapolation	Same but with 26-week cut-point
Subsequent treatments	Pembrolizumab failure → 100% BV BV failure → 55.2% bendamustine; 44.8% nivolumab	Same although considers associated with considerable uncertainty
Utility values	KEYNOTE- 204 3L+ EQ-5D data	BV PD utility value applied to both treatment arms
Methods for extrapolating time on treatment	KEYNOTE-204 3L+ KM data to 80-week cut-point, with exponential distribution extrapolation	Same but with 26-week cut-point (same cut-point for extrapolation of PFS)
Dose intensity	98% in both treatment arms	100% in both treatment arms

Abbreviations: PFS – progression-free survival; KM – Kaplan Meier; BV – brentuximab vedotin; PD – progressed disease; ToT – time on treatment

Company's probabilistic sensitivity analysis

- 1000 simulations
- Results discounted

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case 3L+ population (probabilistic sensitivity analysis)					
Pembrolizumab	[redacted]	4.14	-	-	-
BV	[redacted]	3.58	-11,558	0.57	Dominant

ERG's cost effectiveness results – scenario analyses 3L+ pooled

Scenario	Arm	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case (3L+ pooled)	Pembro	[redacted]	4.13	-	-	-
	BV	[redacted]	3.54	-11,872	0.59	Dominant
ERG base case (3L+ pooled)	Pembro	[redacted]	3.92	-	-	-
	BV	[redacted]	3.52	-5,587	0.41	Dominant
Utility same in both arms in PD state (BV PD utility)	Pembro	[redacted]	3.95	-	-	-
	BV	[redacted]	3.54	-11,872	0.40	Dominant
Utility same in both arms in PF and PD state (BV PD and PF utilities)	Pembro	[redacted]	3.67	-	-	-
	BV	[redacted]	3.54	-11,872	0.13	Dominant
Waning of pembrolizumab PFS treatment effect	Pembro	[redacted]	4.11	-	-	-
	BV	[redacted]	3.54	-10,247	0.57	Dominant
OS KEYNOTE-087 data	Pembro	[redacted]	9.89	-	-	-
	BV	[redacted]	8.39	-7,854	1.51	Dominant
26-week cut-point for modelling ToT	Pembro	[redacted]	4.13	-	-	-
	BV	[redacted]	3.54	-4,241	0.59	Dominant
Subsequent treatment – pooled 3L+ KEYNOTE-204 data	Pembro	[redacted]	4.13	-	-	-
	BV	[redacted]	3.54	-24,924	0.59	Dominant
Combined PFS (generalised gamma) and OS KEYNOTE-204 data	Pembro	[redacted]	9.92	-	-	-
	BV	[redacted]	8.37	-13,750	1.56	Dominant

Abbreviations: QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PD – progressed disease; BV – brentuximab vedotin; OS – overall survival; PFS – progression-free survival; ToT – time on treatment

KEYNOTE-087

Trial design	Single arm, phase 2 trial; multi-national including 3 UK centres
Population	• Relapsed/refractory cHL • ≥18 years • ECOG status 0 or 1 • 3 cohorts: 1. Relapsed/refractory to autoSCT and subsequent BV (n=69) 2. Refractory to salvage chemotherapy (no autoSCT) and n=81 relapsed/refractory to subsequent BV 3. Relapsed/refractory to autoSCT and not received subsequent BV (n=60) *Cohort 3 relevant to decision problem (SCT+3L+ subgroup only)*
Intervention	**Pembrolizumab** 200mg IV every 3 weeks, for up to 35 cycles
Outcomes	• Safety and tolerability • Overall response rate • Complete remission rate • PFS • OS

Abbreviations: cHL - classical Hodgkin's lymphoma; IV - intravenous; SCT - stem cell transplant; PFS - progression-free survival; OS - overall survival

KEYNOTE-051

Trial design	Single arm, phase 1-2 trial; multi-national including UK centres
Population	• Various solid tumours or relapsed/refractory HL • 6 months to 18 years • Relapsed/refractory HL
Intervention	**Pembrolizumab** 2mg/kg IV every 3 weeks
Outcomes	• Safety and tolerability • Overall response rate • PFS • OS

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Abbreviations: cHL, classical Hodgkin's lymphoma; IV, intravenous; SCT, stem cell transplant; PFS, progression-free survival; OS, overall survival

KEYNOTE-204 3L+ subgroup: response rate

Overall response based on BICR		
	Pembrolizumab [redacted]	BV [redacted]
Number with objective response (%; 95% CI)	[redacted]	[redacted]
Number of complete responders (%; 95% CI)	[redacted]	[redacted]
Number of partial responders (%; 95% CI)	[redacted]	[redacted]
Overall response based on investigator review		
	Pembrolizumab [redacted]	BV [redacted]
Number with objective response (%; 95% CI)	[redacted]	[redacted]
Number of complete responders (%; 95% CI)	[redacted]	[redacted]
Number of partial responders (%; 95% CI)	[redacted]	[redacted]

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Pembrolizumab increases response rate compared with BV

Abbreviations: BICR, blinded independent central review; BV, brentuximab vedotin; CI, confidence interval

Uncertainty in the maintenance of PFS benefit after treatment discontinuation (1)

Background

- Company base case assumed after 2 year treatment discontinuation, PFS benefit for pembrolizumab would be maintained (efficacy did not diminish after stopping treatment)

