BAVENCIO® (avelumab) Metastatic MCC Overview Deck

Please see the full BAVENCIO® (avelumab) US Prescribing Information available at https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

US-AVE-01310 | February 2024

Important Notices

- Avelumab has been approved by the FDA and is under investigation for the treatment of various diseases. Efficacy and safety of avelumab are still under investigation for various indications. Regulatory approval is dependent on the completion of the study programs and review by the FDA. Clinical trial information is available at www.clinicaltrials.gov.

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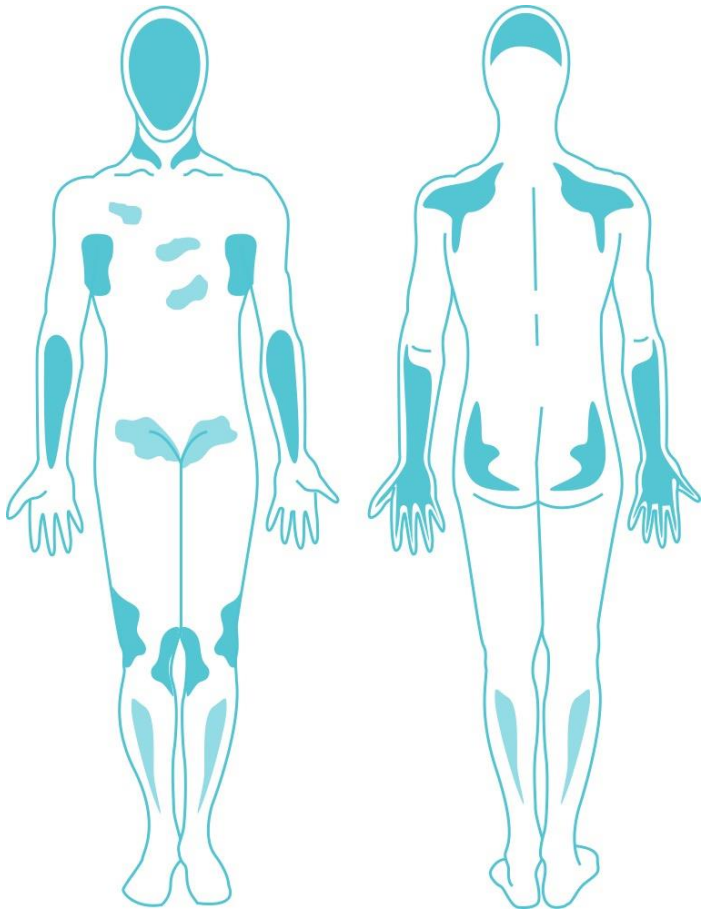
1L, first line; 2L, second line; ISI, Important Safety Information; MCC, Merkel cell carcinoma.

MCC Disease Overview

Clinical Presentation

ANATOMICAL DISTRIBUTION OF MCC AT PRESENTATION[1]



CLINICAL CHARACTERISTICS OF MCC[1]

The acronym **AEIOU** is often used to summarize the classical clinical characteristics of MCC:

Asymptomatic

Expanding rapidly

Immune suppression

Older than 50 years of age

UV exposure on fair skin

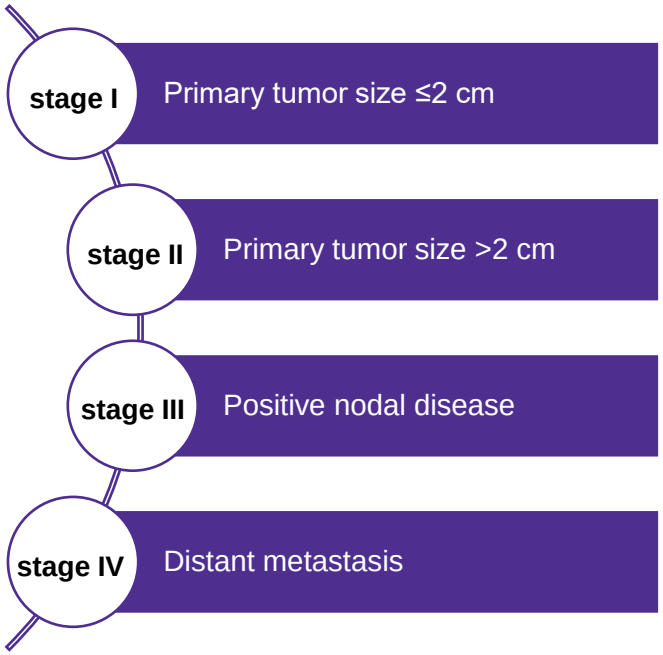
- MCC is an ultra-rare neuroendocrine, cutaneous malignancy that occurs more frequently in elderly individuals and has a poor prognosis[2]
- Patients present with a firm, painless, rapidly enlarging, red-violet, cutaneous, dome-shaped tumor nodule[2]
- MCC nodules are often located in **sun-exposed areas** of the head and neck or upper extremities[3]
- MCC commonly occurs on the **face and neck** (40-60%), followed by the trunk (23%), and the extremities (10-20%)[4]

***MCC distribution evaluated in 195 patients: 168 patients with primary skin lesions and 27 patients with nodal involvement and no known primary lesions.
MCC, Merkel cell carcinoma.

1. Heath M et al. J Am Acad Dermatol. 2018;58(3):375–81; 2. Dellambra E et al. Biomedicines. 2021;9(7):718–41; 3. Smith VA et al. Laryngoscope. 2012;122(6):1283–90; 4. Medina-Franco H et al. Ann Surg Oncol. 2001;8(3):204–8.

TNM Classification: MCC Is Classified in Stages I to IV

The **consensus staging system** for MCC was introduced by the AJCC in 2010[1] and updated in 2016 to help clinicians better stratify patients into groups based on their predicted survival, emphasizing the difference between clinically and pathologically determined staging[2]



Clinical stage groups (cTNM)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-3	N0	M0
IIB	T4	N0	M0
III	T0-4	N1-3	M0
IV	T0-4	Any N	M1

Pathological stage groups (pTNM)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-3	N0	M0
IIB	T4	N0	M0
IIIA	T1-4 T0	N1a(sn) or N1a N1b	M0 M0
IIIB	T1-4	N1b-3	M0
IV	T0-4	Any N	M1

AJCC, American Joint Commission on Cancer; **M**, metastasis; **MCC**, Merkel cell carcinoma; **N**, node; **T**, tumor.

1. Edge SB et al. AJCC Cancer Staging Manual. 7th ed. 2010; 2. Harms KL et al. Ann Surg Oncol. 2016;23(11):3564–71.

TNM Classification: MCC Is Classified in Stages I to IV, cont'd

The **consensus staging system** for MCC is classified by tumor, node, and metastasis criteria

T	N		M
Tx, primary tumor cannot be assessed	cNx, regional lymph nodes cannot be clinically assessed (eg, previously removed for another reason, body habitus)	pNx, regional lymph nodes cannot be assessed (eg, previously removed for another reason) or not removed for pathological evaluation	M0, no distant metastasis
T0, no primary tumor	cN0, no regional lymph node metastasis by clinical or radiological evaluation	pN0, no regional lymph node metastasis detected on pathological evaluation	M1, distant metastasis
Tis, in situ primary tumor	cN1, clinically detected regional nodal metastasis	pN1a(sn), clinically occult nodal metastasis identified only by sentinel lymph node biopsy	M1a, metastases to distant skin, distant subcutaneous tissue, or distant lymph nodes
T1, primary tumor ≤2 cm	cN2, in-transit metastasis without lymph node metastasis	pN1a, clinically occult regional lymph node metastasis following lymph node dissection	M1b, metastasis to lung
T2, primary tumor >2 cm but ≤5 cm	cN3, in-transit metastasis with lymph node metastasis	pN1b, clinically or radiologically detected regional lymph node metastasis, pathologically confirmed	M1c, metastasis to all other visceral sites
T3, primary tumor >5 cm		pN2, in-transit metastasis without lymph node metastasis	
T4, primary tumor invades fascia, muscle, cartilage, or bone		pN3, in-transit metastasis with lymph node metastasis	

AJCC, American Joint Commission on Cancer; **c**, clinical; **M**, metastasis; **MCC**, Merkel cell carcinoma; **N**, node; **p**, pathologic; **T**, tumor.

Harms KL et al. Ann Surg Oncol. 2016;23(11):3564–71.

Stage at Diagnosis and Sites of Metastasis

MCC

Percentage of patients with MCC per clinical stage, as presented at diagnosis[1,*]

Stage	Patients, %
I	53.5
II	21.4
III	13.8
IV	**3.1**
Unknown	8.2

- MCC develops at an exponential rate on chronically sun-damaged skin, with a doubling time of 5 days to 12 days[2,3]
- MCC grows in an infiltrating manner in the initial stages of disease, and satellite metastases may occur early in development of the disease[4]

Metastatic MCC

Common metastatic sites of MCC[5,6]

Metastatic site	Patients, %
Lymph nodes	**60**
Skin	30
Lung	23
CNS	18
Bone	15

- Progression to metastatic disease is a frequent phenomena post locally advanced disease and typically observed within the first 2 years following diagnosis[7]
- Recurrence in MCC is high, particularly in patients with a positive SLNB[8]

*Based on 159 patients with a median age of 75 years treated for MCC between 2002 and 2020 at a single institution.

CNS, central nervous system; **MCC**, Merkel cell carcinoma; **SLNB**, sentinel lymph node biopsy.

1. Esposito A et al. Ann Surg Oncol. 2022;29(1):415–24; 2. Poulsen M. Drugs Aging 2005;22(3):219–29; 3. Swann MH, Yoon J. Semin Oncol 2007;34(1):51–6; 4. Becker JC. Ann Oncol 2010;21(suppl 7):vii81–5; 5. Medina-Franco H et al. Ann Surg Oncol 2001;8(3):204–8; 6. Voog E et al. Cancer 1999;85(12):2589–95; 7. Allen PJ et al. J Clin Oncol 2005;23(10):2300–9; 8. Gupta SG et al. Arch Dermatol 2006;142(6):685–90.

Epidemiology

MCC is a very rare form of skin cancer with an incidence rate of **0.7 cases per 100,000 PYs** in the US in 2013, corresponding to **2488 cases per year**[1]

The number of reported MCC cases is rapidly growing, with **an increase of 95% from 2000 to 2013** according to a study of 6,600 patients with MCC registered in the SEER database[1]

Due to aging of the Baby Boomer generation, US MCC incident **cases are predicted to climb to 2835 cases per year in 2020 and 3284 cases per year in 2025**[1]

MCC incidence **increases exponentially with age**, from 0.1 to 1.0 to 9.8 (per 100,000 PYs) among age groups 40-44 years, 60-64 years, and ≥85 years, respectively[1]

- Consequently, MCC is primarily a **disease of the elderly** with a **median age of 76 years (1986 to 2004)**[2]

The **incidence of MCC is higher in men than in women** as shown in a study of 3,870 MCC cases identified in the SEER database between 1973 and 2006 (0.41 [95% CI: 0.38-0.43] per 100,000 PYs in men vs. 0.18 [95% CI: 0.17–0.19] per 100,000 PYs in women; p<0.05)[3]

Patients with MCC are **mostly Caucasian (96.4%)** with African American (1.2%) and Asian (0.8%) descent making up a very small portion[4]

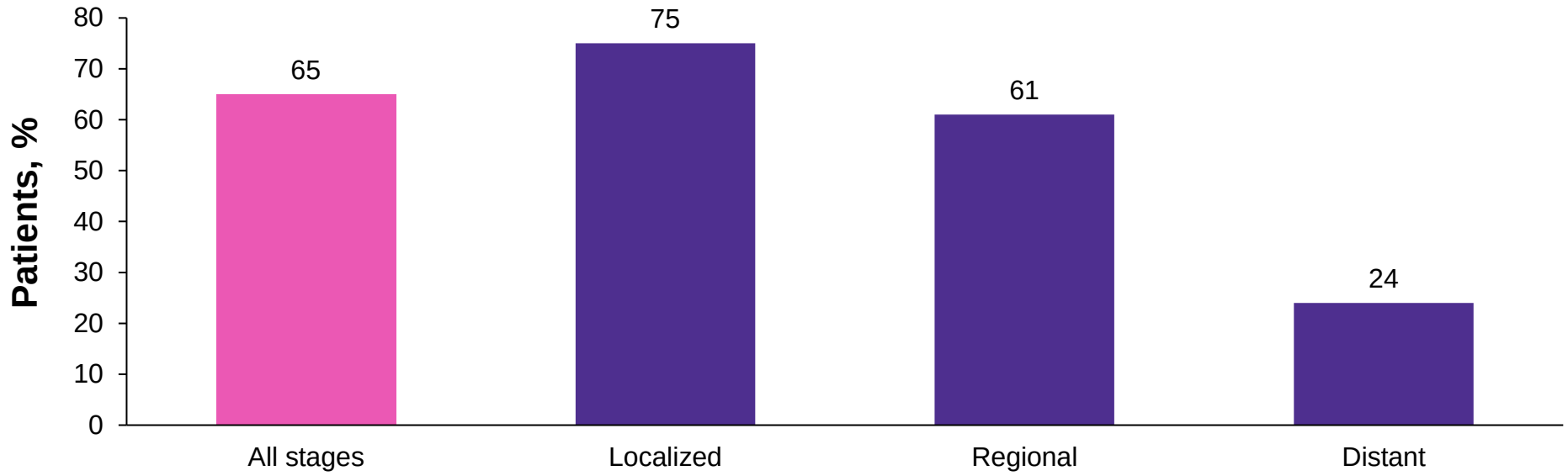
MCC, Merkel cell carcinoma; **PY**, person-year; **SEER**, Surveillance, Epidemiology, and End Results Program; **US**, United States.

