Avelumab for treating metastatic Merkel cell carcinoma (CDF review of TA517)

Cancer Drugs Fund Review Addendum

December 2020

Source of funding

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1 Introduction

The Evidence Review Group (ERG) has provided an addendum to the ERG report for the Cancer Drugs Fund (CDF) review of avelumab for treating metastatic Merkel cell carcinoma (TA517) as the company has provided an addendum to their submission, which includes revised base case results with a patient access scheme (PAS) discount of [redacted] on the list price of avelumab applied.

Section 2 of the addendum provides the company's base case results, sensitivity and scenario analyses with the PAS discount applied and Section 3 presents the ERG's scenarios and base-case, also inclusive of the PAS discount. All the results in the addendum supersede results presented in the ERG report, which are based on the list price of avelumab.

2 Company base case results with PAS

The company's base case results, with the [redacted] patient access scheme (PAS) discount applied, are presented in Table 1, showing an incremental cost-effectiveness ratio (ICER) of £17,947 per quality-adjusted life-year (QALY) gained for avelumab compared to chemotherapy.

Table 1. Company's deterministic cost effectiveness results (Table 1 of the company's Results addendum with PAS)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy	11,116	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,947

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

2.1 Company sensitivity analysis

The company provided a probabilistic sensitivity analysis (PSA) based on 1,000 samples, to assess the impact of parameter when all parameters are varied simultaneously in the economic model. The results of the PSA are given in Table 2, showing a slightly decreased ICER of £17,939 per QALY compared to the deterministic base case ICER. The results of all 1,000 sampled results are presented on the cost effectiveness plane in Figure 1.

Table 2. Company's probabilistic cost effectiveness results (Table 2 of the company's Results addendum with PAS)

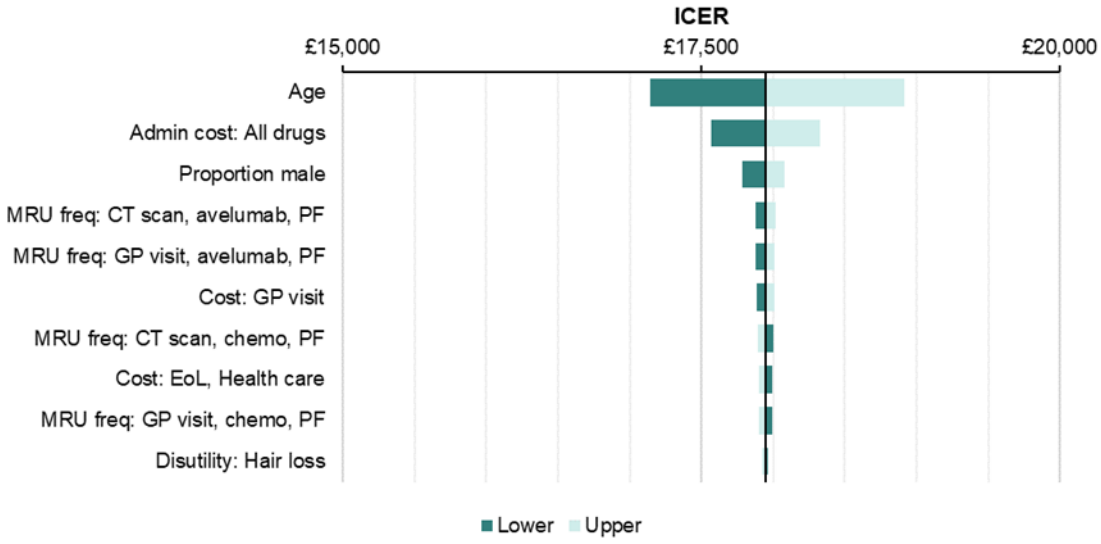
Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	1.95	1.33	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,939

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Figure 1. Scatterplot of probabilistic results, with PAS (Figure 1 of the company's Results addendum with PAS)

The company also conducted a range of one-way sensitivity analyses to assess the impact of varying each parameter individually. The results of these are shown in the tornado plot in Figure 2.

Figure 2. One-way sensitivity analyses, with PAS (Figure of the company's Results addendum with PAS)



2.1.1 Company's scenario analyses

The company presented a range of scenario analyses in the company submission using alternative approaches for overall survival (OS), time on treatment (ToT) and utility values. These scenarios are described alongside the results in Table 3.

