THE LANCET Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol* 2016; published online Sept 1. http://dx.doi.org/10.1016/S1470-2045(16)30364-3.

This appendix is a supplement to: Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab, an anti-PD-L1 antibody, in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-arm, phase 2 study

The authors' full names and academic degrees are as follows: Howard L. Kaufman, MD, Jeffery Russell, MD, PhD Omid Hamid, MD, Shailender Bhatia, MD, Patrick Terheyden, MD, Sandra P. D'Angelo, MD, Kent C. Shih, MD, Céleste Lebbé, MD, Gerald P. Linette, MD, PhD, Michele Milella, MD, Isaac Brownell, MD, PhD, Karl D. Lewis, MD, Jochen H. Lorch, MD, Kevin Chin, MD, MS, Lisa Mahnke, MD, PhD, Anja von Heydebreck, PhD, Jean-Marie Cuillerot, MD, Paul Nghiem, MD, PhD

The authors' affiliations are as follows: Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, NJ (H.L.K.); H. Lee Moffitt Cancer Center and Research Institute, Inc., Tampa, FL (J.R.); The Angeles Clinic & Research Institute, Los Angeles, CA (O.H.); University of Washington Medical Center at South Lake Union, Seattle, WA (S.B., P.N.); University of Lübeck, Lübeck, Germany (P.T.); Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY (S.P.D.); Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN (K.C.S.); Diderot Hôpital Saint Louis, Paris, France (C.L.); Washington University School of Medicine, St. Louis, MO (G.P.L.); Regina Elena National Cancer Institute, Rome, Italy (M.M.); National Cancer Institute, Bethesda, MD (I.B.); University of Colorado Denver School of Medicine, Denver, CO (K.D.L.); Dana-Farber Cancer Institute, Boston, MA (J.H.L.); EMD Serono, Billerica, MA (K.C., L.M., J.-M.C.); Merck KGaA, Darmstadt, Germany (A.v.H.).

Corresponding author
Howard L. Kaufman, MD; Professor of Surgery; Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, NJ 08901; Phone: (732)-235-7701; email: hk553@cinj.rutgers.edu

Clinical trial registration number: NCT02155647

Table of contents

Appendix figures

Figure S1. Kaplan-Meier estimate of overall survival in the modified intent-to-treat population (N=88)

