Slides for committee, public and projector

Lead team presentation Avelumab for metastatic Merkel cell carcinoma – STA

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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ERG: BMJ Technology Assessment Group

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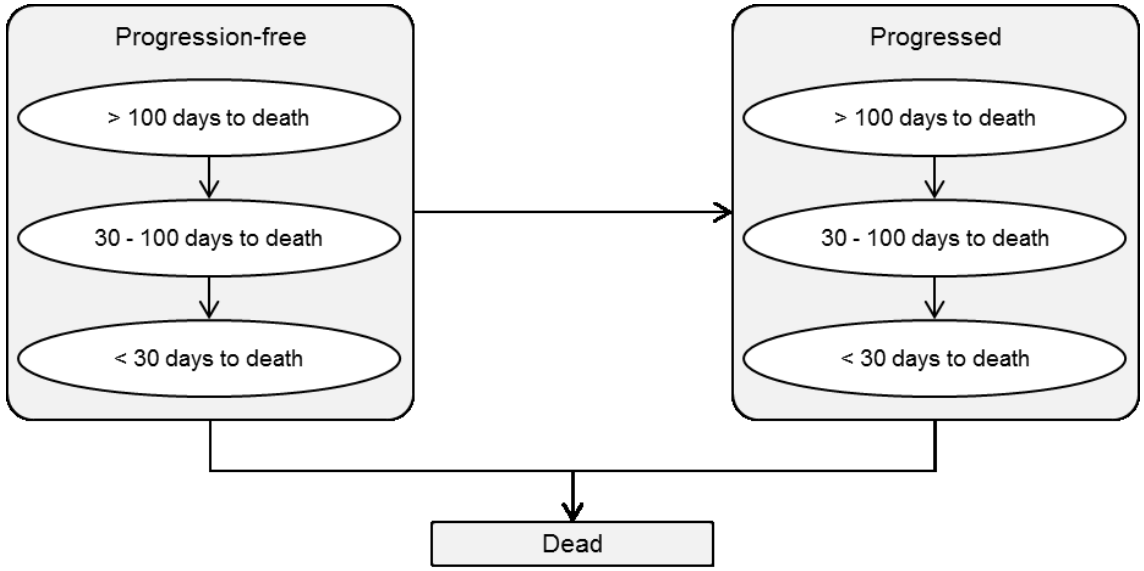
2nd November 2017

Key cost issues for consideration

- Does avelumab meet the end-of life criteria?
- The company has assumed that 2/3 of patients discontinue treatment after 2 years, and that everyone has stopped treatment by 5 years. Is this reasonable?
- The company has used a mix of splines and parametric models to extrapolate PFS and OS estimates from JAVELIN in the treatment-experienced population, and clinical opinion to estimate PFS and OS in the treatment-naive population (rather than using the JAVELIN data in this population directly). Is this reasonable?

Model structure

- Partitioned-survival model.
- 3 mutually exclusive health states: PFS, PD, death.
- 3 sub-states in PFS and PD to incorporate time to death: >100 days to death; 30-100 days until death; <than 30 days until death.
- 2 separate populations: treatment-experienced (2L+), treatment-naïve (1L).
- Time horizon: 40 years; cycle length: 7 days.



- ERG considers the time to death approach reasonable.

PFS and OS estimates

- **Avelumab**
  - 2L+ PFS and OS: JAVELIN data (censored at 18 months for PFS), extrapolated using spline-based models.
  - 1L OS: hazard ratios from 2L+ multiplied by hazard ratio (0.8) elicited from clinical opinion.
  - 1L PFS: assumed same as 2L+ PFS.

- **BSC**
  - Assumed equivalent to chemotherapy.
  - Pooled data from observational studies.

    2L+: EU/US observational studies conducted by company.