Table 3. Company's key scenario analyses (Table 3 of the company's Results addendum with PAS)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (£) (+/- from base case)
Base case			**17,947**
OS for avelumab	Use generalised gamma model to estimate OS for patients treated with avelumab	This scenario explores the use of a model (generalised gamma) which projects higher OS versus the base-case analysis	17,363 (-584)
	Use 1-knot normal spline-based model to estimate OS for patients treated with avelumab	This scenario explores the use of a model (1-knot normal spline) which projects lower OS versus the base-case analysis	19,276 (+1,329)
Clinical expectation of ToT	Assume all patients discontinued by 10 years, with no interim capping at 2 years	Approach intended to serve as an upper bound of potential long-term treatment with avelumab. In practice, discontinuation with avelumab is expected to occur before 5 years	18,895 (+948)
	Assume one-third of patients continue treatment after 2 years, and all discontinue by 5 years	Approach aligned with clinical expert opinion at the time of the original TA517 CS, and is still expected to be broadly representative of clinical practice	15,278 (-2,671)
Utility values	Use original utility values from TA517	Allows for assessment of impact on cost-effectiveness results through updating utility values	18,655 (+708)
	Use only data from JM200: Part B to inform utility values (28 & 84 cut off points)	Allows exploration of using utility values derived only from a treatment-naïve metastatic MCC population	18,395 (+448)

Abbreviations: BSC, best supportive care; CS, company submission; ICER, incremental cost-effectiveness ratio; JM200, JAVELIN Merkel 200; OS, overall survival.

In response to the ERG clarification questions, the company also provided the following range of additional analyses:

- Range of propensity score matching (PSM) and propensity score weighting (PSW) analyses for PFS and OS (Table 4);
- Immunocompetent subgroup analysis (Table 5); and,
- A range of scenarios to include subsequent treatments (Table 6).

Table 4. Scenario analyses with alternative adjusted OS and PFS analyses

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Company's base-case analysis							
Chemotherapy	11,116	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,947
PSW, all patients (stable weights), using age, sex, ECOG (0 vs 1+), excluding immunosuppression as a variable							
Chemotherapy	11,947	2.19	1.49	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,135
PSW, all patients (stable weights), using age, sex, ECOG (0 vs 1), excluding immunosuppression as a variable and removing ECOG 2+ pts							
Chemotherapy	12,022	2.20	1.50	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,352
PSM using age, sex, ECOG (0 vs 1+), excluding immunosuppression as a variable							
Chemotherapy	11,481	1.85	1.27	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,269
PSM using age, sex, ECOG (0 vs 1), excluding immunosuppression as a variable and removing ECOG 2+ pts							
Chemotherapy	11,559	1.92	1.31	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,797

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSM, propensity score matched; PSW, propensity score weighted; QALYs, quality-adjusted life years.

Table 5. Scenario analyses with alternative subgroup OS and PFS analysis

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Company's base-case analysis							
Chemotherapy	11,116	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,947
Analysis using only the immunocompetent subgroup							
Chemotherapy	11,499	1.83	1.25	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,225

Abbreviations: CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 6. Scenario analyses with alternative subsequent treatment approaches applied

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Company's base-case analysis							
Chemotherapy	11,116	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,947
Include all subsequent therapies as per study sources							
Chemotherapy	11,374	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,474
Update topotecan costs to standard chemotherapy cost							
Chemotherapy	11,249	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,527
Remove monoclonal antibodies and update topotecan costs							
Chemotherapy	11,249	1.94	1.32	-	-	-	-
Avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,966

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

3 ERG preferred analysis

3.1 Exploratory and sensitivity analyses undertaken by the ERG

The Evidence Review Group (ERG) conducted a range of scenario analyses to assess the impact of different assumptions applied for overall survival (OS), progression-free survival (PFS) and time on treatment (ToT) in terms of the best fitting curves as well as the assumption of weight-based dosing. The ERG also explored the impact of using the SACT data to inform OS and TTD, as well as using the TTD data as a proxy to inform PFS. The ERG applied the curves described in Section **Error! Reference source not found.** of the ERG report for OS, PFS, and TTD, individually, and then applied all changes in a combined scenario analysis. The results are presented in Table 7.