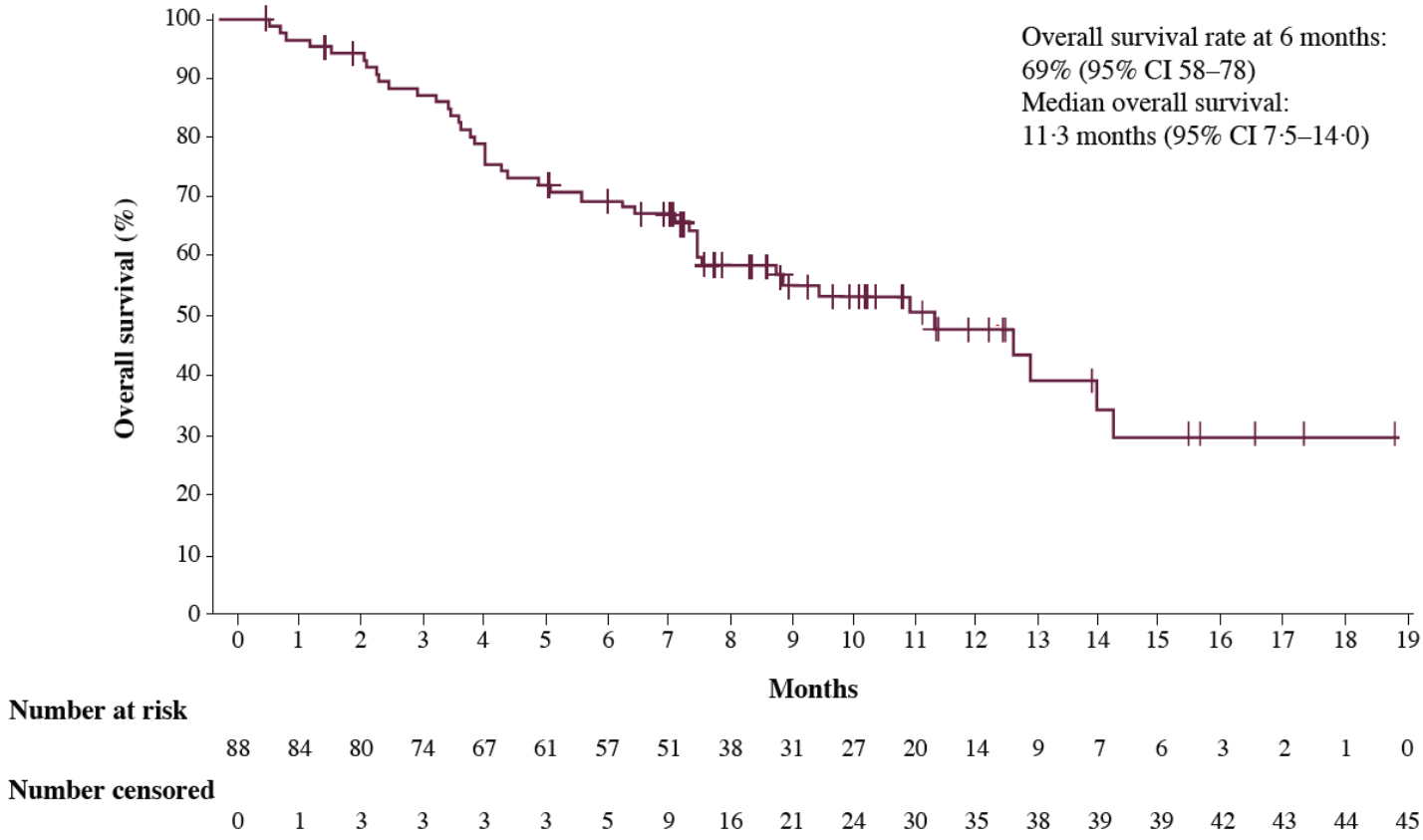

Figure S2. Tumour response with avelumab

Patient with a partial response. Panel A shows a baseline image of an 82-year–old patient with an ECOG performance score of 1 and bulky MCC lesions in the head and neck. He was diagnosed with MCC 8·4 months before trial enrolment. He had received one prior line of treatment for metastatic disease consisting of carboplatin plus etoposide, resulting in progressive disease. The patient's tumour tested negative for PD-L1 and MCPyV by immunohistochemistry and no tumour-infiltrating lymphocytes were present. The patient received a total of 7 doses of avelumab. At Week 7 (first tumour assessment), there was notable tumour regression, and a punch biopsy of one of the remaining neck nodules demonstrated a complete pathological response with a robust inflammatory infiltrate and no tumour cells as shown in Panel D and compared with baseline histopathology in Panel C. Panel B shows shrinkage of visible lesions at 5·3 months from the first dose of avelumab. By independent review committee assessment and RECIST v1.1, the patient had a best overall response of partial response. Histopathological assessments included haematoxylin-eosin (H & E), cytokeratin 20 (CK20), and chromogranin A (ChrA) staining and CD4 and CD8 T-cell staining. Response in this patient was ongoing at the time of data cut-off, for a duration of response of 3·9 months at the time of data cut-off and 1·4 months beyond treatment discontinuation. One treatment-related adverse event of grade 1 diaphoresis was recorded.

