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Lead team presentation
Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (ID1062)

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

Lead team: Adrian Griffin, David Evans, Mohit Sharma

ERG: Kleijnen Systematic Reviews

NICE technical team: Thomas Walker, Rebecca Albrow

5 December 2017

Key issues: Clinical management and effectiveness

- Is TA462 (Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma) relevant for this appraisal? (Does not include subgroup of patients who have not had stem cell transplant: cohort 2)
- How long would pembrolizumab treatment be continued in clinical practice?
- Does the population in the comparator study (Cheah et al. 2016) adequately represent the UK clinical population?
- How well does the population in Cheah et al. (2016) match cohorts 1 and 2 from KEYNOTE-087 (i.e. with and without previous autoSCT)?
- Is it more appropriate to use a naïve indirect comparison or matched adjusted indirect treatment comparison (MAIC) to compare KEYNOTE-087 and Cheah et al. (2016) data?

Hodgkin lymphoma

- A malignancy of the lymphoreticular system; mostly in lymph node tissues, spleen, liver, and bone marrow
- 2 subgroups: classical Hodgkin lymphoma (cHL; ~95% cases) and nodular lymphocyte predominant Hodgkin lymphoma
- 2,106 new cases of Hodgkin lymphoma in the UK in 2014 (3.3 per 100,000 people)
- Bimodal distribution of cases: first peak at 20 to 24 years, second at 75 to 79 years. ~50% cases in people 45 years and over
- Presence of 'B symptoms' (fever, weight loss, night sweats) associated with advanced condition
- 1 year survival 91%; 5 year survival 85%; 10 year survival 80%
  - However population considered for this assessment likely to have poorer prognosis compared to people who have responded to therapy
  - Retrospective trial of people with relapsed or refractory disease (n=81) cited in company submission reported 5 year survival of less than 20%