Table 7. Results of the ERG's scenario analyses

	Results per patient	Avelumab	Chemotherapy	Incremental value
0	**Company base case**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**17,947**
1	**Weight-based dosing for avelumab acquisition costs**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**18,938**
2	**OS: 1-knot hazard spline**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**20,097**
3	**PFS: 3-knot odds spline**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**17,852**

4	**ToT: 3-knot hazard spline**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**18,290**
5	**ToT: No change to treatment-experienced data**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**19,332**
6	**OS: ERG's SACT OS curves applied**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**24,957**
7	**PFS: ERG's SACT TTD curves used as a proxy for PFS**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**18,243**
8	**ToT: ERG's SACT TTD curves applied**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**16,852**
9	**ERG's SACT curves applied for OS, PFS and TTD (Scenarios 6+7+8)**			
	Total costs (£)	[redacted]	11,116	[redacted]
	QALYs	[redacted]	1.32	[redacted]
	ICER			**23,485**

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time on treatment.

3.2 ERG preferred assumptions

The ERG's preferred base case includes the following changes compared to the company's base case analysis:

Scenario 2a. PSW analyses for OS and PFS with immunocompetency excluded from the estimation of propensity scores and patients with ECOG score 2 or more removed;

Scenario 3. 1-knot hazard spline for OS;

Scenario 4. 3-knot odds spline for PFS;

Scenario 5. 3-knot hazard spline for ToT;

Scenario 6. Removing the adjustment to the ToT curve using the treatment-experienced population data;

Scenario 7. Weight-based acquisition costs for avelumab in line with effectiveness data.

These changes resulted in an ICER of £21,958 per QALY for the ERG's preferred base case. The cumulative results as each change is applied are given in Table 8. NICE requested additional scenarios to be performed and these are also presented in Table 8.

Table 8. ERG's and NICE preferred model assumptions

	Scenario	Technical engagement Issue number	ICER (£/QALY)	Change from company base case ICER
0	**Company base case**	**-**	**17,947**	**-**
1	SACT dataset: ERG's curves for OS, PFS and ToT applied to SACT data (n=52) instead of the updated JAVELIN 1L data	1	23,485	+5,538
2a	Propensity score weighting (PSW): PSW analyses for OS and PFS using updated JAVELIN 1L data for avelumab (n=116) and company's part A 1L study for chemotherapy (n=67) instead of a naïve comparison. PSW4 (n=162) applied: with adjustments for age (aged ≥75 vs <75 years), sex	2	18,352	+405

	(female vs male), and ECOG PS (0 vs 1).			
2b	Using only immunocompetent patients in the company's part A 1L study (n=51) for OS and PFS instead of the pooled naïve estimate for chemotherapy.	2	17,225	-722
3	Using 1-knot hazard spline for OS instead of 1-knot odds spline for JAVELIN 1L data	3	20,097	+2,150
4	Using 3-knot odds spline for PFS instead of 2-knot odds spline for JAVELIN 1L data	4	17,852	-95
5	Using 3-knot hazard spline for ToT instead of Weibull for JAVELIN 1L data	5	18,290	+343
6	Removing the adjustment to the ToT curve using the JAVELIN 2L+ data	5	19,332	+1,385
7	Weight-based avelumab dose instead of flat dose of 800 mg	6	18,938	+991
8	**Cumulative changes with PSW4: 2a + 3 to 6 (flat dose)**	**-**	**20,780**	**+2,833**
9	**Cumulative changes with PSW4: 2a + 3 to 7 (weight-base dose) - ERG's base case ICER**	**-**	**21,958**	**+4,011**
10	**Cumulative changes with immunocompetent group: 2b + 3 to 6 (flat dose)**	**-**	**19,832**	**+1,885**
11	**Cumulative changes with immunocompetent group: 2b + 3 to 7 (weight-base dose)**	**-**	**20,914**	**+2,967**
12	**Cumulative changes with SACT dataset: 1 + 2b (flat dose)**	**-**	**22,252**	**+4,305**
13	**Cumulative changes with SACT dataset: 1 + 2b + 7 (weight-base dose)**	**-**	**23,486**	**+5,539**

Abbreviations: 1L, first-line; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; mg, milligram; OS, overall survival; PFS, progression-free survival; PSW, propensity score weighting; QALY, quality adjusted life year; ToT, time on treatment.