1. Paulson KG et al. J Am Acad Dermatol 2018;78(3):457–63.e2; 2. Lemos BD et al. J Am Acad Dermatol 2010;63(5):751–61; 3 Albores-Saavedra J et al. J Cutan Pathol 2010;37(1):20–7; 4. Harms KL et al. Ann Surg Oncol. 2016;23(11):3564–71.

5-Year Survival by Stage at Diagnosis

- MCC exhibits aggressive clinical features and is associated with a poorer prognosis and lower survival compared with other aggressive skin malignancies, such as melanoma[1-4]
- According to an analysis of data from the SEER database between 2012 and 2018, tumor stage significantly affects survival, with higher mortality rates with more advanced disease[5]

Five-year relative survival by MCC stage at diagnosis, 2012-2018[5]



MCC, Merkel cell carcinoma; **SEER**, Surveillance, Epidemiology, and End Results Program.

1. Saini AT, Miles BA. Onco Targets Ther 2015;8:2157–67; 2. Chen MM et al. JAMA Otolaryngol Head Neck Surg 2015;141(2):137–41; 3. Smith VA et al. Laryngoscope 2012;122(6):1283–90; 4. Grabowski J et al. Clin Med Oncol 2008;2:327–33; 5. American Cancer Society. Survival Rates for Merkel Cell Carcinoma. Accessed November 29, 2023. https://www.cancer.org/cancer/types/merkel-cell-skin-cancer/detection-diagnosis-staging/survival-rates.html

Etiology

The etiology of MCC is likely multifactorial, with immunosuppression, UV-induced skin damage, and viral factors contributing to its development[1]

MCPyV infection

- MCPyV, a DNA virus, is detected in approximately 80% of MCC cases[2]
- Likely to be part of the normal skin flora, MCPyV DNA is nearly ubiquitous in the normal skin of healthy individuals[3]
- Infection likely occurs during childhood, but remains largely asymptomatic in adults[4,5]
- The early gene region of MCPyV encodes ST and LT, both of which are independently required for modulation of the host cell and viral replication[6]
- The oncogenic potential of MCPyV is thought only to occur upon clonal integration into the host genome; spontaneously or through exogenous mutations in the 3' end of the LT[3,7]
- ST appears to be the major transforming oncogene in MCC[7]

Immunosuppression

- A key factor in the development of MCC, which appears to be associated with a worse prognosis[8,9]
- The relative risk for MCC is approximately 13-fold higher in HIV and about 5-fold higher in solid organ transplantation recipients than the general population[9]

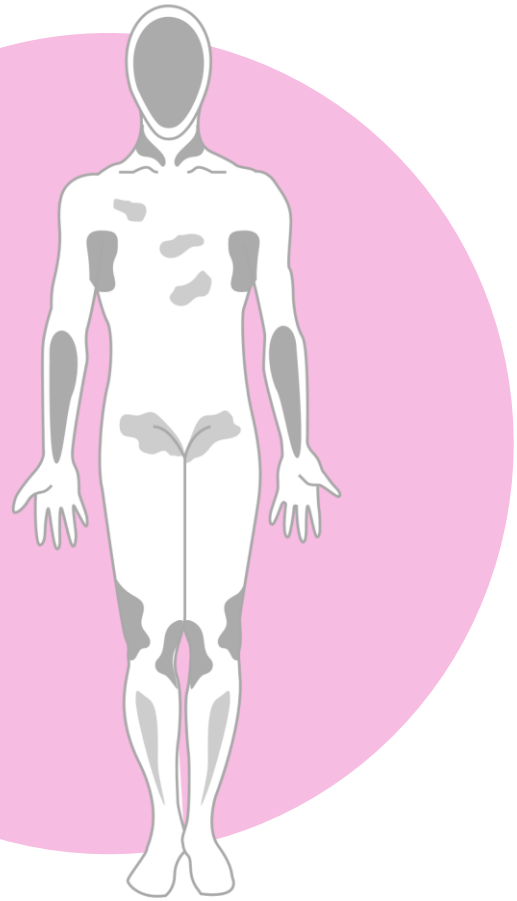
Solar radiation

- UV-B rays induce mutations in the tumor suppressor p53 and Ha-ras genes, increasing the risk of cancer[8]
- The UV-B index is positively associated with MCC incidence[8]
- MCPyV-negative tumors exhibit a high mutation burden associated with UV-induced DNA damage[10,11]

HIV, human immunodeficiency virus; **LT**, large T antigen; **MCC**, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **ST**, small T antigen; **UV**, ultraviolet.

1. Saini AT, Miles BA. Onco Targets Ther. 2015;8:2157–67; 2. Feng H et al. Science. 2008;319(5866):1096–100; 3. Tothill R et al. Am Soc Clin Oncol Educ Book. 2015; e519–26; 4. Martel-Jantin C et al. J Clin Virol 2013;58(1):288–91; 5. Tolstov YL et al. Emerg Infect Dis 2011;17(8):1371–80; 6. Liu W, You J. Annu Rev Virol 2020; 7(1): 289-307; 7. Arora R et al. Curr Opin Virol 2012;2(4):489–98; 8. Ma JE, Brewer JD. Cancers (Basel) 2014;6(3):1328–50; 9. Desch L, Kunstfeld R. J Skin Cancer 2013;2013:327150; 10. Wong SQ et al. Cancer Res 2015;75(24):5228–34; 11. Harms PW et al. Cancer Res 2015;75(18):3720–7.

Select Risk Factors Influencing Clinical Outcome



TUMOR STAGE

Patients with advanced disease (stage III and stage IV) have an increased risk of MCC-specific mortality compared with patients with stage I tumors[1,2]

TUMOR HISTOLOGY & LOCATION

Lymphovascular invasion, tumor growth pattern, and lymph node number have all been shown to affect disease outcome[1,3-5]

BIOMARKERS

PD-L1, p63, VEGFR-2, MMP, and KIT are predictive of a worse disease prognosis in patients with MCC[2,6-11]

HOST FACTORS

Male sex, advanced age, CD8+ infiltration, vitamin D deficiency, and immunosuppression are prognostic host factors for MCC[12-17]

MCPyV INFECTION

MCPyV-negative MCC may represent a more aggressive subtype and may warrant closer clinical follow-up[18]

SECONDARY MALIGNANCIES

Patients diagnosed with MCC are at risk of developing secondary cancers[19]

MCC, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **MMP**, matrix metalloproteinase; **PD-L1**, programmed death-ligand 1; **VEGFR-2,** vascular endothelial growth factor receptor-2.

1. Andea AA et al. Cancer. 2008;113(9):2549–58; 2. Stetsenko GY et al. Am J Clin Pathol. 2013;140(6):838–44; 3. Iyer JG et al. J Am Acad Dermatol. 2014;70(4):637–43; 4. Ko JS et al. Mod Pathol. 2016;29(2):122–30; 5. Henderson SA et al. J Cutan Pathol. 2014;41(11):846–52; 6. Lipson EJ et al. Cancer Immunol Res. 2013;1(1):54–63; 7. Asioli S et al. Cancer. 2007;110(3):640–47; 8. Asioli S et al. Mod Pathol. 2011;24(11):1451–61; 9. Kukko H et al. Anticancer Res. 2007;27(4C):2587–89; 10. Fernandez-Figueras MT et al. Mod Pathol. 2007;20(1):90–101; 11. Andea AA et al. Hum Pathol. 2010;41(10):1405–12; 12. Chen MM et al. JAMA Otolaryngol Head Neck Surg. 2015;141(2):137–41; 13. Smith VA et al. Laryngoscope. 2012;122(6):1283–90; 14. Paulson KG et al. Am J Clin Pathol. 2014;142(4):452–8; 15. Asgari MM et al. JAMA Dermatol. 2014;150(7):716–23; 16. Paulson KG et al. J Invest Dermatol. 2013;133(3):642–46; 17. Schadendorf et al. Eur J Cancer. 2017;(71):53-69; 18. Shantha E, Nghiem P. Merkel cell carcinoma multicenter interest group: Summary of 10th Annual Meeting. 2015; 19. Saxena A et al. J Skin Cancer. 2014;2014:184245.

Causal Link Between Merkel Cell Polyomavirus (MCPyV) and MCC Pathogenesis[1,2]

- As immunosuppressed patients have an increased risk for MCC, it is highly likely that the immune system plays a central role in preventing and controlling MCC[1]
- MCPyV oncoproteins are a major contributor to MCC pathogenesis[2]
  - Expressed in 80% of MCC tumors[2]
    - In the other 20%, immune responses to unknown antigens are implicated[1]
- Immunomodulation (including reduction of immunosuppression) could therefore result in regression of MCC[1]
  - Evidence suggests that high TIL counts and immune transcripts are associated with better prognosis[1]

MCC, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **TIL**, tumor-infiltrating lymphocytes.

1. Triozzi PL, Fernandez AP. Cancers 2013;5:234–54; 2. Rabinowits G. Cancers 2014;6:1180–94.

Role of the Immune System in MCC Pathogenesis

- Immunosuppressed individuals have an estimated 15-fold higher risk of MCC and earlier onset than the general population[1,2]
  - However, immunosuppressed individuals account for only ~10% of MCC cases[2]
- Most patients newly diagnosed with MCC do not have a history of immune dysfunction, suggesting that tumor cells are escaping immune surveillance[1,3]
- Current evidence suggests that MCC develops only after a series of mutational events and loss of cell-mediated immune surveillance[4]
- Local tumor-specific and potentially MCPyV-specific immune responses drive MCC tumor PD-L1 expression – similar to previous observations in melanoma and head and neck squamous cell carcinomas[5]
  - Geographic association of immune infiltrates with PD-L1^{+} MCC tumor cells[5]
  - High PD-L1 expression among specimens with high TIL intensities[5]
  - Significant associations between presence of MCPyV DNA, a brisk inflammatory response, and tumor cell PD-L1 expression (MCPyV^{-} tumor cells have been shown to be uniformly PD-L1^{-})[5]

MCC, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **PD-L1**, programmed death ligand 1; **TIL**, tumor-infiltrating lymphocytes.

1. Triozzi PL, Fernandez AP. Cancers 2013;5:234–54; 2. Ma JE, Brewer JD. Cancers 2014;6:1328–50; 3. Rabinowits G. Cancers 2014;6:1180–94; 4. Bhatia S et al. Curr Oncol Rep 2011;13:488–97; 5. Lipson EJ et al. Cancer Immunol Res 2013;1:54–63.

MCC Treatment Landscape

MCC Treatment Landscape

- Treatment is dependent on tumor staging[1]
- 50% of patients without distant metastasis at presentation may be cured with surgery ± radiotherapy[2]
- The remaining 50% are likely to experience disease recurrence resulting in fatal metastatic disease, typically within 1-2 years[2]
- For patients with metastatic disease at diagnosis, 5-year relative survival rate is 24%[3]
- Initial response rate with chemotherapy is 53-76%[4]
  - Responses are sustained for a range of 4-15 months[4]
- In the last 5 years, immunotherapies have become a treatment option in patients with metastatic MCC[5]

MCC, Merkel cell carcinoma.

1. American Cancer Society. Treating Merkel Cell Carcinoma Based on the Extent of the Cancer. Accessed May 31, 2022. https://www.cancer.org/cancer/merkel-cell-skin-cancer/treating/common-treatments-by-extent.html; 2. Rabinowits G. Cancers. 2014;6:1180–94; 3. American Cancer Society. Survival Rates for Merkel Cell Carcinoma. Accessed November 29, 2023. https://www.cancer.org/cancer/types/merkel-cell-skin-cancer/detection-diagnosis-staging/survival-rates.html; 4. Villani A et al. Dermatol Ther (Heidelb) 2019;9:209–22; 5. Shalhout SZ et al. Curr Oncol Rep. 2021;23:125.

Indication and Important Safety Information

Indication

Metastatic Merkel cell carcinoma

BAVENCIO® (avelumab) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

Important Safety Information

Avelumab can cause **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for avelumab is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue avelumab depending on severity. In general, withhold avelumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue avelumab for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if avelumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

Avelumab can cause **immune-mediated pneumonitis**. Withhold avelumab for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.1% (21/1854) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

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Important Safety Information, continued

Avelumab can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (27/1854) of patients, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions. Systemic corticosteroids were required in all (27/27) patients with colitis.

Avelumab can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue avelumab based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with avelumab as a single agent in 1.1% (20/1854) of patients, including fatal (0.1%), Grade 3 (0.8%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (20/20) patients with hepatitis.

Avelumab can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency.

Avelumab can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1854) of patients, which was a Grade 2 (0.1%) adverse reaction.

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Important Safety Information, continued

Avelumab can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1854) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (8/1854) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (97/1854) of patients, including Grade 3 (0.2%) and Grade 2 (3.6%) adverse reactions. Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism.