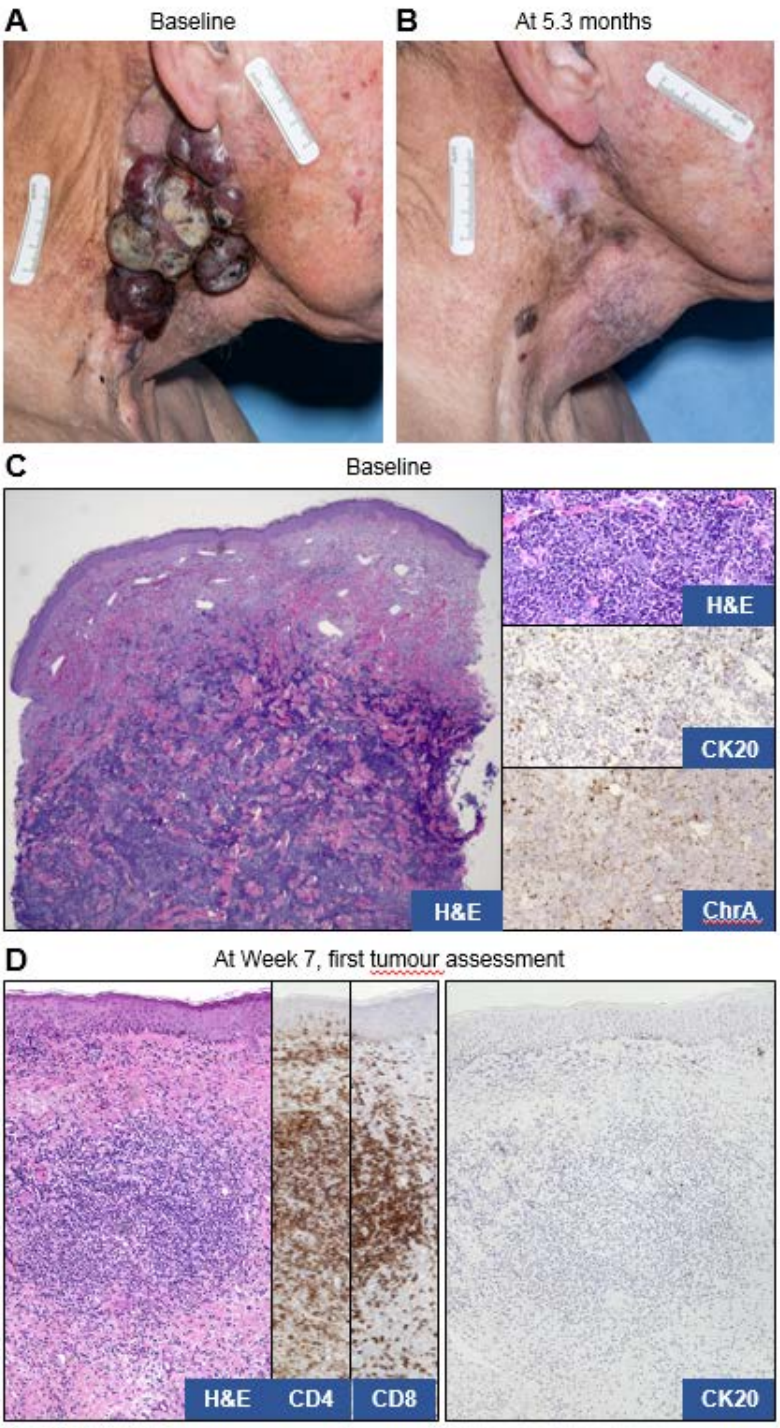

Table S1. Investigator sites, principle investigators, and enrolment by site

Site - country	Site number	Principle investigator	Site - institution	Number of patients treated N=88
United States	133	Russell, Jeffery	H. Lee Moffitt Cancer Center and Research Institute, Inc	8
United States	204	Kaufman, Howard L.	Rutgers Cancer Institute of New Jersey	7
United States	206	Bhatia, Shailender	University of Washington - Seattle Cancer Care Alliance	7
United States	209	Hamid, Omid	The Angeles Clinic and Research Institute - West Los Angeles	7
United States	105	D'Angelo, Sandra P.	Memorial Sloan Kettering Cancer Center	5
Germany	608	Terheyden, Patrick	Universitaetsklinikum Schleswig Holstein - Campus Lübeck	5
United States	102	Shih, Kent C.	Tennessee Oncology	4
United States	101	Brownell, Isaac	National Cancer Institute	3
United States	135	Linette, Gerald P.	Washington University School of Medicine	3
United States	136	Lewis, Karl D.	University of Colorado	3
Italy	303	Milella, Michele	Istituto Nazionale Tumori Regina Elena IRCCS	3
France	404	Lebbé, Céleste	Hôpital Saint-Louis	3
United States	107	Ferrarotto, Renata	University of Texas MD Anderson Cancer Center	2
Italy	301	Ascierto, Paolo	Istituto Nazionale Tumori Fondazione G.Pascale	2
Italy	302	Buzzoni, Roberto	Fondazione IRCCS Istituto Nazionale dei Tumori	2
France	405	Mortier, Laurent	Hopital Claude Huriez - CHU Lille	2
France	407	Robert, Caroline	Institut Gustave Roussy	2
Japan	901	Yamazaki, Naoya	National Cancer Center Hospital	2
Australia	956	Hill, Andrew	Tasman Oncology Research Ltd	2
United States	104	Chmielowski, Bartosz	UCLA Medical Center	1
United States	106	Rabinowits, Guilherme	Dana Farber Cancer Institute	1
Italy	305	Maio, Michele	A.O.U. Senese Policlinico Santa Maria alle Scotte	1
France	401	Saiag, Philippe	Hôpital Ambroise Paré - Boulogne-Billancourt	1
France	403	Grob, Jean-Jacques	Hôpital de la Timone	1
France	408	Dutriaux, Caroline	Groupe Hospitalier Saint André - Hôpital Saint André	1
Spain	502	Arance Fernandez, Ana Maria	Hospital Clinic i Provincial de Barcelona	1
Spain	504	Capdevila Castrillon, Jaume	Hospital Universitari Vall d'Hebron	1
Germany	601	Fluck, Michael	Fachklinik Hornheide	1
Germany	604	Hassel, Jessica	Universitaetsklinikum Heidelberg	1
Germany	605	Kiecker, Felix	Charite Universitaetsmedizin Berlin - Campus Charite Mitte	1
Switzerland	801	Dummer, Reinhard	Universitaetsspital Zuerich	1
Japan	902	Kiyohara, Yoshio	Shizuoka Cancer Center	1
Australia	951	Begbie, Stephen	Port Macquarie Base Hospital	1
Australia	953	Sandhu, Shahneen	The Queen Elizabeth Hospital	1
Australia	955	Patterson, William	Peter MacCallum Cancer Centre	1

Table S2. Eligibility criteria for trial enrolment

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Histologically confirmed diagnosis of MCC including immunohistochemical detection of CK 20 (or other appropriate cytokeratin expression) in the tumour cell • Patients must have had metastatic disease that had progressed after at least 1 line of prior chemotherapy – Treatments much have included one of the following: cyclophosphamide, topotecan, doxorubicin, epirubicin, vincristine, carboplatin, cisplatin, etoposide in combination with carboplatin or cisplatin • Biopsy material was required (archival tissue was acceptable if patient could not provide fresh or recent biopsy) • ECOG performance status score of 0 to 1 at study entry • Estimated life expectancy ≥12 weeks • At least one unidimensional measurable lesion by RECIST v1.1 (including skin lesions) • Adequate haematological, hepatic, and renal function • If the risk of conception exists, patients were required to use highly effective contraception	• Participation in other clinical trials within the past 30 days • Concurrent treatment with an anticancer treatment or other nonpermitted drug • Radiotherapy was not allowed if lesions were considered target lesions in the efficacy evaluation or may influence efficacy evaluation of this study • Prior therapy with any drug targeting T cell coregulatory proteins • Major surgery for any reason within 4 weeks or if the patient had not fully recovered within 4 weeks • Concurrent systemic therapy with corticosteroids or other immunosuppressive agents, or use of any investigational drug within 28 days before starting trial drug; short-term administration of systemic steroids (that is, for allergic reactions or the management of immune-mediated adverse events) while on study was allowed • Patients with active central nervous metastases were excluded, and patients with previously treated CNS metastases were not eligible unless they had fully recovered from treatment, demonstrated no progression for at least 2 months, and did not require steroid therapy • Previous malignant disease (other than MCC) within the last 5 years, with the exclusion of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ • Prior organ transplantation, including allogenic stem-cell transplantation • Known history or testing positive for HIV/AIDS, HBV, or HCV (including acute and chronic infection) • Active or history of any autoimmune disease or immune-deficiencies that required treatment with a systemic immunosuppressant • Known monoclonal antibody hypersensitivity • Persisting toxicity related to prior therapy that was grade >1 according to NCI-CTCAE v4.0; grade ≤2 sensory neuropathy was allowed • Pregnancy or lactation • Known alcohol or drug use • Clinically significant cardiovascular disease • All other significant diseases, which in the investigator's opinion may have influenced the patient's tolerance of trial treatment • Legal incapacity or limited legal capacity, including any psychiatric condition that would have prohibited the understanding or rendering of informed consent • Nononcology vaccine therapies for prevention of infectious disease (eg, seasonal flu vaccine, human papilloma virus vaccine) within 4 weeks of trial drug administration. Vaccination while on trial was also prohibited except for administration of inactivated vaccines (eg, inactivated seasonal influenza vaccine)