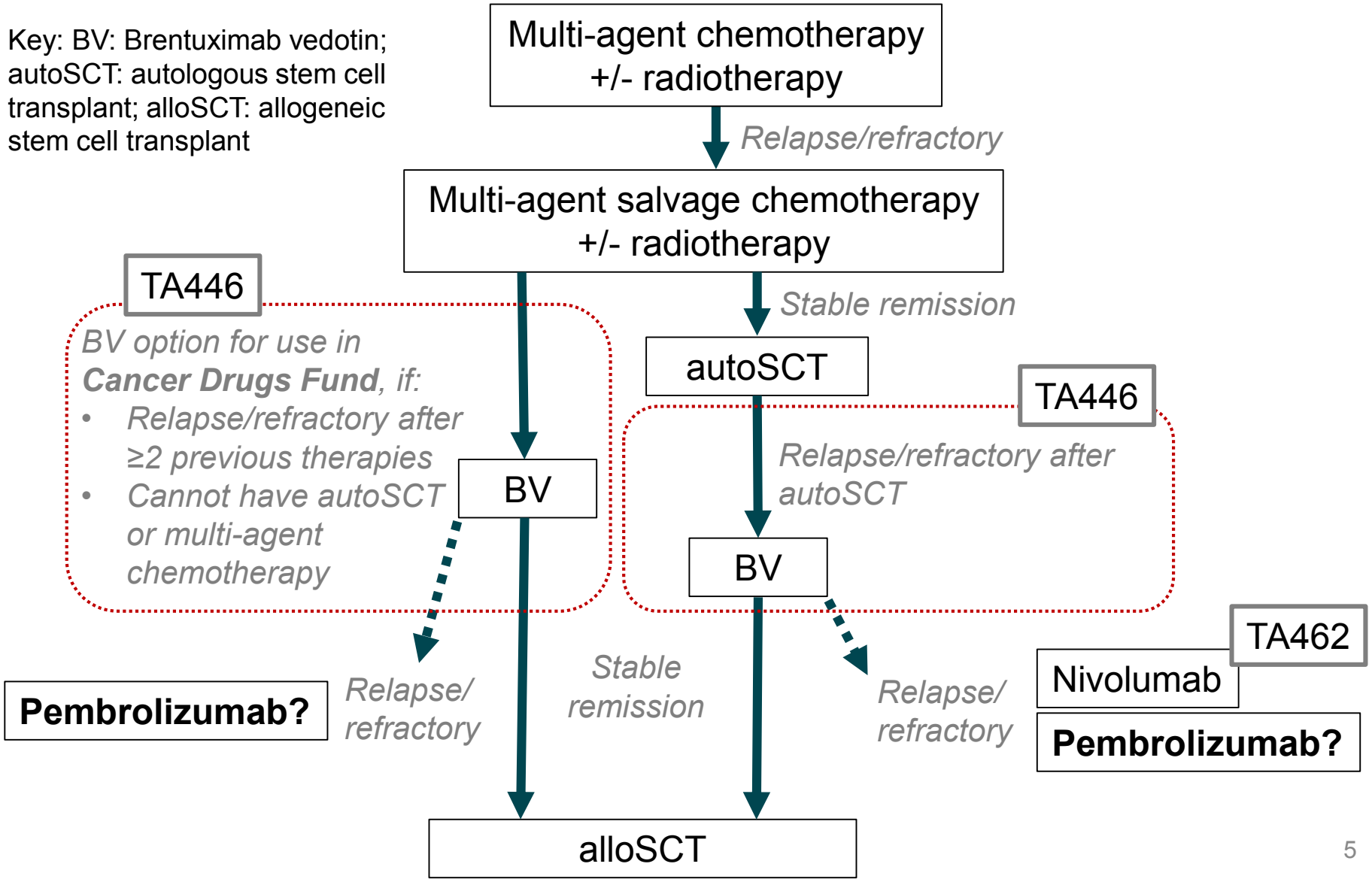
Pembrolizumab

Mechanism of action	Humanised monoclonal antibody that blocks PD-1 to promote anti-tumour response
Marketing authorisation	Indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autoSCT and BV, or who are transplant-ineligible and have failed BV
Administration and dose	Intravenous infusion • Induction dose: 200mg • 200mg every 3 weeks until disease progression or unacceptable toxicity
Cost	List price £2,630 (100mg vial) Company has agreed a commercial access agreement (CAA) with the Department of Health

BV: Brentuximab vedotin; autoSCT: autologous stem cell transplant

Treatment pathway

Key: BV: Brentuximab vedotin; autoSCT: autologous stem cell transplant; alloSCT: allogeneic stem cell transplant



Patient and professional feedback

- Areas of unmet need:
  - People who don't have a good enough remission from initial lines of therapy to proceed to autoSCT
  - Older people who are not fit enough for autoSCT or alloSCT
- Pembrolizumab has a wider licence for use than nivolumab; allowing use in people who have had BV but who can't have autoSCT
- In UK, most patients with a durable remission are moved on to potentially curative treatment (usually alloSCT); will not need prolonged pembrolizumab use

From patient feedback for TA462:

- Patients with relapsed or refractory classical Hodgkin Lymphoma (RRcHL) have symptoms which can be debilitating and distressing
- Patients have to choose between treatments that may have little success or many side effects, or palliative care and short life expectancy
- Many patients are young and fit with the potential for a long and active life if they can undergo transplant
- Patients and carers would like to see a cure, or strong, durable remission, and treatments with lower toxicity profiles or reduced/manageable side effects

Decision problem

	NICE scope	Company submission	ERG's comments
Population	People with RRcHL who have received: • autoSCT and BV • BV when autoSCT is not a treatment option	As per NICE scope	-
Comparators	Single or combination chemotherapy including drugs such as gemcitabine, vinblastine and cisplatin Best supportive care (BSC)	Standard of care as per Cheah et al. (2016) BSC assessed as a subsequent therapy in base case and as a comparator in a scenario analysis	Cheah et al. includes multiple comparators – some of which are within scope, others are not. Broadly matches comparator in NICE scope. This study was used to provide comparator data in TA462. ERG not aware of a more appropriate data source for SOC comparator
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per NICE scope; except no long term overall survival data	Mostly in-line with final scope. However survival data is immature and only 2 outcomes (progression-free survival and overall response) have been included in indirect comparisons

Company's clinical evidence
KEYNOTE-087

	KEYNOTE-087	
Design	Phase II single arm, open label trial	
Population	Adults with RRcHL after:	
	Cohort 1 (n=69; 4 from UK):	autoSCT and BV (post-autoSCT)
	Cohort 2 (n=81; 10 from UK)	Salvage chemotherapy and BV (no autoSCT)
Setting	51 study sites: 26 Europe (3 in UK), 11 US, 7 Japan, 4 Israel, 2 Australia, 1 Canada.	
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 includes: ORR (investigator assessment), progression-free survival, duration of response and overall survival	

Company's clinical evidence

KEYNOTE-087: Response rates

	Response at week 12		Best overall response (at March 2017)	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
Complete remission (n)	[redacted]	[redacted]	27.5% (19)	24.7% (20)
Partial remission (n)	[redacted]	[redacted]	47.8% (33)	42.0% (34)
Objective response [complete remission + partial remission] (n)	[redacted]	[redacted]	75.4% (52)	66.7% (54)
Stable disease (n)	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease (n)	[redacted]	[redacted]	[redacted]	[redacted]
No assessment	[redacted]	[redacted]	[redacted]	[redacted]
Median time to response (range)			[redacted]	[redacted]

Company's clinical evidence

KEYNOTE-087: Progression-free survival total treatment period

Cohort 1

Cohort 2

Company's clinical evidence

KEYNOTE-087: Overall survival

	Cohort 1	Cohort 2
Overall survival (median)	[redacted]	[redacted]
Overall survival at 6 months	[redacted]	[redacted]
Overall survival at 12 months	[redacted]	[redacted]
Overall survival at 18 months	[redacted]	[redacted]