Avelumab can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold avelumab for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.2% (3/1854) of patients, including Grade 3 (0.2%) adverse reactions.

Avelumab can cause **immune-mediated nephritis with renal dysfunction**. Withhold avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (2/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in all (2/2) patients with nephritis with renal dysfunction.

Avelumab can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold avelumab for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients, including Grade 3 (0.1%) and Grade 2 (1.9%) adverse reactions. Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions.

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EMD SERONO

Important Safety Information, continued

Avelumab can result in **other immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received avelumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue avelumab for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold avelumab for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

Avelumab can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue avelumab for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 26% of patients, including three (0.2%) Grade 4 and ten (0.5%) Grade 3 infusion-related reactions. Eleven (85%) of the 13 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Avelumab can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab. It is not known whether avelumab is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of avelumab due to the potential for serious adverse reactions in breastfed infants.

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https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

Important Safety Information, continued

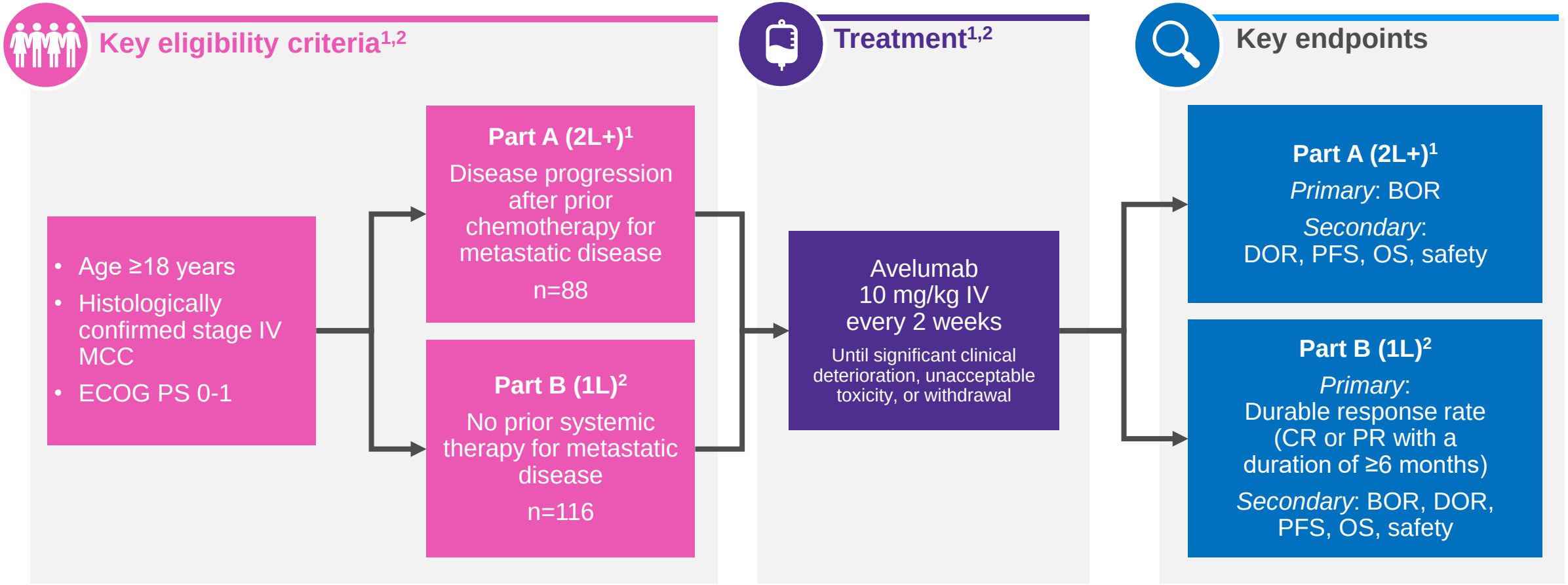
The most common adverse reactions (all grades, ≥20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (47%), musculoskeletal pain (29%), infusion-related reaction (26%), rash (25%), nausea (23%), constipation (22%), cough (22%), and diarrhea (21%).

Laboratory abnormalities worsening from baseline (all grades, ≥20%) in patients with **metastatic MCC** were decreased lymphocyte count (51%), decreased hemoglobin (40%), increased aspartate aminotransferase (31%), decreased platelet count (23%), increased alanine aminotransferase (22%), and increased lipase (21%).

BAVENCIO® (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc.
https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

JAVELIN Merkel 200 Clinical Trial

JAVELIN Merkel 200 (NCT02155647) Is a Phase 2, Prospective, Single-arm, Open-label, Multicenter Trial



1L, first line; **2L**, second line; **BOR**, best overall response; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **MCC**, Merkel cell carcinoma; **OS**, overall survival; **PFS**, progression-free survival.

1. Kaufman HL et al. J Immunother Cancer 2018;6(1):7; 2. ClinicalTrials.gov. NCT02155647. Accessed January 11, 2022. https://clinicaltrials.gov/ct2/show/NCT02155647?term=NCT02155647&draw=2&rank=1

JAVELIN Merkel 200 (Part A)
Clinical Trial MCC – 2L

JAVELIN Merkel 200 (Part A)

Phase 2, prospective, single-arm, open-label, multicenter trial designed to investigate the clinical activity and safety of avelumab in patients with mMCC; Part A of the study enrolled patients who received ≥1 line of chemotherapy in the metastatic setting[1,3]

JAVELIN Merkel 200 (Part A) regimen with avelumab as 2L treatment in mMCC

INCLUSION AND EXCLUSION CRITERIA

KEY ELIGIBILITY CRITERIA:[1]

- ≥18 years
- Histologically confirmed stage IV mMCC
- ECOG PS 0-1
- Disease progression on or after ≥1 line of chemotherapy in the metastatic setting
- ≥1 unidimensional measurable lesion defined by RECIST v1.1 (including skin lesions)
- Unselected for PD-L1 expression or MCPyV status
- Adequate hematologic, hepatic and renal function

KEY EXCLUSION CRITERIA:[2,3]

- Immune-compromising conditions
  - Patients with HIV, hepatitis B, or hepatitis C infection; autoimmune disease; medical conditions requiring systemic immunosuppression; hematologic malignancies; prior organ or allogeneic stem cell transplantation
- CNS metastases
- Prior treatment with anti–PD-1 , anti–PD-L1, or anti–CTLA-4 antibodies
- ECOG PS ≥2

Enrollment started: July 2014[2]
Estimated study completion date: May 2024[2]

n=88[1]

Avelumab 10 mg/kg intravenous infusion every 2 weeks until disease progression,[a] unacceptable toxicity, or withdrawal[1,2]

Locations: 35 sites in Europe, Australia, Japan and USA[4]

ENDPOINTS[1]

Primary:

- **BOR[b]**

Secondary:

- DOR
- PFS
- OS
- Safety and tolerability, PK

Exploratory:

- Biomarker analysis, including PD-L1 expression (73-10 IHC assay)

- All patients received premedication with an antihistamine (eg, diphenhydramine) and paracetamol (acetaminophen) 30-60 min prior to avelumab infusion[3]
- Clinical activity was assessed every 6 weeks according to RECIST v1.1 for 12 months and then every 12 weeks thereafter[5]

[a] Patients were allowed to continue avelumab beyond radiological disease progression in the absence of significant clinical deterioration and based on investigator assessment of potential benefit from continued treatment; in patients achieving a confirmed CR for ≥6-12 months, avelumab could be continued beyond 12 months or discontinued per protocol and investigator choice.
[b] Per the prescribing information, overall response rate and DOR were the major efficacy outcomes.

2L, second-line; **BOR**, best overall response; **CNS**, central nervous system; **CTLA-4**, cytotoxic T-lymphocyte-associated protein 4; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HIV**, human immunodeficiency virus; **IHC**, immunohistochemistry; **IV**, intravenous; **MCPyV**, Merkel cell polyomavirus; **mMCC,** metastatic Merkel cell carcinoma; **OS**, overall survival; **PD-1**, programmed death-1; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival; **PK**, pharmacokinetics; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

1. Kaufman HL et al. J Immunother Cancer 2018;6(1):7; 2. ClinicalTrials.gov. NCT02155647. https://clinicaltrials.gov/ct2/show/NCT02155647 (Accessed 27 June 2022); 3. BAVENCIO® (avelumab) Prescribing Information. Rockland, MA: EMD Serono Inc https://www.emdserono.com/us-en/pi/bavencio-pi.pdf; 4. Kaufman HL et al. Lancet Oncol 2016;17(0):1374-85; 5. D'Angelo SP et al. J Immunother Cancer 2021;9(0):e002646.

JAVELIN Merkel 200 (Part A): Patient and Disease Characteristics

A total of **88 patients** with mMCC were enrolled and treated with avelumab

All patients had received **≥1 prior line** of systemic anticancer treatment

1 **52 patients (59.1%)** had 1 prior treatment

≥2 **36 patients (40.9%)** had ≥2 prior treatments

Baseline characteristics	N=88
Median age (range), years	72.5 (33-88)
Sex, n (%)	
Male	65 (73.9)
Female	23 (26.1)
Site of primary tumor, n (%)	
Skin	67 (76.1)
Nonskin[a]	14 (15.9)
Missing	7 (8.0)
Visceral disease at study entry, n (%)	
Present	47 (53.4)
Absent	41 (46.6)
ECOG PS, n (%)	
0	49 (55.7)
1	39 (44.3)
No. of previous systemic anticancer treatments, n (%)[b]	
1	52 (59.1)
2	25 (28.4)
≥3	11 (12.5)
Tumor PD-L1 status, n (%)†	
Positive	57 (64.8)
Negative	16 (18.2)
Not evaluable	15 (17.0)
Tumor Merkel cell polyomavirus status, n (%)	
Positive	46 (52.3)
Negative	31 (35.2)
Not evaluable	11 (12.5)

[a] Nonskin sites include lymph node (n=12 [13.6%]) and other sites (cheek mucosa and rectosigmoid junction; n=2 [2.3%]). †PD-L1+ status was defined as PD-L1 expression in ≥1% of tumor cells.
[b] In the avelumab prescribing information, 65% of patients were reported to have had one prior anticancer therapy for metastatic MCC and 35% had two or more prior therapies.

ECOG PS, Eastern Cooperative Oncology Group performance status; **mMCC**, metastatic Merkel cell carcinoma; **PD-L1**, programmed death ligand 1.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

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JAVELIN Merkel 200 (Part A): Patient Disposition

- The data cutoff was **September 25, 2020**
- **Median follow-up** was **65.1 months** (range, 60.8-74.1)

One patient (1.1%) remained on treatment

- First dose was in September 2014
- Initially had a PR that deepened to a CR (ongoing; DOR, 64.9 months)

One patient (1.1%) had reinitiated treatment

- First dose was in June 2015
- Had a CR and subsequently discontinued avelumab in July 2016 due to ongoing CR
- After PD in November 2019 (DOR, 47.5 months), patient reinitiated avelumab and is currently still receiving treatment, with a best response of PR

The most common reason for discontinuation was disease progression (n=45 [51.1%])

Patient disposition, n (%)	N=88
Received ≥1 dose of study treatment	**88 (100)**
Treatment ongoing	1 (1.1)
Off treatment	87 (98.9)
Reason for discontinuation of treatment	**87 (98.9)**
Adverse event	11 (12.5)
Lost to follow-up	1 (1.1)
Protocol noncompliance	1 (1.1)
Death	10 (11.4)
Disease progression	45 (51.1)
Withdrawal of consent	9 (10.2)
Other*	10 (11.4)
Discontinued treatment but still in follow-up	**19 (21.6)**
Reinitiated treatment with avelumab	**1 (1.1)**
Discontinued from the trial	**68 (77.3)**
Lost to follow-up	3 (3.4)
Death	58 (65.9)
Withdrawal of consent	7 (8.0)

* Other reasons included CR for 6 months on treatment (per protocol) in 5 patients (5.7%) and switch to commercial avelumab for patient convenience in 2 (2.3%).

CR, complete response; **DOR,** duration of response; **PD,** progressive disease; **PR**, partial response.

D'Angelo SP et al. ESMO Open. 2021;6(6):100290

JAVELIN Merkel 200 (Part A): Efficacy Results from the Prescribing Information

Overall responses

	N=88
ORR, n (%) [95% CI]	29 (33%) [23-44]
Complete responses, n (%)	10 (11%)
Partial responses, n (%)	19 (22%)

	N=29
Median DOR in months (range)	40.5 (2.8-41.5+)
Patients with DOR ≥6 months, n (%)	26 (90%)
Patients with DOR ≥12 months, n (%)	19 (66%)

CI, confidence interval; **DOR**, duration of response; **ORR**, overall response rate.

BAVENCIO® (avelumab) Prescribing Information. Rockland, MA: EMD Serono Inc https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

JAVELIN Merkel 200 (Part A): Efficacy Results (≥3 Years of Follow-up)[1]

Overall responses

Response	N=88
Confirmed best overall response, n (%)	
Complete response	10 (11.4)
Partial response	19 (21.6)
Stable disease	9 (10.2)
Progressive disease	32 (36.4)
Not evaluable	18 (20.5)
ORR (95% CI), %	33.0 (23.3-43.8)
Disease control rate, %	43.2
Response durability	**n=29**
Median duration of response (95% CI), months	40.5 (18.0-NE)
Range	2.8-41.5
Proportion with duration of response (95% CI), %	
≥6 months	93 (75-98)
≥1 year	71 (51-85)
≥2 years	67 (47-82)
≥3 years	52 (26-73)

The ORR was unchanged from that observed after 1 year of follow-up in all patients[2]

CI, confidence interval; **NE**, not estimable; **ORR**, overall response rate.