Table S3. Schedule of select assessments

Measure	Screening/baseline assessments	Treatment phase*											Discontinuation (x)/end-of-treatment (X)†	Safety follow-up	Post-treatment follow-up‡
	Day -18 to first dose	W1	W2	W3	W4	W5	W6	W7	W9	W11	W13	Until progression	Up to 7 / 28 days after last dose	10 weeks after last dose	Every 3 months
Eligibility criteria	X														
Medical history	X														
Demographic data	X														
Physical examination	X	X		X		X		X	X	X	X	Every 6 weeks	x/X	X	
Vital signs	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	
Weight	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	
ECOG performance status	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	
ECG	X	X		X		X		X	X	X	X	Every 6 weeks	x/X	X	
Haematology/haemostaseology	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	
Core serum chemistry§		X	X		X		X	X	X	X		Every 2 weeks		X	
Full serum chemistry|	X			X		X					X	Every 6 weeks	x/X		
Tumour evaluation¶	X							X			X	Every 6 weeks	-/X		X
Adverse events assessment	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	X
Concomitant medications	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	X
PK sampling**		X		X		X		X	X	X	X	Week 15 and 25, then every 12 weeks		X	
Immunogenicity testing††		X		X		X		X			X	Every 6 weeks	-/X		
Pretreatment and trial drug administration‡‡		X		X		X		X	X	X	X	Every 2 weeks			
Soluble factors and MCPyV-specific antibodies	X	X		X		X		X	X	X	X	Every 2 weeks	x/X	X	X
Tumour tissue biopsy§§	X														
Superficial tumor biopsy‖		X						X			X				

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetic; W, treatment week.

* A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) was permitted for all trial procedures.

† Tumour evaluation at the end-of-treatment visit was generally performed if no disease progression had been documented previously. If another antineoplastic therapy was administered before the end of the 28-day period, the end-of-treatment visit was conducted, if possible, prior to the start of this new therapy.

‡ Patients with an adverse drug reaction ongoing at the end-of-treatment visit and for any serious adverse event suspected to be related to trial treatment occurring up to 3 months after the last dose of avelumab and thereafter will continue to be followed. Patients without progressive disease at end-of-treatment visit will be followed up for disease progression (CT/MRI scans every 6 weeks) for up to 1 year. In addition, patients will be followed quarterly for survival (including assessment of any further tumour therapy). The survival follow-up will continue until 1 year after the last patient receives the last dose of avelumab.

§ Core serum chemistry included liver function panel (alkaline phosphatase, ALT, AST, bilirubin), acute chemistry panel (sodium, potassium, chloride, BUN / total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). For patients with liver metastases at baseline, additional blood samples for ALT, AST, total bilirubin, and alkaline phosphatase determination will be drawn at Weeks 2, 4, and 6.

| Full chemistry panel (including core chemistry) and other laboratory studies.

¶ In general, the tumour visit time window was 5 days prior to dosing. Confirmation of the response was performed according to RECIST v1.1, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5 weeks after the initial documentation of complete response or partial response. Confirmation of partial response at an assessment later than the next assessment after the initial documentation of partial response was permitted. Tumour assessment was by CT scan or MRI and by physical examination (mapping) of skin lesions.

** Blood samples for PK determinations were collected from all patients within 2 hours prior to each study drug administration through Week 15, then at Week 25, and then at 12-week intervals while on treatment. Post-study drug administration samples were collected at the end of infusion and 2 to 8 hours after the end of infusion (later was preferred, depending on how long the patients stayed in the clinic) at Weeks 1, 7, 13, and 25, and then at 12-week intervals while on treatment. Exact sampling times were recorded. Samples were also collected at the 10-week safety follow-up visit.

†† The blood sample for screening/baseline immunogenicity testing by anti-therapeutic antibody analysis was collected prior to trial drug administration and on Day 1. On-trial samples were collected within 2 hours prior to study drug infusion on Days 15, 29, 43 (every 2 weeks), then every 6 weeks thereafter while on treatment, and at the end-of-treatment visit.