Company's clinical evidence
ERG's comments

- [redacted]
- Although KEYNOTE-087 was well conducted, it is low-level evidence by design (non-comparative and open-label)
- Size of population small (n=150; 14 from UK) – but available population matching scope for assessment is small; conducting a larger trial challenging
- People over 65 years underrepresented in trial
  - All participants in cohort 1 and 85.1% in cohort 2 were under 65 years
- [redacted] in cohort 1 and [redacted] in cohort 2 had 5 or more prior therapies before pembrolizumab and could be more heavily treated than typical in UK practice
- Adequate follow-up for main outcome (overall response rates); but progression-free and overall survival data are not fully mature

Company's clinical evidence

Indirect treatment comparison with SOC (Cheah et al. 2016)

- No data providing direct comparison between pembrolizumab and comparator
- Single study (Cheah et al. 2016) considered relevant to the decision problem – used in naïve indirect comparison and matched adjusted indirect treatment comparison (MAIC)

Cheah et al. (2016)

- Retrospective observational study from the US (2007 to 2015)
- Included participants who had:
  - BV treatment for relapsed Hodgkin lymphoma
  - Disease progression at any time after BV treatment
- Before having BV treatment:
  - ~70% had previous stem cell transplant (66 autoSCT; 4 alloSCT),
  - ~30% had no stem cell transplant

Key: BV: Brentuximab vedotin; autoSCT: autologous stem cell transplant; alloSCT: allogeneic stem cell transplant

Company's clinical evidence

Indirect treatment comparison with SOC (Cheah et al. 2016)

ERG's comments

- Committee for TA462 accepted Cheah et al. (2016) as appropriate comparator study for people with RRcHL who have had autoSCT and BV (equivalent to cohort 1 in this assessment)
- Cheah et al. population is a mixture of cohorts 1 and 2; population most comparable to cohort 1 (~70% had autoSCT)
- Separate cohort analysis (corresponding to cohorts 1 and 2 from KEYNOTE-087) from Cheah et al. not provided
- Using whole population data from Cheah et al. likely to overestimate pembrolizumab effect in cohort 1 and underestimate effect in cohort 2 in a naïve comparison (based on observed KEYNOTE-087 results between cohorts)

Company's clinical evidence

Indirect comparison: **Progression-free survival**

Cohort	Comparison	Hazard ratio (95% CI) Pembrolizumab (KEYNOTE-087) versus SOC (Cheah)	
		From study initiation to week 12	From study initiation to most recent observation
1	Naïve	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]
2	Naïve	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]

MAIC: Matched adjusted indirect treatment comparison; SOC: Standard of care

- Hazard ratio for cohort 1 more favourable to pembrolizumab in the MAIC

ERG comments

- Almost all PFS results show significant benefit for pembrolizumab versus SOC
- One exception: naïve comparison in cohort 1 at week 12 – non-significant difference favouring pembrolizumab

Company's clinical evidence

Indirect comparison: **Objective response rate (ORR)**

Cohort	Comparison	Odds ratio (95% CI) Pembrolizumab (KEYNOTE-087) versus SOC (Cheah)	
		Response at week 12 (KEYNOTE-087) versus best overall response (Cheah et al.)	**Best overall response**
1	Naïve	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]
2	Naïve	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]

MAIC: Matched adjusted indirect treatment comparison; SOC: Standard of care

- MAIC increases odds ratio (relative to naïve comparison)

ERG comment

- All results for ORR significantly favour pembrolizumab over SOC

ERG's comments
Indirect comparisons (KEYNOTE-087 and Cheah et al.)

- Baseline characteristics and methods of outcome assessment differ between KEYNOTE-087 and Cheah; MAIC does try to match populations
- Full Cheah population as comparator for cohort 1 probably acceptable
- Full Cheah population as comparator for cohort 2 problematic:
  - Only 28% participants did not have stem cell transplant
  - Population differences in age, ECOG scores, B symptoms, Haemoglobin, Lymphocytes, Albumin, White cell count and Bulky Lymphadenopathy
- MAIC based on Cheah et al. population characteristics – may not represent UK population
- Naïve indirect comparison based on 2 different populations and study designs (prospective and retrospective)
- MAIC likely to include systematic error
  - Reliant on variables reported in Cheah et al; unlikely to be all relevant prognostic variables and effect modifiers
- Major limitations for both naïve and MAIC analyses; neither fully reliable for decision making

Company's clinical evidence

Adverse events: KEYNOTE-087

	Cohort 1 (n=69)	Cohort 2 (n=81)
1 or more adverse events (n)	[redacted]	[redacted]
Drug related adverse event* (n)	[redacted]	[redacted]
Toxicity grade 3-5 adverse event (n)	[redacted]	[redacted]
Toxicity grade 3-5 drug-related adverse events (n)	[redacted]	[redacted]
Non-serious adverse events (n)	[redacted]	[redacted]
Serious adverse events (n)	[redacted]	[redacted]
Serious drug-related adverse events (n)	[redacted]	[redacted]
Discontinued due to an adverse event (n)	[redacted]	[redacted]
Discontinued due to drug related adverse event (n)	[redacted]	[redacted]
Discontinued due to a serious drug-related adverse event (n)	[redacted]	[redacted]

* Determined by investigator to be related to the drug

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