1. D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674; 2. Kaufman HL et al. J Immunother Cancer 2018;6(1):7.

JAVELIN Merkel 200 (Part A): Efficacy Results in Subgroups

ORR in select subgroups after ≥36 months of follow-up

Subgroup	ORR (95% CI)
Prior systemic therapy received in any disease stage:	
1 (n=52)	40.4% (27.0-54.9)
≥2 (n=36)	22.2% (10.1-39.2)
Visceral metastases at baseline (n=47)	34.0% (20.9-49.3)
No visceral metastases at baseline (n=41)	31.7% (18.1-48.1)
PD-L1+ tumors (n=57)*	36.8% (24.4-50.7)
PD-L1− tumors (n=16)*	18.8% (4.0-45.6)
MCPyV+ tumors (n=46)*	28.3% (16.0-43.5)
MCPyV− tumors (n=31)*	35.5% (19.2-54.6)

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

* In evaluable patients.

CI, confidence interval; **MCPyV**, Merkel cell polyomavirus; **ORR**, overall response rate; **PD-L1**, programmed death-ligand 1.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

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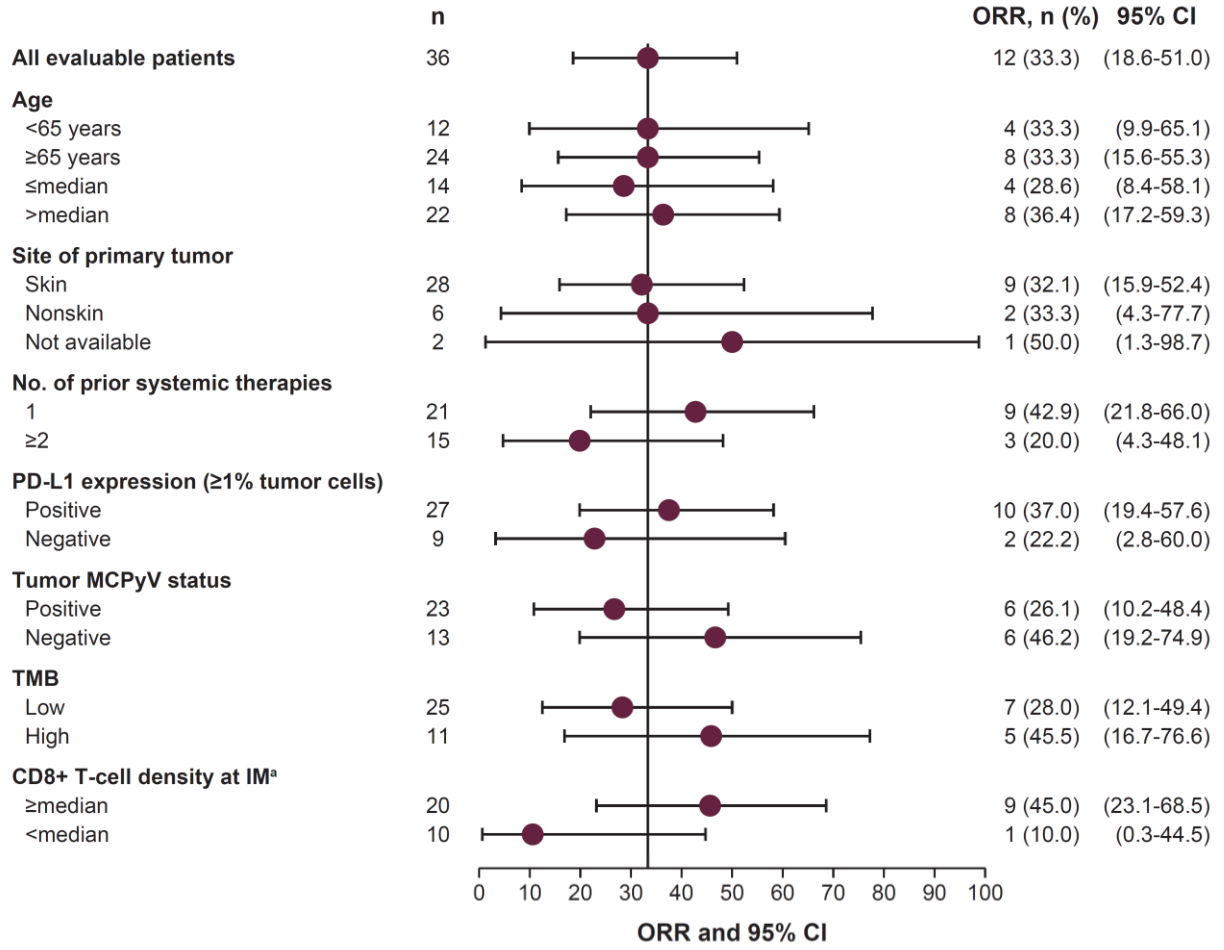
JAVELIN Merkel 200 (Part A): ORR in Selected Subgroups Evaluable for TMB Analysis After ≥24 Months of Follow-up



- **High TMB:** ORR of 45.5% (95% CI, 16.7-76.6)
- **Low TMB:** ORR of 28.0% (95% CI, 12.1-49.4)

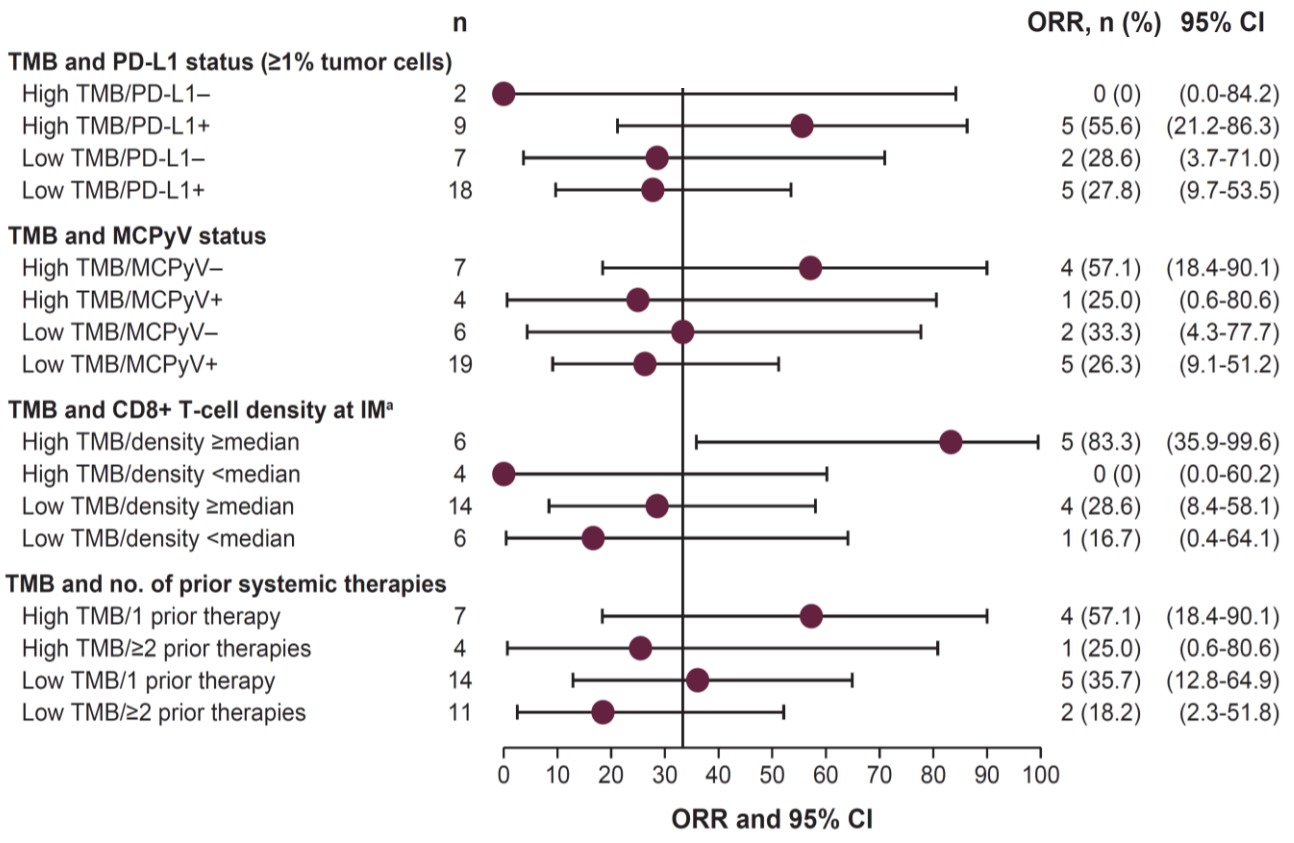
Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

[a] CD8+ T-cell density data were missing for 6 patients.

CI, confidence interval; **IM,** invasive margin; **MCPyV,** Merkel cell polyomavirus; **ORR,** overall response rate; **PD-L1**, programmed death-ligand 1; **TMB,** tumor mutational burden.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

JAVELIN Merkel 200 (Part A): ORR in Selected Subgroups Evaluable for TMB Analysis After ≥24 Months of Follow-up



Among the exploratory subgroups, ORR was highest:

- In patients with tumors with high TMB that were also MCPyV−, PD-L1+
- In patients with a >median CD8+ T-cell density at the IM
- In patients with only 1 prior systemic anticancer treatment

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

[a] CD8+ T-cell density data were missing for 6 patients.

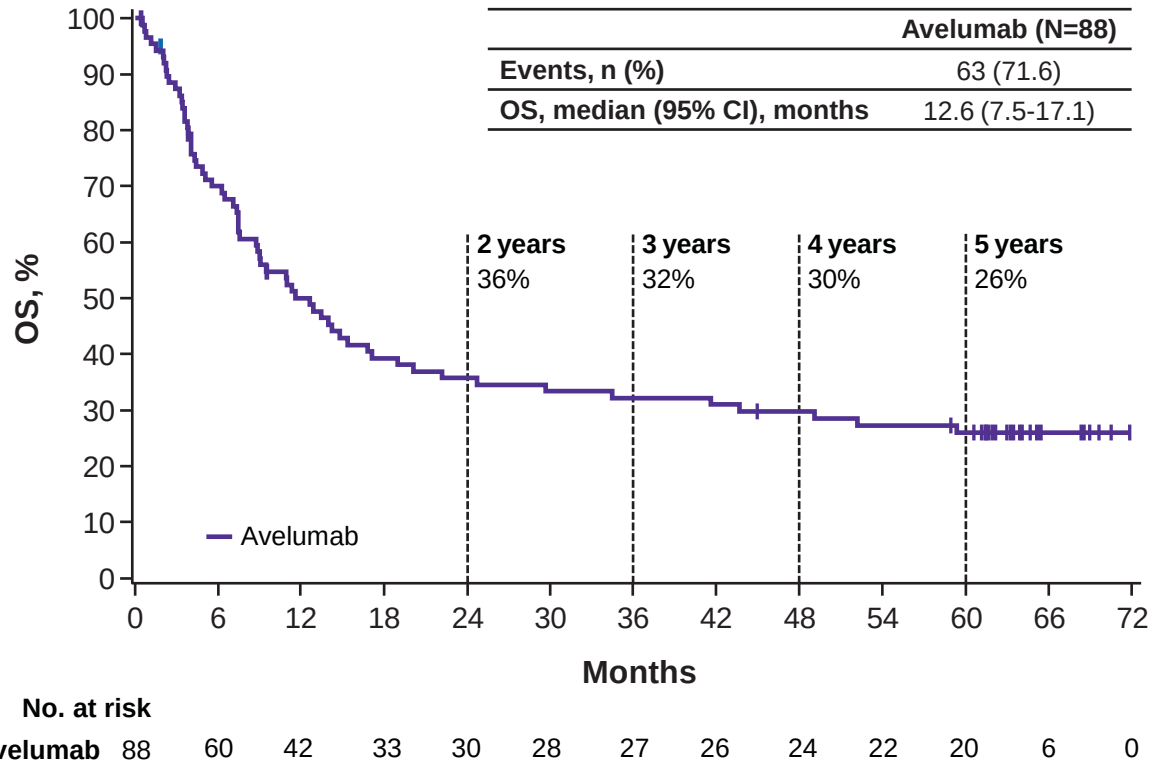
CI, confidence interval; **IM,** invasive margin; **MCPyV,** Merkel cell polyomavirus; **ORR,** overall response rate; **PD-L1**, programmed death-ligand 1; **TMB,** tumor mutational burden.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

JAVELIN Merkel 200 (Part A): OS* in Patients With mMCC That Had Progressed Following Chemotherapy

OS* in patients with mMCC following progression on chemotherapy[1,2]

	Avelumab (N=88)
Events, n (%)	63 (71.6)
OS, median (95% CI), months	12.6 (7.5-17.1)



- **Median OS** was **12.6 months** (95% CI, 7.5-17.1)
- **5-year OS rate** was **26%** (95% CI, 17-36)