‡‡ Patients received pretreatment with H1 antihistamine blockers (diphenhydramine 50 mg IV, or equivalent) and acetaminophen 500 to 650 mg (oral or IV), 30 to 60 minutes prior to infusion of avelumab (10 mg/kg IV over 1 hour [-10 minutes / +20 minutes, that is, over 50 to 80 minutes]).

[§§] A biopsy was collected at screening, unless tissue (blocks or slides) from a recent biopsy (within 4 weeks) was available. Samples were provided as block or slides (blocks were preferable). For patients unable to provide a fresh or recent biopsy, archival material was acceptable.
[||] Superficial tumour biopsies were optional.

Table S4. Prior anticancer treatments

	N=88
Prior anticancer treatment	
Any treatment	88 (100·0)
Any drug therapy	88 (100·0)
Any drug therapy for metastatic disease	88 (100·0)
Number of prior anticancer therapy regimens, n (%)	
1	52 (59·1)
2	26 (29·5)
3	7 (8·0)
≥4	3 (3·4)
Number of prior anticancer lines for locally advanced disease, n (%)	
0	84 (95·5)
1	4 (4·5)
≥2	0
Number of prior anticancer lines for metastatic disease, n (%)	
1	57 (64·8)
2	27 (30·7)
3	3 (3·4)
≥4	1 (1·1)
Types of prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	88 (100·0)
Chemotherapy for non-metastatic disease	3 (3·4)
Hormonal therapy	0
Antibody therapy	1 (1·1)
Kinase inhibitors	3 (3·4)
Vaccines	0
Other	4 (4·5)
Disease setting of prior anticancer treatment, n (%)	
Neoadjuvant	3 (3·4)
Adjuvant	6 (6·8)
Metastatic	88 (100·0)
Locally advanced	4 (4·5)
Prior anticancer radiotherapy, n (%)	70 (79·5)
Prior anticancer surgery, n (%)	75 (85·2)

Table S5. Prior systemic anticancer therapy with antineoplastic regimens

	n (%)
Any agent	88 (100·0)
Etoposide	66 (75·0)
Carboplatin	49 (55·7)
Cisplatin	27 (30·7)
Cisplatin/carboplatin + etoposide	12 (13·6)
Anthracyclines*	11 (12·5)
Cyclophosphamide	8 (9·1)
Paclitaxel/paclitaxel albumin	8 (9·1)
Vincristine/vinblastine	8 (9·1)
Targeted agents†	8 (9·1)
Topotecan	5 (5·7)
Other chemotherapy combinations‡	4 (4·5)
Irinotecan	2 (2·3)
Docetaxel	1 (1·1)
Melphalan	1 (1·1)

* Doxorubicin (n=9), epirubicin (n=1), and amrubicin hydrochloride (n=1).
† Pazopanib (n=5), cabozantinib (n=1), everolimus (n=1), and imatinib mesilate (n=1).
‡ Paclitaxel + carboplatin (n=2), cisplatin + irinotecan (n=1), and cyclophosphamide + doxorubicin/vincristine (n=1).

Table S6. Key clinical, biomarker, and response characteristics of patients with a complete response to avelumab (by RECIST v1.1)

Age, yrs	Sex	Race	ECOG PS status	Site of primary tumour	Number of target lesions	Non-target lesions (Y/N)	Subsites	Site of target lesions	Sum of target lesion diameters at baseline (mm)	Duration of response (mos)	Number of prior lines of systemic anticancer therapy	PD-L1 expression (1% staining cut-off)	MCPyV status by IHC
65	M	White	1	Skin of upper limb and shoulder	1	N	N/A	Adrenal nodule	17	5.8	1	NE	NE
79	F	White	1	Pelvic lymph node	2	N	Lymph nodes of inguinal region or leg	Lymph node	50	12.4+	1	+	+
78	F	White	1	Skin	0	Y	Axillary lymph node	Skin	No target lesion listed	6.8+	1	+	+
75	M	White	0	Skin of lower limb and hip	0	Y	Sentinel lymph node	Lymph node	No target lesion listed	8.2+	1	+	+
47	F	White	0	Axillary lymph node	2	Y	Lymph nodes	Peritoneal nodule	37	17.5+	2	+	−
59	M	White	0	Skin of scalp and neck	2	Y	Lymph nodes	Lymph node	39	6.0	1	NE	NE
60	M	White	0	Skin of upper limb and shoulder	2	Y	Left wrist	Lymph node	45	12.9+	4	+	+
74	M	Asian	0	Skin of the trunk	3	Y	None listed	Soft tissue mass	143	8.3	1	+	+

NE, not evaluable

Table S7. Objective response rate and median duration of response for select subgroups