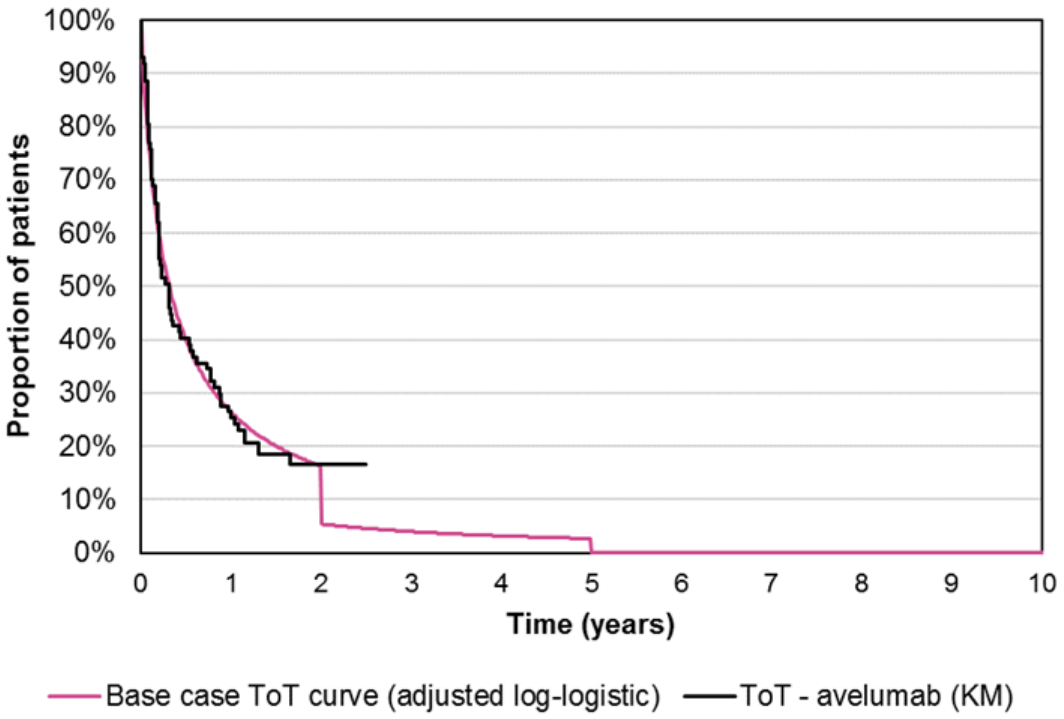
    1L: 1 US observational study conducted by company, and 6 other studies identified by literature review.
  - Extrapolation using parametric models.

ERG critique on OS and PFS estimates

- Unadjusted (non-randomised) comparison of data from JAVELIN and observational studies.
- Spline-based vs parametric models for extrapolation.
- Hazard Ratio for 1L vs 2L+ groups based on clinical opinion rather than data. Requires proportional hazards assumption.
- Inclusion of 6 observational studies from literature review when estimating PFS and OS for 1L BSC.

Treatment discontinuation

- **Avelumab**
  - 2L+: JAVELIN data, 2/3 patients stop treatment after 2 years, remainder extrapolated to 5 years using log-logistic curve, then stop.
  - 1L: assumed same as 2L+.



- **Chemotherapy:**
  2L+ and 1L: max. 6 cycles with a relative dose intensity of 2/3.

ERG critique on treatment discontinuation

- Company's approach is flawed.
- Very strong assumption about discontinuation at 2 years.
- A "morally difficult decision" to withdraw treatment from patients who are still receiving benefit.
- Implausible assumption that time on treatment equivalent for both 1L and 2L+. Will underestimate treatment costs in 1L.
- Weibull function without truncation gives a plausible extrapolation in both 1L and 2L+.

Health-related quality of life

- EQ-5D-5L from JAVELIN mapped to EQ-5D-3L (van Hout 2012 algorithm*).
- Regression analysis to identify utility values for 3 periods before death.
- Utilities implicitly include effect of treatment-related AEs.

Health state	Utility value
>100 days to death	0.7744
30-100 days to death	0.7540
<30 days to death	0.7082

- ERG commented that baseline utility (0.823) was higher than expected, but differences in utilities between health states are plausible.

*In line with NICE position statement on EQ-5D-5L

Costs

- Costs for drug acquisition, administration and medical resource use, and managing of adverse events (same for 2L+ and 1L cohorts).
- Avelumab
  - Dose is weight-based; weight data for European patients (JAVELIN Merkel 200 – Part B) used in base-case drug dosing calculations.
  - ERG notes that cost of premedication with an antihistamine and with paracetamol were omitted (added as part of ERG's scenario analysis).
- Comparators
  - BSC is associated with no cost.
  - Chemotherapy regimen cost weighted by market share of chemotherapy regimen (50/50 split of carboplatin and etoposide/cisplatin and etoposide regimens).
- End-of-life costs taken from literature.