At data cutoff, **63 patients (71.6%) had died**

- The most common cause of death was disease progression (n=49 [55.7%])
- Other causes were:
  - Unknown reason (n=9 [10.2%])
  - AE not related to study treatment (n=3 [3.4%])
  - Other reason (n=2 [2.3%])
- No deaths due to treatment-related AE were reported†

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

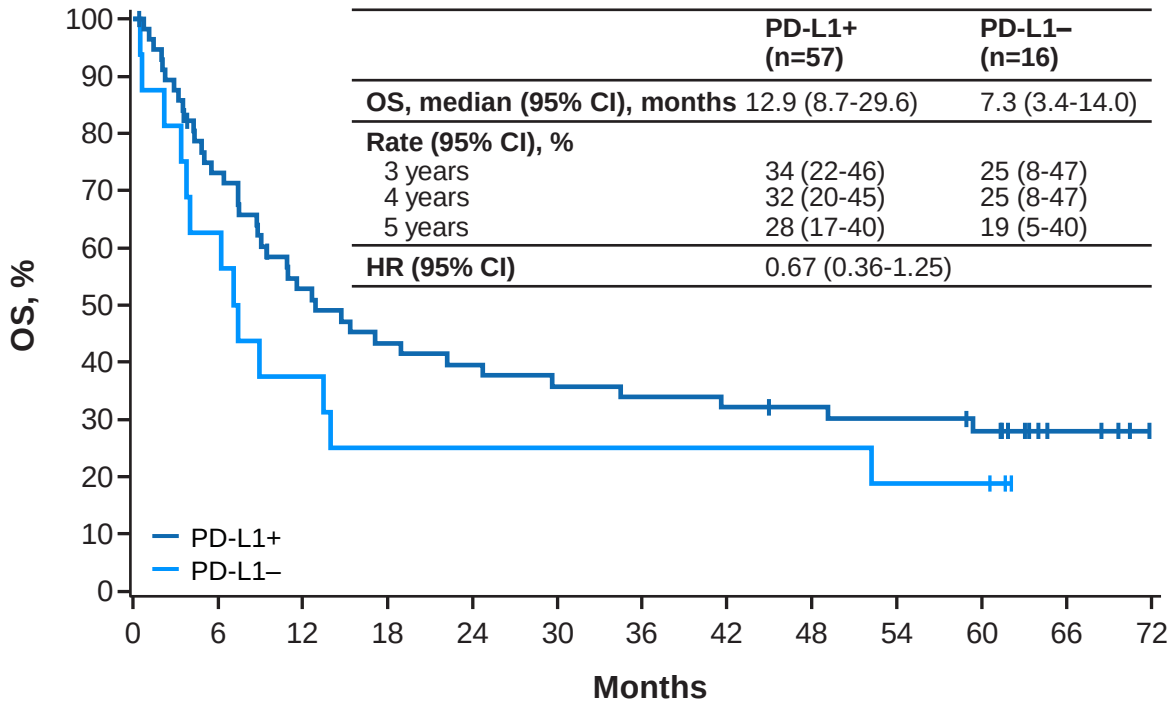
*OS was measured from time of treatment initiation until death from any cause.[3] †The most common (at least 10%) TRAEs were fatigue, diarrhea, and nausea.
OS was a secondary endpoint.

2L+, second line or later; **AE**, adverse event; **CI**, confidence interval; **mMCC**, metastatic Merkel cell carcinoma; **OS**, overall survival; **TRAE**, treatment-related adverse events.

1. D'Angelo SP et al. ESMO Open 2021;6(6):100290; 2. D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674; 3. ClinicalTrials.gov. NCT02155647. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/results/NCT02155647?term=JAVELIN+MERKEL+200&draw=2&rank=1&view=results.

JAVELIN Merkel 200 (Part A): OS* in PD-L1+ and PD-L1− Tumors

OS in subgroups defined by PD-L1 status



	PD-L1+ (n=57)	PD-L1− (n=16)
OS, median (95% CI), months	12.9 (8.7-29.6)	7.3 (3.4-14.0)
Rate (95% CI), %		
3 years	34 (22-46)	25 (8-47)
4 years	32 (20-45)	25 (8-47)
5 years	28 (17-40)	19 (5-40)
HR (95% CI)	0.67 (0.36-1.25)	

No. at risk													
PD-L1+	57	40	28	23	21	19	18	17	16	15	13	4	0
PD-L1−	16	10	6	4	4	4	4	4	4	3	3	0	0

PD-L1+ population (n=57)

- **Median OS** was **12.9 months** (95% CI, 8.7-29.6)
- **OS rates** were:

3 y **34%** 4 y **32%** 5 y **28%**

PD-L1− population (n=16)

- **Median OS** was **7.3 months** (95% CI, 3.4-14.0)
- **OS rates** were:

3 y **25%** 4 y **25%** 5 y **19%**

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

*OS was measured from time of treatment initiation until death from any cause.[2] OS was a secondary endpoint.

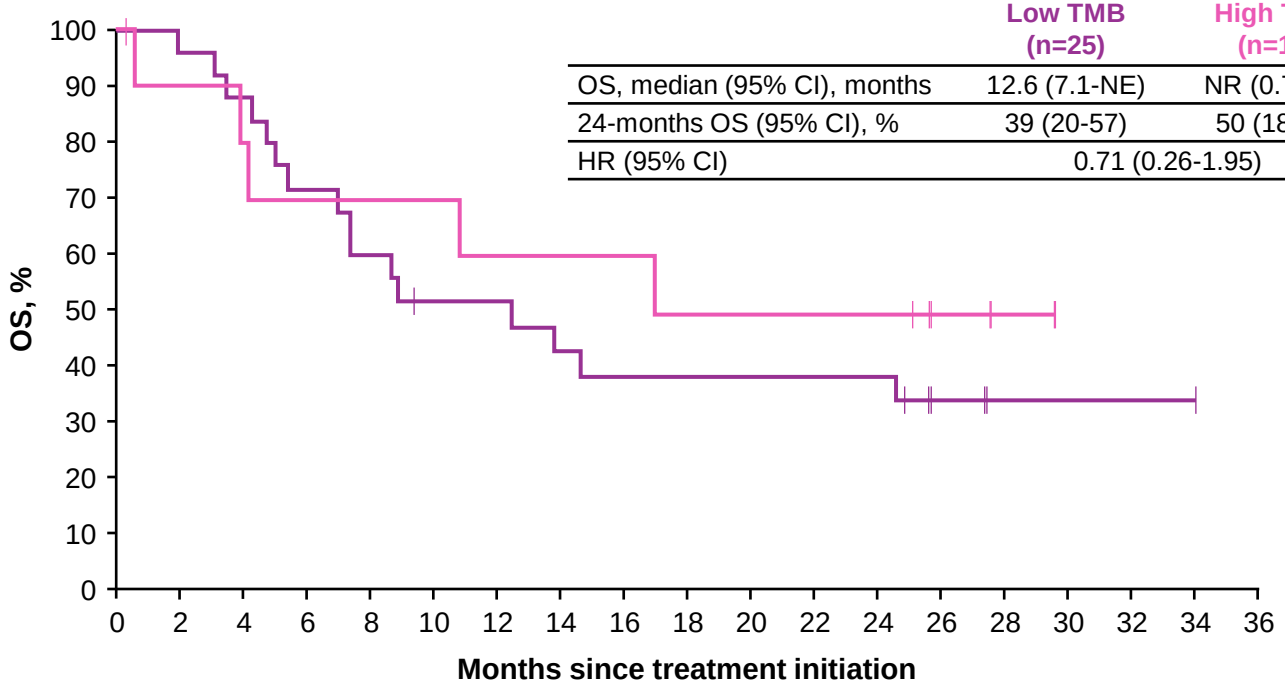
CI, confidence interval; **HR**, hazard ratio; **OS**, overall survival; **PD-L1**, programmed death ligand 1.

1. D'Angelo SP et al. ESMO Open 2021;6(6):100290; 2. ClinicalTrials.gov. NCT02155647. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/results/NCT02155647?term=JAVELIN+MERKEL+200&draw=2&rank=1&view=results.

JAVELIN Merkel 200 (Part A): OS* by TMB Subgroup at ≥44 Months of Follow-up

Patients with long-term OS (those with >36 months of OS after ≥44 months of follow-up; n=27)

	Low TMB (n=25)	High TMB (n=11)
OS, median (95% CI), months	12.6 (7.1-NE)	NR (0.7-NE)
24-months OS (95% CI), %	39 (20-57)	50 (18-75)
HR (95% CI)	0.71 (0.26-1.95)	



No. at risk																			
Low TMB	25	25	22	18	15	12	12	10	9	9	9	9	9	3	1	1	1	1	0
High TMB	11	9	9	7	7	7	6	6	6	5	5	5	5	2	1	0	0	0	0

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

*OS was measured from time of treatment initiation until death from any cause.[2] Data reflect post hoc analysis. Small patient numbers can be a limitation of subgroup analyses. These results are presented for descriptive purposes and cannot be interpreted as demonstration of efficacy in any particular subgroup.

CI, confidence interval; **HR,** hazard ratio; **NE,** not estimable; **NR**, not reached; **OS**, overall survival; **TMB,** tumor mutational burden.

1. D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674; 2. ClinicalTrials.gov. NCT02155647. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/results/NCT02155647?term=JAVELIN+MERKEL+200&draw=2&rank=1&view=results

JAVELIN Merkel 200 (Part A): Exploratory Biomarkers

TMB was analyzed in 36 evaluable patients

- Median TMB was 0.58 NSSV/Mb (range, 0.16-31.6 NSSV/Mb)
- TMB was higher in patients with MCPyV− (n=13) vs MCPyV+ (n=23) tumors (2.72 vs 0.49 NSSV/Mb)
  - TMB did not differ by PD-L1 status
- In patients with high vs low (≥2 vs <2 NSSV/Mb) TMB values:
  - Median OS was not reached vs 12.6 months

MHC class I gene expression

- Expression of MHC class I HLA genes appeared to be downregulated in tumors compared with normal tissues
- MHC class I genes were among the top 0.2% of genes expressed in normal tissue, but only in the top 5% to 10% in tumors
- Of 32 patients with paired tumor and normal profiles, 9 (28.1%) had LOH at the HLA locus

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

HLA, human leukocyte antigen; **LOH,** loss of heterozygosity; **MCPyV,** Merkel cell polyomavirus; **MHC,** major histocompatibility complex; **NSSV/Mb,** nonsynonymous somatic variant per megabase; **OS**, overall survival; **PD-L1**, programmed death-ligand 1; **TMB,** tumor mutational burden.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

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JAVELIN Merkel 200 (Part A): Subsequent Anticancer Therapy

Subsequent treatment	N=88
Received subsequent therapy, n (%)	**26 (29.5)**
Avelumab	4 (4.5)
Carboplatin + etoposide	4 (4.5)
Pembrolizumab	4 (4.5)
Everolimus	3 (3.4)
Nivolumab	3 (3.4)
Pazopanib	3 (3.4)
Capecitabine	2 (2.3)
Cyclophosphamide + doxorubicin + vincristine	2 (2.3)
Paclitaxel	2 (2.3)
Pegylated liposomal doxorubicin hydrochloride	2 (2.3)
Temozolomide	2 (2.3)
Topotecan	2 (2.3)
Amrubicin	1 (1.1)
Carboplatin	1 (1.1)
Carboplatin + paclitaxel	1 (1.1)
Cisplatin	1 (1.1)
Combinations of antineoplastic agents	1 (1.1)
Cyclophosphamide	1 (1.1)
Ipilimumab + nivolumab	1 (1.1)
Octreotide	1 (1.1)
Sunitinib	1 (1.1)
Somatostatin	1 (1.1)
Other therapeutic product	1 (1.1)

26 patients (29.5%) received subsequent anticancer therapy

4 patients (4.5%) received avelumab as subsequent therapy

The most common subsequent therapies were chemotherapy or other immune checkpoint inhibitors (including patients who switched to commercial avelumab)

Nghiem PT et al. Abstract No. 9517. Presented at 2021 ASCO Annual Meeting, June 4-8, 2021; Virtual.

JAVELIN Merkel 200 (Part A): TRAEs and IRRs (N=88)

	Any grade, n (%)	Grade ≥3, n (%)
Any TRAE[a]	68 (77.3)	10 (11.4)
Fatigue	22 (25.0)	0
Diarrhea	11 (12.5)	0
Nausea	11 (12.5)	0
Rash	8 (9.1)	0
Asthenia	7 (8.0)	0
Decreased appetite	7 (8.0)	0
Hypothyroidism	6 (6.8)	1 (1.1)
Pruritus	6 (6.8)	0
Arthralgia	5 (5.7)	0
Aspartate aminotransferase increased	5 (5.7)	0
Blood creatine phosphokinase increased	5 (5.7)	3 (3.4)
Chills	5 (5.7)	0
Rash maculopapular	5 (5.7)	0
Alanine aminotransferase increased	4 (4.5)	1 (1.1)
Lymphopenia	3 (3.4)	2 (2.3)
Gamma glutamyltransferase increased	2 (2.3)	1 (1.1)
Autoimmune disorder	1 (1.1)	1 (1.1)
Blood cholesterol increased	1 (1.1)	1 (1.1)
Ileus	1 (1.1)	1 (1.1)
Neutrophil count decreased	1 (1.1)	1 (1.1)
Thrombocytopenia	1 (1.1)	1 (1.1)
Transaminases increased	1 (1.1)	1 (1.1)
Any IRR[b]	19 (21.6)	0

Shown are individual TRAEs of any grade that occurred in >5% of patients and grade ≥3 TRAEs that occurred in any patient.
[a] The incidence of treatment-related IRR based on the single MedDRA Preferred Term is not listed. [b] Composite term that includes AEs categorized as IRR, anaphylactic reaction, drug hypersensitivity, type I hypersensitivity, or hypersensitivity reaction that occurred on the day of or day after infusion, in addition to signs/symptoms of IRR that occurred on the day of infusion (during or after the infusion) that resolved on the day of onset or next day; includes AEs classified by investigators as related or unrelated to treatment.