Subgroup	ORR n (% [95% CI])	Odds ratio in response rate* (95% CI [p-value])	Median duration of response, months (range [95% CI])
Modified ITT population (N=88)	28 (31·8 [22·3–42·6])	-	ne (2·8, 17·5 [8·3–ne])
Age categorization (years)			
<65 (n=22)	7 (31·8 [13·9–54·9])	1·00 (0·32, 3·35 [1·000])	ne (2·8, 17·5 [6·0–ne])
≥65 (n=66)	21 (31·8 [20·9–44·4])		ne (2·8, 12·5 [8·3–ne])
Sex			
Male (n=65)	21 (32·3 [21·2–45·1])	0·92 (0·28, 2·82 [1·000])	ne (2·8, 12·9 [7·0–ne])
Female (n=23)	7 (30·4 [13·2–52·9])		ne (6·8, 17·5 [ne–ne])
Pooled region[†]			
North America (n=51)	17 (33·3 [20·8–47·9])	1·57 (0·51, 5·22 [0·4538])	ne (3·9, 17·5 [ne–ne])
Europe (n=29)	7 (24·1 [10·3–43·5])	3·14 (0·44, 21·40 [0·2035])	ne (2·8, 9·8 [2·8–ne])
Rest of world (n=8)	4 (50·0 {15·7–84·3])		8·3 (2·8, 8·3 [ne–ne])
Site of primary tumor			
Skin (n=67)	23 (34·3 [23·2–46·9])	1·31 (0·33, 6·32 [0·7645])	ne (2·8, 12·9 [7·0–ne])
Non-skin (n=14)	4 (28·6 [8·4–58·1])		ne (4·2, 17·5 [ne–ne])
Missing (n=7)	1 (14·3 [0·4–57·9])		ne (8·8, 8·8 [ne–ne])
Visceral metastases at baseline			
Present (n=47)	16 (34·0 [20.9–49·3])	1·25 (0·46, 3·42 [0·6542])	ne (2·8, 17·5 [5·8–ne])
Absent (n=41)	12 (29·3 [16·1–45·5])		ne (3·9, 12·9 [6·0–ne])
Disease burden according to median sum of longest diameter (mm)[‡]			
≤Q1 (n=21)	9 (42·9 [21·8–66·0])	0·51 (0·17. 1·49 [0·2295])	
>Q1 and ≤median (n=18)	7 (38·9 [17·3–64·3])		ne (4·2, 17·5 [6·0–ne])
>Median and ≤Q3 (n=19)	7 (36·8 [16·3–61·6])		
>Q3 (n=19)	3 (15·8 [3·4–39·6])		ne (2·8, 12·5 [2·8–ne])
Not evaluable (n=11)	2 (18·2 [2·3–51·8])		ne (6·8, 8·2 [ne–ne])
ECOG PS score			
0 (n=49)	17 (34·7 [21·7–49·6])	0·74 (0.27, 2·01 [0.6459])	ne (2·8, 17·5 [7.0–ne])
1 (n=39)	11 (28·2 [15·0–44·9])		ne (3·9, 12·5 [5.8–ne])
Number of prior systemic treatments			
1 (n=52)	21 (40·4 [27·0–54·9])	0·36 (0·11, 1·05 [0·0616])	ne (2·8, 12·5 [7·0–ne])
≥2 (n=36)	7 (19·4 [8·2–36·0])		ne (5·5, 17·5 [ne–ne])
Number of prior systemic treatments for metastatic disease			
1 (n=57)	22 (38·6 [26·0–52·4])	0·38 (0·11, 1·17 [0·0931])	ne (2·8, 12·5 [7·0–ne])
≥2 (n=31)	6 (19·4 [7·5–37·5])		ne (5·6, 17·5 [ne–ne])
Tumour PD-L1 expression			
PD-L1–positive (n=58)	20 (34·5 [22·5–48·1])	2·28 (0·53, 13·78 [0·3610])	ne (2·8, 17·5 [8·3–ne])
PD-L1–negative (n=16)	3 (18·8 [4·0–45·6])		ne (3·9, 5·6 [ne–ne])
Not evaluable (n=14)	5 (35·7 [12·8–64·9])		6·0 (2·8, 12·5 [2·8–ne])

Tumour MCPyV status			
MCPyV-positive (n=46)	12 (26·1 [14·3–41·1])	1·56 (0·51, 4·67 [0·4497])	ne (5·6, 12·9 [7·0–ne])
MCPyV-negative (n=31)	11 (35·5 [19·2–54·6])		ne (2·8, 17·5 [ne–ne])
Not evaluable (n=11)	5 (45·5 [16·7–76·6])		6·0 (2·8, 12·5 [2·8–ne])
Combined PD-L1/MCPyV status[§]			
PD-L1+/MCPyV+ (n=36)	11 (30·6 [16·3–48·1])	3·52 (0·38, 170·16 [0·4069])	ne (6·8, 12·9 [7·0–ne])
PD-L1+/MCPyV− (n=19)	7 (36·8 [16·3–61·6])	4·67 (0·43, 236·14 [0.2144])	ne (2·8, 17·5 [ne–ne])
PD-L1−/MCPyV+ (n=9)	1 (11·1 [0.3–48·2])		ne (5·6, 5·6 [ne–ne])
PD-L1−/MCPyV− (n=7)	2 (28·6 [3·7–71·0])	3·20 (0·12, 211·93 [0·5500])	ne (3·9, 5·5 [ne–ne])
Not evaluable (n=17)	7 (41·2 [18·4–67·1])		ne (2·8, 12·5 [2·8–ne])

ne, not estimable.

* Odds ratio in response rate based on the first subgroup category over the second subgroup category except where noted.

† Odds ratio based on pooled region North America and rest of world over Europe, respectively.

‡ Odds ratio in response rate based on disease burden at baseline sum of longest diameter above the median over sum of longest diameter at or below the median.

§ Odds ratio in response rate based on PD-L1+/MCPyV+, PD-L1+/MCPyV−, and PD-L1−/MCPyV− over PD-L1−/MCPyV+, respectively.