Company's base case results

2L+ cohort

Treatment	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
BSC	£7,465	0.31	-	-	-
Avelumab	£78,752	2.22	£71,287	1.91	**£37,350**

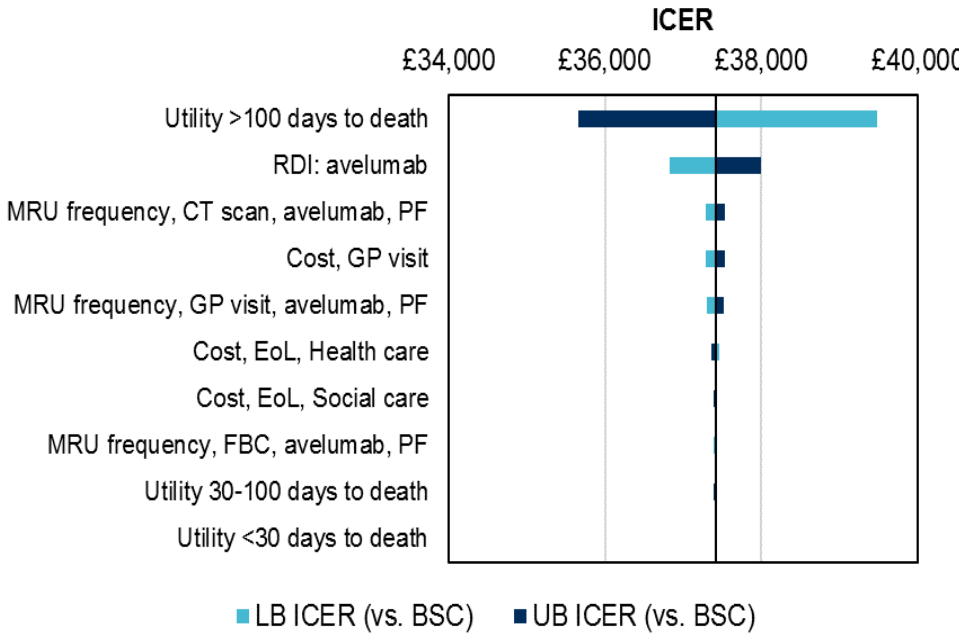
1L cohort

Treatment	Total		Incremental		ICER incremental	ICER pairwise *(avelumab vs.)*
	Costs	QALYs	Costs	QALYs		
BSC	£7,217	1.38	-	-	-	**£46,148**
Chemo.	£10,608	1.37	£3,392	-0.01	Dominated	**£43,553**
Avelumab	£78,588	2.93	£71,371	1.55	**£46,148**	-

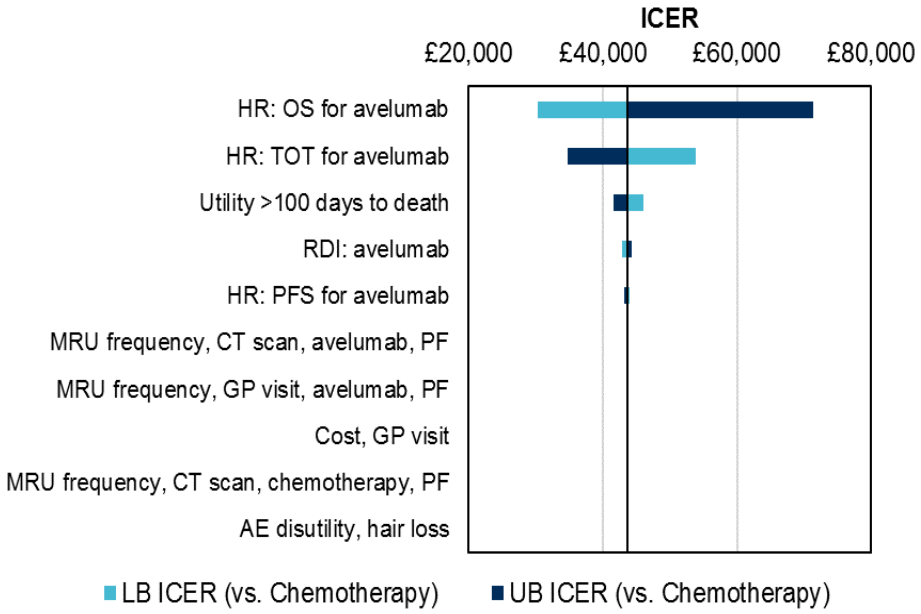
Deterministic results presented. ICERs from probabilistic analysis are similar.