AE, adverse event; **IRR,** infusion-related reaction; **MedDRA,** Medical Dictionary for Regulatory Activities; **TRAE,** treatment-related adverse event.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

JAVELIN Merkel 200 (Part A): irAEs (N=88) After ≥36 Months of Follow-up

	Any grade, n (%)	Grade ≥3, n (%)
Any irAE	19 (21.6)	4 (4.5)
Hypothyroidism	5 (5.7)	1 (1.1)
Rash	5 (5.7)	0
Diarrhea	2 (2.3)	0
Erythema	2 (2.3)	0
Abnormal thyroid function test	1 (1.1)	0
Alanine aminotransferase increased	1 (1.1)	1 (1.1)
Aspartate aminotransferase increased	1 (1.1)	0
Autoimmune disorder	1 (1.1)	1 (1.1)
Autoimmune colitis	1 (1.1)	0
Hemophagocytic lymphohistiocytosis	1 (1.1)	0
Hyperthyroidism	1 (1.1)	0
Pruritus	1 (1.1)	0
Rash maculopapular	1 (1.1)	0
Transaminases increased	1 (1.1)	1 (1.1)
Tubulointerstitial nephritis	1 (1.1)	0

irAE, immune-related adverse event.

D'Angelo SP et al. J Immunother Cancer 2020;8(1):e000674.

Summary

This is the longest follow-up (>5 years) reported to date for a cohort of patients with mMCC treated with an immune checkpoint inhibitor[1]

These updated data show OS in patients with mMCC whose disease had progressed following chemotherapy

- 5-year OS rate was 26%[1]
- ≥3-year ORR was 33% (CR of 11.4% and PR of 21.6%)
- Safety results were consistent with those from previous studies of avelumab monotherapy in mMCC and other tumors

Although responses to avelumab occurred irrespective of PD-L1 status,[1] longer OS was observed in patients with PD-L1+ vs PD-L1− tumors[1]

This study does have limitations, including its single-arm, phase 2 design and the small sample size

- Study was not designed or powered to show statistical significance. Long-term analyses reported are limited to OS

This 5-year follow-up analysis further supports the role of avelumab as a treatment option for patients with mMCC[1]

2L+, second line or later; **CR**, complete response; **mMCC**, metastatic Merkel cell carcinoma; **OS**, overall survival; **ORR**, overall response rate; **PD-L1,** programmed death ligand 1; **PR**, partial response.

D'Angelo SP et al. ESMO Open 2021;6(6):100290.

EMD SERONO

JAVELIN Merkel 200 (Part B) Clinical Trial MCC – 1L

JAVELIN Merkel 200 (Part B)

Phase 2, prospective, single-arm, open-label, multicenter trial designed to investigate the clinical activity and safety of avelumab in patients with mMCC; Part B of the study enrolled patients who did not receive any prior systemic treatment for mMCC[1,2]

JAVELIN Merkel 200 (Part B) regimen with avelumab as 1L treatment in mMCC

INCLUSION AND EXCLUSION CRITERIA

KEY ELIGIBILITY CRITERIA:[1]

- ≥18 years
- Histologically confirmed stage IV mMCC
- ECOG PS 0-1
- No prior systemic therapy for metastatic disease
- Prior adjuvant chemotherapy if treatment ended ≥6 months before study initiation
- ≥1 unidimensional measurable lesion defined by RECIST v1.1 (including skin lesions)
- Unselected for PD-L1 expression or MCPyV status
- Adequate hematologic, hepatic and renal function

KEY EXCLUSION CRITERIA:[2]

- Immune-compromising conditions
  - Patients with HIV, hepatitis B, or hepatitis C infection; autoimmune disease; medical conditions requiring systemic immunosuppression; hematologic malignancies; prior organ or allogeneic stem cell transplantation
- CNS metastases
- Prior treatment with anti–PD-1, anti–PD-L1, or anti–CTLA-4 antibodies

Enrollment started: July 2014[2]
Estimated study completion date: May 2024[2]

n=116[1]

Avelumab 10 mg/kg intravenous infusion every 2 weeks until disease progression,[a] unacceptable toxicity, or withdrawal[1]

Locations: 35 sites in Europe, Australia, Japan and USA[3]

ENDPOINTS[1]

Primary:

- Durable response (CR or PR with DOR ≥6 months by RECIST v1.1 per IRC)

Secondary:

- BOR, DOR, PFS, OS
- Safety and tolerability

Exploratory:

- Pre-specified biomarker analyses including, PD-L1, MCPyV
- Exploratory biomarker analyses including, CD8, tumor mutational burden (TMB), MHC Class I gene expression

- All patients received premedication with an antihistamine and acetaminophen prior to the first 4 infusions to mitigate infusion-related reactions[1]
- Clinical activity was assessed every 6 weeks and then every 12 weeks thereafter[1]
- [a] Continuation beyond radiological disease progression was permitted in absence of significant clinical deterioration and based on investigator assessment potential benefit from continued treatment[1]

1L, first-line; **BOR**, best overall response; **CNS**, central nervous system; **CR**, complete response; **CTLA-4**, cytotoxic T-lymphocyte-associated protein 4; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HIV**, human immunodeficiency virus; **IRC**, independent review committee; **IV**, intravenous, **MCPyV**, Merkel cell polyomavirus; **mMCC**, metastatic Merkel cell carcinoma; **MHC**, major histocompatibility complex; **OS**, overall survival; **PD-1**, programmed death-1; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival; **PR**, partial response; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **TMB**, tumor mutational burden.

1. D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646; 2. ClinicalTrials.gov. NCT02155647. https://clinicaltrials.gov/ct2/show/NCT02155647 (Accessed February 28, 2022); 3 Kaufman HL et al. Lancet Oncol 2016;17(0):1374–85.

JAVELIN Merkel 200 (Part B): Patient Characteristics

Median duration of treatment (May 2, 2019, data cutoff)[1]:
24.0 weeks (range, 2.0-154.0 weeks)

Median follow-up (February 2, 2022, data cutoff)[2]:
54.3 months (range, 48.0-69.7 months)

Median number of avelumab infusions (May 2, 2019, data cutoff)[1]:
11.5 (range, 1-76)

Characteristic[1]	Patients (N=116)
Age	
<65 y, n (%)	22 (19.0)
≥65 y, n (%)	94 (81.0)
Median (range), years	74 (41-93)
Sex, n (%)	
Male	81 (69.8)
Female	35 (30.2)
ECOG PS, n (%)	
0	72 (62.1)
1	44 (37.9)
Geographic region, n (%)	
North America	29 (25.0)
Western Europe	75 (64.7)
Australia	9 (7.8)
Asia	3 (2.6)
Time since initial diagnosis, median (range), months	10.6 (0.7-120.9)
Time since diagnosis of metastatic disease, median (range), months	2.2 (0.4-49.6)

Characteristic[1]	Patients (N=116)
Site of primary tumor, n (%)	
Skin	104 (89.7)
Lymph node	1 (0.9)
Not reported	11 (9.5)
Visceral metastases at baseline, n (%)	
Present	79 (68.1)
Absent	35 (30.2)
Not reported	2 (1.7)
PD-L1 status, n (%)[a]	
Positive	21 (18.1)
Negative	87 (75.0)
Not evaluable	8 (6.9)
MCPyV status, n (%)[b]	
Positive	70 (60.3)
Negative	37 (31.9)
Not evaluable	9 (7.8)
Prior anticancer drug therapy, n (%)	
No	110 (94.8)
Yes	6 (5.2)[c]

[a] PD-L1+ status was defined as expression in ≥1% of tumor cells, assessed using a Dako PD-L1 73-10 IHC assay. [b] Assessed by IHC. [c] Either cisplatin or carboplatin, combined with etoposide in 3 patients; given either for locally advanced disease (n=4; 3.4%) or as adjuvant therapy (n=2; 1.7%).

ECOG PS, Eastern Cooperative Oncology Group performance status; **PD-L1**, programmed death ligand 1.

1. D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646; 2. D'Angelo SP et al. Abstract No. 604. Presented at: SITC 2022. November 8-12, 2022; Boston, MA, USA.

EMD SERONO

JAVELIN Merkel 200 (Part B): Patient Disposition

Follow-up Analysis
Data cutoff: Feb 2, 2022

	N = 116
Received ≥1 dose of avelumab, n (%)	116 (100)
Study treatment ongoing	7 (6.0)
Discontinued study treatment	109 (94.0)
Reason for discontinuation of study treatment, n (%)	
Disease progression	54 (46.6)
Adverse event	27 (23.3)
Withdrawal of consent	6 (5.2)
Death	5 (4.3)
Loss to follow-up	1 (0.9)
Other	16 (13.8)

	N = 116
Re-initiated study treatment with avelumab, n (%)	2 (1.7)
Discontinued study treatment but remained in follow-up, n (%)	22 (19.0)
Discontinued from the trial, n (%)	87 (75.0)
Reason for discontinuation from the trial, n (%)	
Death	71 (61.2)
Loss to follow-up	4 (3.4)
Withdrawal of consent	4 (3.4)
Other	8 (6.9)

D'Angelo SP et al. Abstract No. 604. Presented at: SITC 2022. November 8-12, 2022; Boston, MA, USA.

JAVELIN Merkel 200 (Part B): Efficacy Results from the Prescribing Information

Overall responses

	N=116
ORR, n (%) [95% CI]	46 (40%) [31,49]
Complete responses, n (%)	19 (16%)
Partial responses, n (%)	27 (23%)

	N=46
Median DOR in months (range)	18.2 (1.2+, 28.3+)
Patients with DOR ≥6 months, n (%)	35 (76%)
Patients with DOR ≥12 months, n (%)	24 (52%)

CI, confidence interval; **DOR**, duration of response; **ORR**, overall response rate.
BAVENCIO® (avelumab) Prescribing Information. Rockland, MA: EMD Serono Inc https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

JAVELIN Merkel 200 (Part B): 1L Avelumab DRR and ORR

Primary Analysis
Data cutoff: May 2, 2019

DRR

35 patients had a durable response lasting ≥6 months

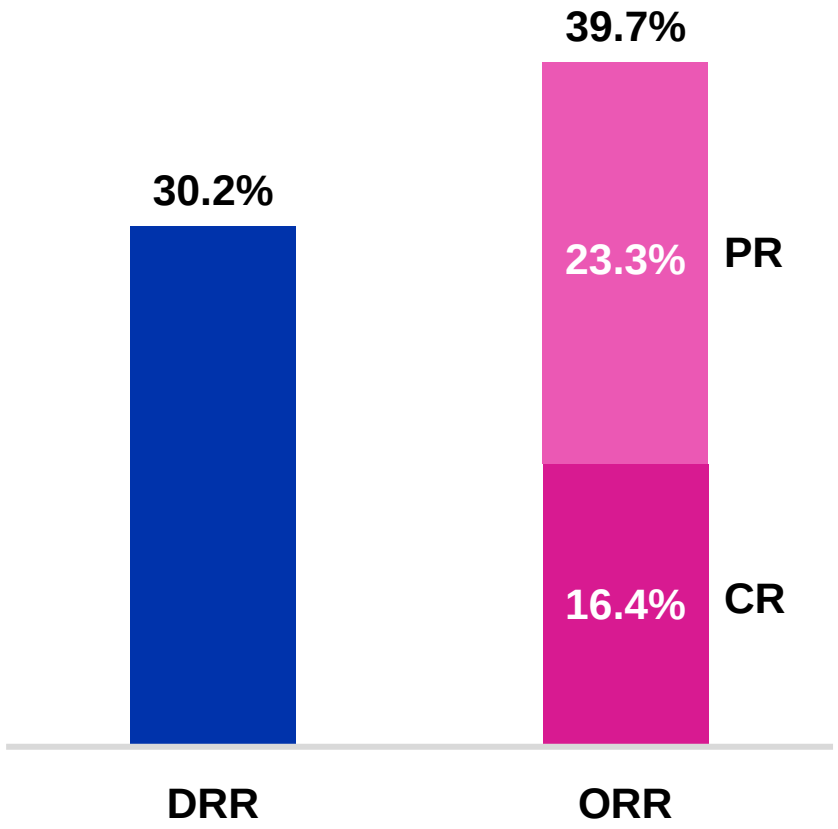
DRR was 30.2% (95% CI, 22.0%-39.4%)

ORR

46 patients had a confirmed BOR of CR (n=19) or PR (n=27)

ORR was 39.7% (95% CI, 30.7%-49.2%)