Table S8. Overall summary of safety

N=88	n (%)
Any adverse event (AE)	86 (97·7)
Any treatment-related AE	62 (70·5)
Any serious AE*	36 (40·9)
Any treatment-related serious AE*	5 (5·7)
Any grade ≥3 AE	54 (61·4)
Any treatment-related grade ≥3 AE	4 (4·5)
Any AE leading to death	8 (9·1)
Any treatment-related AE leading to death	0
Any AE leading to permanent treatment discontinuation	2 (2·3)
Any treatment-related AE leading to permanent treatment discontinuation†	1 (1·1)
Any immune-mediated AE	13 (14·8)
Any treatment-related immune-mediated AE	6 (6·8)

* Serious AE was defined as an AE that results in death, is life-threatening, requires in-patient hospitalisation or prolongs existing hospitalization, results in persistent or significant disability/incapacity, or is otherwise considered medically important.
† In addition, one discontinuation occurred due to a non-emergent event (increased creatinine) that followed an event of grade 2 treatment-related acute interstitial nephritis.

Table S9. Treatment-emergent adverse events

N=88	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any adverse event	32 (36.4)	38 (43.2)	8 (9.1)	8 (9.1)
Fatigue	31 (35.2)	2 (2.3)	0	0
Diarrhoea	20 (22.7)	0	0	0
Nausea	18 (20.5)	0	0	0
Oedema peripheral	16 (18.2)	0	0	0
Decreased appetite	15 (17.0)	2 (2.3)	0	0
Cough	15 (17.0)	0	0	0
Constipation	14 (15.9)	1 (1.1)	0	0
Infusion-related reaction[†]	13 (14.8)	0	0	0
Arthralgia	13 (14.8)	1 (1.1)	0	0
Weight decreased	12 (13.6)	0	0	0
Pain in extremity	12 (13.6)	1 (1.1)	0	0
Asthenia	11 (12.5)	11 (12.5)		
Dizziness	11 (12.5)	0	0	0
Vomiting	10 (11.4)	0	0	0
Rash	10 (11.4)	0	0	0
Abdominal pain	9 (10.2)	2 (2.3)	0	0
Back pain	9 (10.2)	0	0	0
Hypertension	6 (6.8)	5 (5.7)	0	0
Anaemia	4 (4.5)	8 (9.1)	1 (1.1)	0
Alanine aminotransferase increased	4 (4.5)	2 (2.3)	0	0
Aspartate aminotransferase increased	4 (4.5)	1 (1.1)	0	0
Hyponatraemia	3 (3.4)	2 (2.3)	0	0
Lymphoedema	3 (3.4)	1 (1.1)	0	0

Acute kidney injury	3 (3.4)	1 (1.1)	0	0
Urinary tract infection	3 (3.4)	1 (1.1)	0	0
Blood creatine phosphokinase increased	3 (3.4)	1 (1.1)	0	0
Pneumonia	2 (2.3)	0	0	1 (1.1)
Hypoalbuminemia	2 (2.3)	1 (1.1)	0	0
Hypokalaemia	2 (2.3)	1 (1.1)	0	0
Flank pain	2 (2.3)	1 (1.1)	0	0
Tumour pain	2 (2.3)	1 (1.1)	0	0
Confusional state	2 (2.3)	1 (1.1)	0	0
Dypsnoea exertional	2 (2.3)	1 (1.1)	0	0
Hypotension	2 (2.3)	2 (2.3)	0	0
Gamma-glutamyltransferase increased	1 (1.1)	3 (3.4)	0	0
Atrial fibrillation	1 (1.1)	1 (1.1)	0	0
Atrial flutter	1 (1.1)	0	1 (1.1)	0
Gastric haemorrhage	1 (1.1)	1 (1.1)	0	0
Pain	1 (1.1)	1 (1.1)	0	0
Erysipelas	1 (1.1)	1 (1.1)	0	0
Blood lactate dehydrogenase increased	1 (1.1)	1 (1.1)	0	0
Hypophosphatemia	1 (1.1)	1 (1.1)	0	0
Bone pain	1 (1.1)	1 (1.1)	0	0
Musculoskeletal pain	1 (1.1)	1 (1.1)	0	0
Squamous cell carcinoma	1 (1.1)	1 (1.1)	0	0
Post-herpetic neuralgia	1 (1.1)	1 (1.1)	0	0
Delirium	1 (1.1)	1 (1.1)	0	0
Hydronephrosis	1 (1.1)	1 (1.1)	0	0
Deep vein thrombosis	1 (1.1)	1 (1.1)	0	0
Pleural effusion	1 (1.1)	2 (2.3)	0	0