One-way sensitivity analysis

2L+ cohort



1L cohort



RDI: relative dose intensity

ERG base case – 2L+

	Avelumab	BSC	Avelumab vs BSC
Company base case			
Costs	78,752	7,465	71,287
QALYs	2.22	0.31	1.91
ICER			**37,350**
1. Weibull curve for time on treatment (without truncation)			
Costs	92,557	7,465	85,091
QALYs	2.22	0.31	1.91
ICER			**44,584**
2. Weibull curves for PFS and OS in BSC (also includes change 1)			
Costs	£92,537	7,413	85,124
QALYs	2.22	0.32	1.90
ICER (including 1 and 2)			**44,857**
ERG base case (includes changes 1, 2 and additional pre-medication costs)			
Costs	92,644	7,413	85,232
QALYs	2.22	0.32	1.90
ICER			**44,914**

ERG base case – 1L

	Avelumab	Chemotherapy	BSC	Ave vs chemo	Ave vs BSC
Company base case					
Costs	78,588	10,608	7,217	67,979	71,371
QALYs	2.93	1.37	1.38	1.56	1.55
ICER				**43,553**	**46,148**
1. Removal of truncation to time on treatment curve					
Costs	141,523	10,608	7,217	130,915	134,306
QALYs	2.93	1.37	1.38	1.56	1.55
ICER				**83,882**	**86,851**
2. Weibull regression models for PFS and OS (also including change 1)					
Costs	159,375	10,608	7,217	148,766	152,158
QALYs	2.65	1.37	1.38	1.28	1.27
ICER				**116,235**	**120,228**
ERG base case ICER (includes changes 1, 2 and additional pre-medication costs)					
Costs	159,570	10,608	7,217	148,962	152,353
QALYs	2.65	1.37	1.38	1.28	1.27
ICER				**116,388**	**120,383**

End-of-life

Criterion		
Treatment is indicated for patients with a short life expectancy, normally < 24 months	1L	Meta-analysis: median 11.8 months, mean 24.3 months.
	2L+	Meta-analysis: median 4.6-5.1 months, mean 5.1-5.5 months
Treatment has the prospect of offering an extension to life, **normally** of a mean value of ≥ 3 months, compared with current NHS treatment	1L	Difference in modelled mean OS: 33.1 months
	2L+	Difference in modelled mean OS: 37.3 months

- ERG considered that end of life criteria were met, despite great uncertainty in results of economic model.

Equality issues

- No equality issues

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Back-up slides

Company's scenario analysis for 2L+ cohort

Requested by ERG at clarification

- Using propensity score: the ICER reduced from £37,409 (company's original base-case without the ERG correction) to £33,796

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Avelumab	£78,051	3.87	2.44	-	-	-	-
BSC	£7,319	0.41	0.31				£33,796

- Using Weibull regression analysis: the results demonstrate an increase in the ICER of approximately £235 versus the company's original base-case (without the ERG correction) .

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Avelumab	£78,218	3.53	2.22	-	-	-	-
BSC	£7,279	0.43	0.32				£37,645

Company's scenario analysis for 1L cohort

Requested by ERG at clarification

Results from fitting different models to the KM curves

Description of scenario	ICER
Company's original base case (without ERG correction) (HR applied to data from JAVELIN Merkel 200 – Part A)	**£43,633**
Same parametric model for each outcome (log-normal for OS, PFS and ToT)	£51,312
Splines for OS and PFS (spline 1-knot hazard for OS, PFS, log-normal for ToT)	£46,978
Most plausible parametric estimates (log-normal for OS, PFS, Weibull for ToT)	£42,935
Most plausible overall estimates (spline 1-knot hazard for OS, PFS, Weibull for ToT)	£39,409

HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Note: Plausibility of estimates were established based on long-term outcomes and comparison to clinical expectation (e.g. low number of patients on treatment at 5 years, immune-response tail in OS etc.)