	N=116
Best overall response, n (%)	
Complete response	19 (16.4)
Partial response	27 (23.3)
Stable disease	12 (10.3)
Noncomplete response/nonprogressive disease	1 (0.9)
Progressive disease	48 (41.4)
Not evaluable	9 (7.8)[a]
Objective response rate (95% CI), %	39.7 (30.7-49.2)

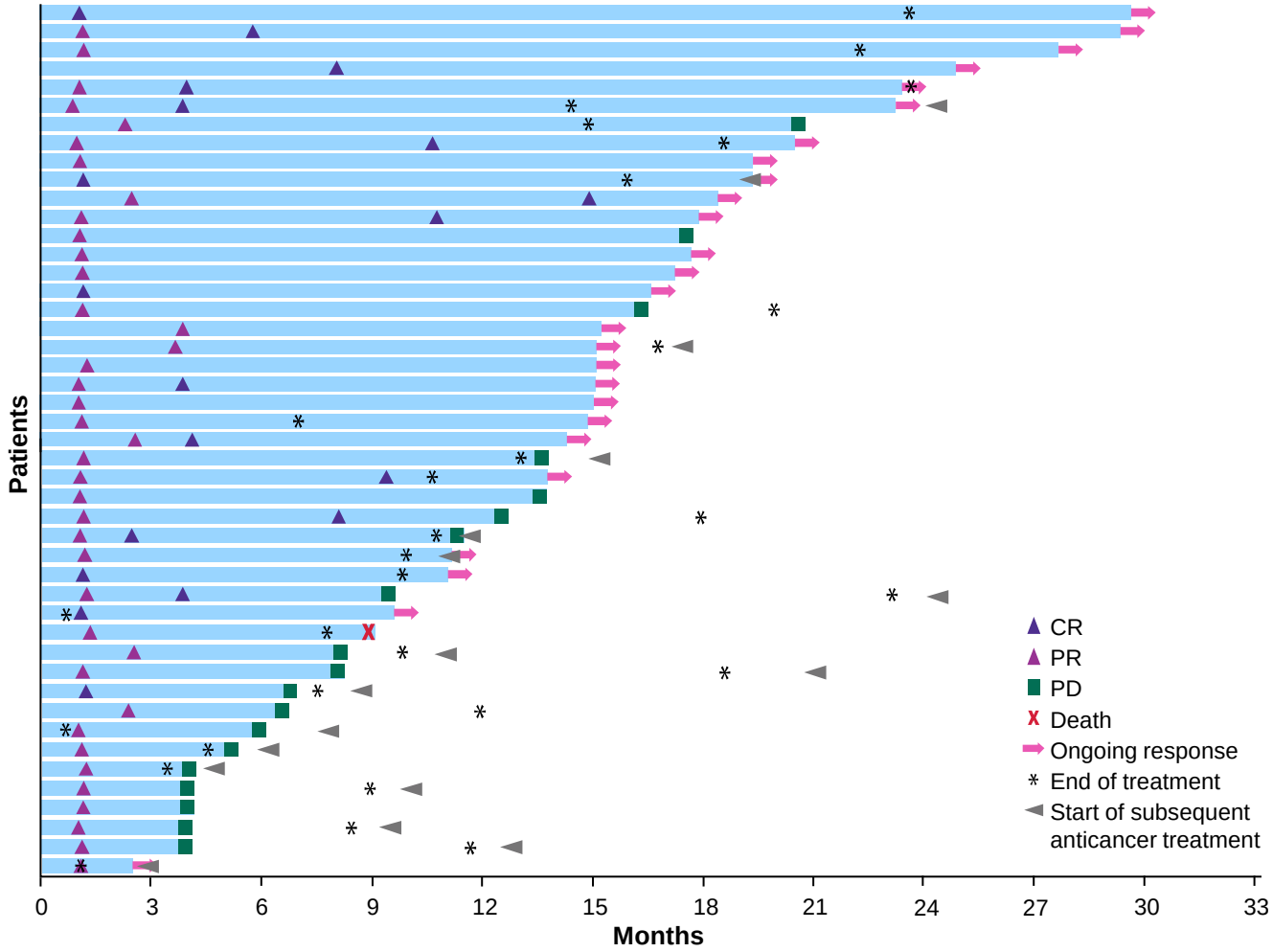


Responses were determined by independent review committee per RECIST v1.1.
[a] No postbaseline assessments due to early death (n=4) or other reasons (n=2), no adequate baseline assessment (n=2), or all postbaseline assessments had overall response of not evaluable (n=1).

1L, first line; **BOR,** best overall response; **CI**, confidence interval; **CR**, complete response; **DRR**, durable response rate; **ORR**, overall response rate; **PR**, partial response; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): Time to and Duration of Response



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93.5% of patients had a **response by 3 months**

Median time to response was **6.1 weeks** (range, 5-36 weeks)

Median DOR was 18.2 months (95% CI, 11.3 months to NE)

56.5% of patients (n=26) had an **ongoing response at data cutoff**

	N=116
Patients with response, n	46
Median duration of response (95% CI), months[a]	18.2 (11.3-NE)
Range, months	1.2-28.3
Proportion with duration of response (95% CI), %[a]	
≥6 months	78 (63-87)
≥12 months	66 (50-78)
≥18 months	52 (34-67)
≥24 months	45 (25-63)

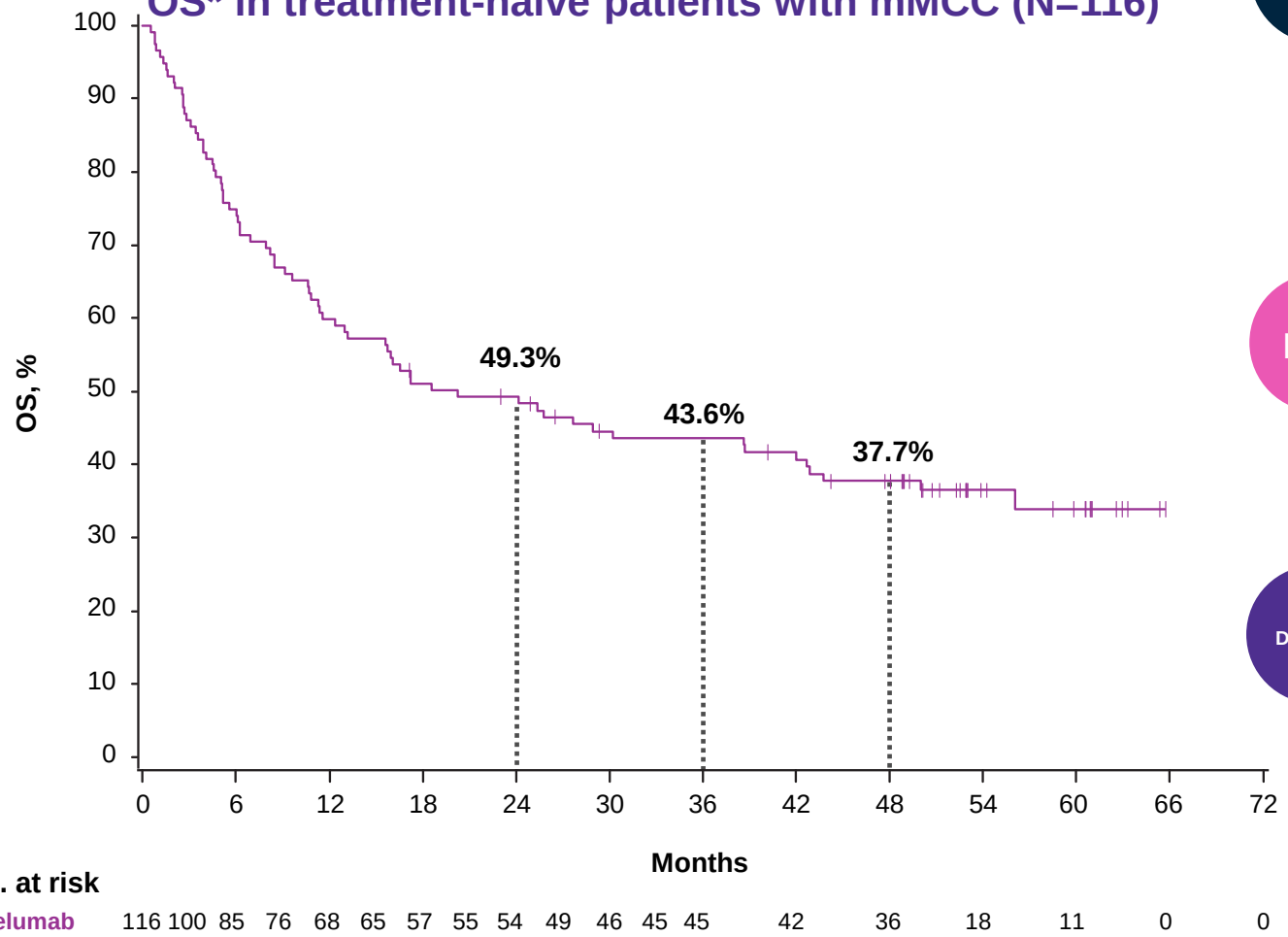
[a] Based on Kaplan-Meier estimates.

1L, first line; **CI**, confidence interval; **CR**, complete response; **DOR**, duration of response; **NE**, not estimable; **PD**, progressive disease; **PR**, partial response.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): Survival Outcome Measures

OS* in treatment-naïve patients with mMCC (N=116)



*OS was measured from time of treatment initiation until death from any cause.[3]

CI, confidence interval; ; **mMCC**, metastatic Merkel cell carcinoma; **OS**, overall survival; **PFS**, progression-free survival.

OS*

Median OS was **20.3 months** (95% CI, 12.4-42.0 months)

(Feb 2, 2022, data cutoff)[1]

- 2-year rate: 49.3% (95% CI, 39.8%-58.0%)
- 3-year rate: 43.6% (95% CI, 34.3%-52.5%)
- 4-year rate: 37.7% (95% CI, 28.7%-46.7%)

PFS

Median PFS was **4.1 months** (95% CI, 1.4-6.1 months)

(May 2, 2019, data cutoff)[2]

- 6-month rate: 41% (95% CI, 32%-50%)
- 12-month rate: 31% (95% CI, 23%-40%)

DEATHS

At data cutoff (Feb 2, 2022), 72 patients (62.1%) had died

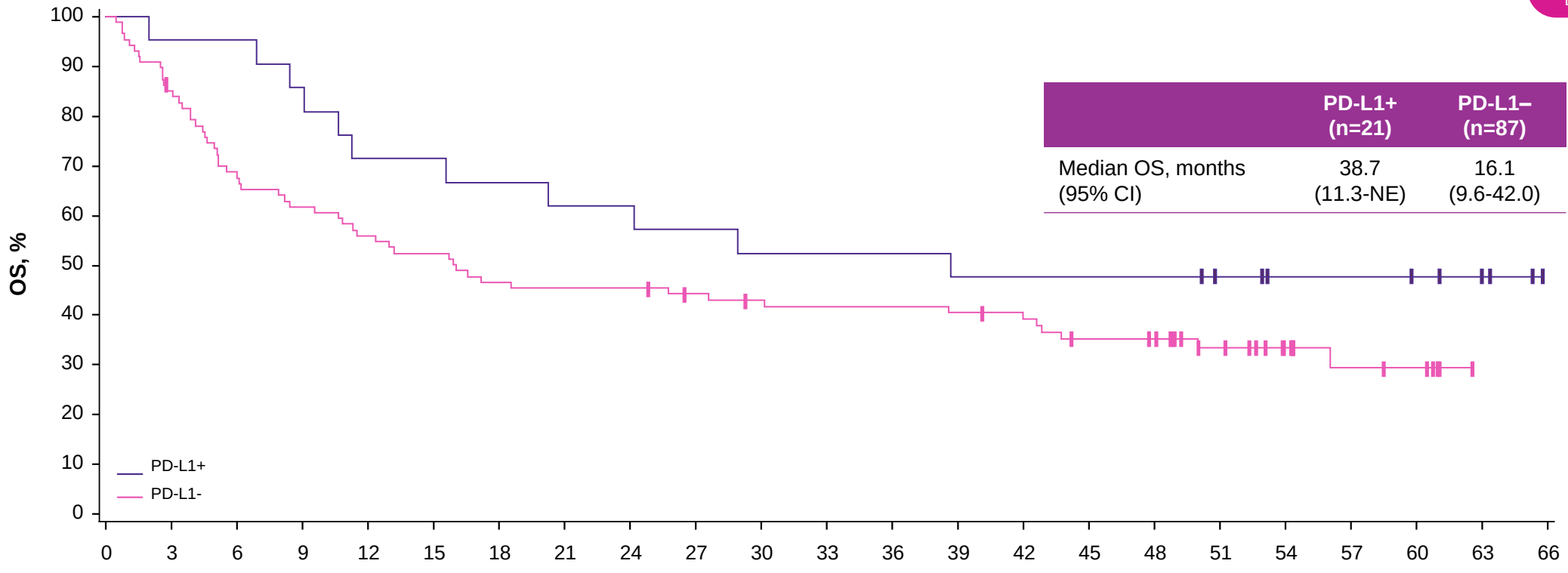
Cause for death, n (%)[1]

Disease progression	57 (49.1)
Unknown	7 (6.0)
AE unrelated to study treatment	3 (2.6)
Other	5 (4.3)

1. D'Angelo SP et al. Abstract No. 604. Presented at: SITC 2022. November 8-12, 2022; Boston, MA, USA; 2. D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646; 3. ClinicalTrials.gov. NCT02155647. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/results/NCT02155647?term=JAVELIN+MERKEL+200&draw=2&rank=1&view=results.