Leukocytosis	0	2 (2.3)	0	0
Microcytic anaemia	0	1 (1.1)	0	0
Normochromatic normocytic anaemia	0	1 (1.1)	0	0
Eyelid function disorder	0	1 (1.1)	0	0
Retinal artery occlusion	0	0	1 (1.1)	0
Ascites	0	1 (1.1)	0	0
Faecaloma	0	1 (1.1)	0	0
Gastrointestinal haemorrhage	0	1 (1.1)	0	0
Ileus	0	0	0	1 (1.1)
Oesphageal spasm	0	1 (1.1)	0	0
Chest pain	0	1 (1.1)	0	0
Disease progression	0	0	0	4 (4.5)
General physical health deterioration	0	2 (2.3)	0	0
Hyperthermia	0	1 (1.1)	0	0
Non-cardiac chest pain	0	1 (1.1)	0	0
Liver injury	0	0	1 (1.1)	0
Hepatic failure	0	0	0	1 (1.1)
Klebsiella sepsis	0	0	1 (1.1)	0
Lung infection	0	1 (1.1)	0	0
Sepsis	0	0	1 (1.1)	0
Streptococcal sepsis	0	0	1 (1.1)	0
Activated partial thromboplastin time prolonged	0	1 (1.1)	0	0
Blood cholesterol increased	0	1 (1.1)	0	0
Blood glucose increased	0	1 (1.1)	0	0
Blood pressure increased	0	1 (1.1)	0	0
Lipase increased	0	2 (2.3)	1 (1.1)	0
Lymphocyte count decreased	0	1 (1.1)	0	0

Transaminases increased	0	1 (1.1)	0	0
Diabetes mellitus	0	1 (1.1)	0	0
Malignant neoplasm progression	0	0	0	1 (1.1)
Metastases to larynx	0	1 (1.1)	0	0
Metastases to meninges	0	1 (1.1)	0	0
Neoplasm progression	0	1 (1.1)	0	0
Pericardial effusion malignant	0	0	1 (1.1)	0
Squamous cell carcinoma of the skin	0	1 (1.1)	0	0
Syncope	0	1 (1.1)	0	0
Agitation	0	1 (1.1)	0	0
Anuria	0	1 (1.1)	0	0
Superior vena cava syndrome	0	1 (1.1)	0	0
Lymphopaenia	0	5 (5.7)	1 (1.1)	0

* Any grade in ≥10% or any grade ≥3 based on the worst grade per patient.

Table S10. Treatment-related adverse events*

N=88	Any grade (1-3) n (%)	Grade 1-2 n (%)	Grade 3 n (%)
Any treatment-related adverse event	62 (70·5)	58 (65·9)	4 (4·5)
Fatigue	21 (23·9)	21 (23·9)	0
Infusion-related reaction†	15 (17·0)	15 (17·0)	0
Nausea	8 (9·1)	8 (9·1)	0
Diarrhoea	8 (9·1)	8 (9·1)	0
Asthenia	7 (8·0)	7 (8·0)	0
Rash	6 (6·8)	6 (6·8)	0
Decreased appetite	5 (5·7)	5 (5·7)	0
Maculopapular rash	5 (5·7)	5 (5·7)	0
Arthralgia	4 (4·5)	4 (4·5)	0
Pruritus	4 (4·5)	4 (4·5)	0
ALT increased	3 (3·4)	3 (3·4)	0
AST increased	3 (3·4)	3 (3·4)	0
Chills	3 (3·4)	3 (3·4)	0
Dizziness	3 (3·4)	3 (3·4)	0
Blood CPK increased	2 (2·3)	1 (1·1)	1 (1·1)
Lymphopaenia	2 (2·3)	0	2 (2·3)
Dry mouth	2 (2·3)	2 (2·3)	0
Dry skin	2 (2·3)	2 (2·3)	0
Dysgeusia	2 (2·3)	2 (2·3)	0
Dyspnaea	2 (2·3)	2 (2·3)	0
Headache	2 (2·3)	2 (2·3)	0
Influenza-like illness	2 (2·3)	2 (2·3)	0
Palpitations	2 (2·3)	2 (2·3)	0
Pyrexia	2 (2·3)	2 (2·3)	0

Vomiting	2 (2·3)	2 (2·3)	0
Blood cholesterol increased	1 (1·1)	0	1 (1·1)
Transaminases increased	1 (1·1)	0	1 (1·1)
Potential immune-mediated TRAEs[‡]			
Any immune-mediated treatment-related adverse event	6 (6·8)	6 (6·8)	0
Hypothyroidism	3 (3·4)	3 (3·4)	0
Hyperthyroidism	2 (2·3)	2 (2·3)	0
Pneumonitis	1 (1·1)	1 (1·1)	0
Type 1 diabetes mellitus	1 (1·1)	1 (1·1)	0

***** Any grade in >1 patient or any grade ≥3 based on the worst grade per patient. There were no grade 4 or grade 5 treatment-related adverse events.

[†] An infusion-related reaction in this analysis was based on a composite definition with 5 different MedDRA terms. Signs and symptoms of a potential infusion-related reaction (eg, fever, chills, or rigors) reported on the day of infusion were queried with investigators to ascertain whether an AE of "infusion-related reaction" should be recorded. Of the 15 treatment-related adverse events recorded as an infusion-related reaction, 13/15 (86·7%) resolved on the same day as the infusion. In one patient, resolution of a grade 1 event occurred within 3 days and without the use of concomitant corticosteroid, and in a second patient, a grade 2 event resolved within 6 days, also without the use of corticosteroid. Three patients received corticosteroid treatment for a grade 2 infusion-related reaction that resolved on the same day as the infusion. All other patients were treated with nonsteroidal supportive medication.

[‡] These events were programmatically derived from a search term list. By manual medical review, potential immune-mediated, treatment-related adverse events were identified in four additional patients: grade 3 increased transaminase (n=1); grade 2 diarrhoea (n=1); grade 2 nephritis (n=1); and grade 1 rash (n=1).