ERG comments

- There is uncertainty around maintenance of pembrolizumab PFS benefit
- Due to conservative approach to OS, treatment waning not included in ERG base case
- Scenario analysis:
  - applying a waning in pembrolizumab PFS treatment effect at year 3, until no difference in hazard assumed by year 5
  - explores uncertainty around assumption of continued PFS treatment effect
  - minimal impact on ICER

Company comments

- Response rates to checkpoint inhibitors (i.e. pembrolizumab) uniquely high in cHL due to overexpression of PD-L1/PD-L2 – results in more durable PFS
- No clinical rationale for using waning approach

Clinical expert comments

- Likely a modest increase in relapse rate after treatment stopped – pembrolizumab doesn't cure
- Expect residual disease to start progressing when drug stopped

Abbreviations: PFS – progression-free survival; OS – overall survival; ICER – incremental cost-effectiveness ratio

Uncertainty in the maintenance of PFS benefit after treatment discontinuation (2)

Company comments

- Response rates to checkpoint inhibitors (i.e. pembrolizumab) uniquely high in cHL due to overexpression of PD-L1/PD-L2 – results in more durable PFS
- No clinical rationale for using waning approach

KEYNOTE-204 Duration of response based on BICR in subjects with response (ITT)

Company evidence of durable PFS benefit:

- KEYNOTE-204: duration of response 20.7 months (pembrolizumab) vs 13.8 months (BV)
- KEYNOTE-087: PFS at 24 months is [redacted] there is a plateau of PFS starting before 3 years
- KEYNOTE-013: pembrolizumab achieved sustained effect in PFS for at least 4 years in cHL patients who failed BV
- Checkmate-205 (nivolumab, single arm trial): median observation time 43 months, reports 48 month PFS estimate of 24.4%

Abbreviations: cHL – classical Hodgkin lymphoma; PFS – progression-free survival; BICR – blinded independent central review; ITT – intention to treat; KM – Kaplan Meier; BV – brentuximab vedotin

Uncertainty in the maintenance of PFS benefit after treatment discontinuation (3)

Treating waning in previous appraisals:

- 3-5 year treatment waning accepted in NSCLC (TA655 and TA428)
- Not used in cHL appraisals for pembrolizumab, nivolumab or BV
- Only used for OS (used for PFS here)

- TA655 (nivolumab in NSCLC):
  - committee conclusion: if nivolumab offered for 2 years of uninterrupted treatment, likely that survival benefit (OS) would continue for 3+ years after it was stopped; lifetime benefit after 2 years treatment optimistic
- TA428 (pembrolizumab in NSCLC):
  - committee conclusion: evidence to support continued benefit for pembrolizumab after stopping treatment, size of effect and its duration unknown; lifetime treatment effect implausible but could not agree a single clinically plausible scenario

Clinical expert comments:

- Likely a modest increase in relapse rate after treatment stopped – pembrolizumab doesn't cure
- Expect residual disease to start progressing when drug stopped

- **Is it appropriate to include treatment waning in the model?**

Abbreviations :NSCLC – non-small-cell lung cancer; cHL – classical Hodgkin lymphoma; BV – brentuximab vedotin; OS – overall survival; PFS – progression-free survival

Time on treatment for BV (1)

Background

- Company updated base case at technical engagement to model costs for maximum 16 doses BV (in KEYNOTE-204 people could have BV up to 35 cycles)
- BV SmPC specifies 16 cycles max
- Company base case estimated ToT using KM data and extrapolation from a cut-point of 80-weeks

Clinical expert comments:

- BV is licenced and funded for up to 16 cycles
- SCT-3L+:
  - if fit for transplant, typically 4 to 8 cycles given
  - if unfit for transplant, given until progression or toxicity; typically ~8 cycles
- SCT+3L+:
  - most being bridged to allogenic SCT; typically 6-8 cycles given

Abbreviations: BV – brentuximab vedotin; SmPC – summary of product characteristics; ToT – time on treatment; KM – Kaplan Meier;

Time on treatment for BV (2)

ERG base case:
- 16 cycles of BV
- ToT estimated using 26-week KM cut point for extrapolation from 3L+ subgroup (consistent with ERG's PFS modelling approach)

ERG scenario analysis – explored impact of alternative ToT assumptions:
- using KM data from KEYNOTE-204 only (no impact on ICER)
- using alternative ToT distributions (log-normal parametric fit) (no impact on ICER)

Company comments
- Assuming 16 cycles of BV is conservative - affects costs in favour of BV but doesn't change benefits from more doses used in KEYNOTE-204
- > 16 cycles of BV tolerated and accrued clinical benefit not adjusted for by ERG:
  - 3L+ population: [redacted] patients in BV arm received > 16 cycles
  - ITT population, [redacted] who received >16 cycles maintained or achieved partial or complete remission after cycle 16; limited severe toxicity: [redacted] patients reported 1 AE equal to grade 3 or higher during extended treatment

- **Is max 16 cycles of BV a conservative assumption?**
- **Which time on treatment extrapolation cut-point is most appropriate?**

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Abbreviations: BV – brentuximab vedotin; ToT – time on treatment; KM – Kaplan Meier; PFS – progression-free survival; ITT – intention to treat; AE – adverse event