JAVELIN Merkel 200 (Part B): OS* With 1L Avelumab in Subgroups Defined by PD-L1 Status

Follow-up Analysis
Data cutoff: Feb 2, 2022



	PD-L1+ (n=21)	PD-L1– (n=87)
Median OS, months (95% CI)	38.7 (11.3-NE)	16.1 (9.6-42.0)

No. at risk

PD-L1+	21	20	20	18	15	15	14	13	13	12	11	11	11	10	10	10	10	8	6	6	5	4	0
PD-L1-	87	73	59	53	48	45	40	39	39	36	34	33	33	32	31	26	25	18	12	7	6	0	0

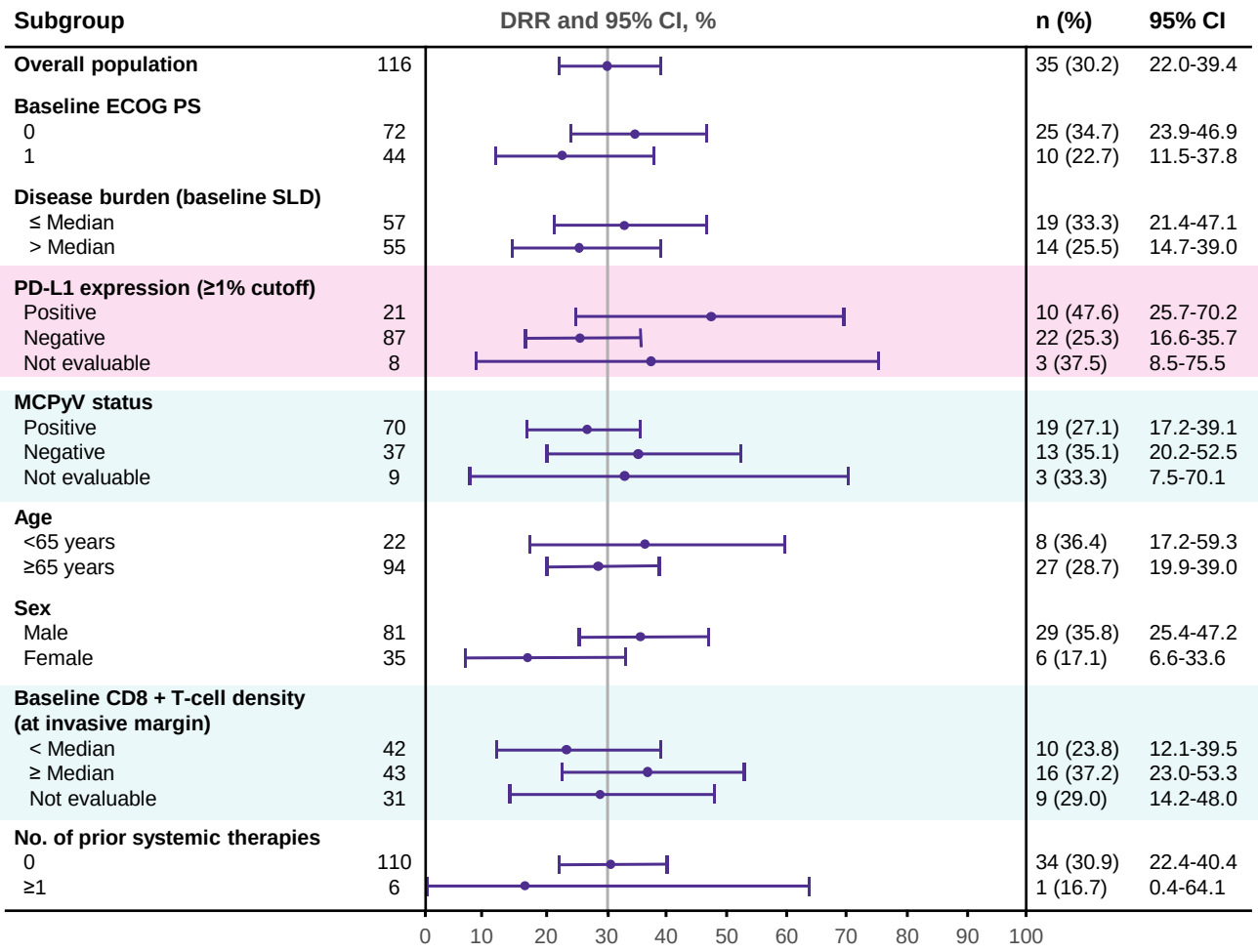
*OS was measured from time of treatment initiation until death from any cause.[2]

CI, confidence interval; **OS**, overall survival; **PD-L1**, programmed death ligand 1; **NE,** not estimable.

1. D'Angelo SP et al. Abstract No. 604. Presented at: SITC 2022. November 8-12, 2022; Boston, MA, USA; 2. ClinicalTrials.gov. NCT02155647. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/results/NCT02155647?term=JAVELIN+MERKEL+200&draw=2&rank=1&view=results.

JAVELIN Merkel 200 (Part B): DRR in Subgroups

Primary Analysis
Data cutoff: May 2, 2019



A trend was seen for **higher DRR** in patients with **PD-L1+** vs PD-L1− tumors (47.6% vs 25.3%, respectively)

Numerically **higher DRRs** were observed in patients with:

- **MCPyV−** (vs MCPyV+) tumors
- **Median or higher CD8+ T-cell density** at the invasive margin (vs less than median)

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

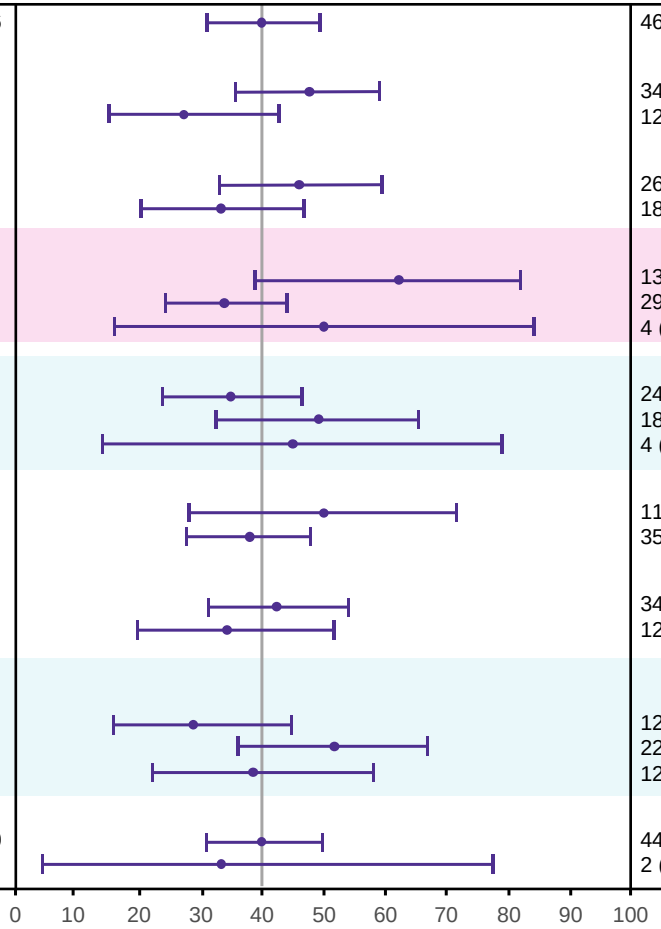
CI, confidence interval; **DRR**, durable response rate; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **MCPyV**, Merkel cell polyomavirus; **PD-L1,** programmed death ligand 1; **SLD**, sum of the longest diameter.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): ORR in Subgroups

Primary Analysis
Data cutoff: May 2, 2019

Subgroup		n (%)	95% CI
Overall population	116	46 (39.7)	30.7-49.2
Baseline ECOG PS			
0	72	34 (47.2)	35.3-59.3
1	44	12 (27.3)	15.0-42.8
Disease burden (baseline SLD)			
≤ Median	57	26 (45.6)	32.4-59.3
> Median	55	18 (32.7)	20.7-46.7
PD-L1 expression (≥1% cutoff)			
Positive	21	13 (61.9)	38.4-81.9
Negative	87	29 (33.3)	23.6-44.3
Not evaluable	8	4 (50.0)	15.7-84.3
MCPyV status			
Positive	70	24 (34.3)	23.3-46.6
Negative	37	18 (48.6)	31.9-65.6
Not evaluable	9	4 (44.4)	13.7-78.8
Age			
<65 years	22	11 (50.0)	28.2-71.8
≥65 years	94	35 (37.2)	27.5-47.8
Sex			
Male	81	34 (42.0)	31.1-53.5
Female	35	12 (34.3)	19.1-52.2
Baseline CD8 + T-cell density (at invasive margin)			
< Median	42	12 (28.6)	15.7-44.6
≥ Median	43	22 (51.2)	35.5-66.7
Not evaluable	31	12 (38.7)	21.8-57.8
No. of prior systemic therapies			
0	110	44 (40.0)	30.8-49.9
≥1	6	2 (33.3)	4.3-77.7



A trend was seen for **higher ORR** in patients with **PD-L1+** vs PD-L1− tumors (61.9% vs 33.3%, respectively)

Numerically **higher ORRs** were observed in patients with:

- **MCPyV−** (vs MCPyV+) tumors
- **Median or higher CD8+ T-cell density** at the invasive margin (vs less than median)

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

CI, confidence interval; **DRR**, durable response rate; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **MCPyV**, Merkel cell polyomavirus; **ORR**, overall response rate; **OS**, overall survival; **PD-L1,** programmed death ligand 1; **SLD**, sum of the longest diameter.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): Exploratory Biomarkers

TMB was analyzed in 52 evaluable patients

- Median TMB was 0.34 NSSV/Mb (range, 0.02-29.4 NSSV/Mb)
- TMB was higher in patients with MCPyV− (n=19) vs MCPyV+ (n=31) tumors (10.52 vs 0.22 NSSV/Mb)
  - TMB did not differ by PD-L1 status or by achievement of objective response
- In patients with high vs low (≥2 vs <2 NSSV/Mb) TMB values:
  - ORRs were 50.0% (95% CI, 26.0%-74.0%) vs 41.2% (95% CI, 24.6%-59.3%)
  - Median OS was not reached vs 17.2 months

MHC class I gene expression

- MHC class I gene expression was higher in tumors with high CD8+ T-cell density
- Expression of MHC class I genes was lower in MCC tumors vs normal tissues; however, MHC class I expression did not appear to correlate with response or OS
- Both T-cell activation and exhaustion gene signatures correlated with higher MHC class I expression, suggesting that the immune response in these tumors is primed but exhausted

Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

CI, confidence interval; **MCC**, Merkel cell carcinoma; **MCPyV**, Merkel cell polyomavirus; **MHC,** major histocompatibility complex; **NSSV/Mb**, nonsynonymous somatic variants per megabase; **ORR**, overall response rate; **OS**, overall survival; **PD-L1**, programmed death ligand 1; **TMB**, tumor mutational burden.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): Safety (N=116)

TRAEs

- Grade 3 TRAEs occurred in 20 patients (17.2%)
- A grade 4 TRAE occurred in 1 patient (0.9%)[c]
- No treatment-related deaths occurred
- TRAEs led to treatment discontinuation in 14 patients (12.1%)

irAE

An irAE of any grade occurred in 35 patients (30.2%), and reached grade ≥3 in 7 (6.0%)

IRR

An IRR[b] occurred in 34 patients (29.3%)
- 1 patient (0.9%) had a grade 3 IRR
- No grade ≥4 IRRs occurred

Safety outcome, n (%)	N=116
AE, any grade	116 (100.0)
TRAE, any grade	94 (81.0)
AE, grade ≥3	70 (60.3)
TRAE, grade ≥3	21 (18.1)
Serious AE	58 (50.0)
Serious TRAE	17 (14.7)
AE leading to death	15 (12.9)
TRAE leading to death	0
AE leading to permanent treatment discontinuation	30 (25.9)
TRAE leading to permanent treatment discontinuation	14 (12.1)
irAE,[a] any grade	35 (30.2)
irAE,[a] grade ≥3	7 (6.0)
IRR,[b] any grade	34 (29.3)
IRR,[b] grade ≥3	1 (0.9)

[a] Based on a prespecified list of Medical Dictionary for Regulatory Activities terms followed by comprehensive medical review. [b] Composite term, which includes AEs categorized as IRR, anaphylactic reaction, drug hypersensitivity, type I hypersensitivity, or hypersensitivity reaction that occurred on the day of or day after infusion, in addition to signs/symptoms of infusion-related reaction that occurred on the day of infusion (during or after the infusion) that resolved on the day of onset or next day; includes AEs classified by investigators as related or unrelated to treatment. [c] Dermatitis psoriasiform.

AE, adverse event; **irAE**, immune-related adverse event; **IRR**, infusion-related reaction; **TRAE**, treatment-related adverse event.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): Most Common TRAEs (N=116)

	N=116	
	Any grade	Grade ≥3
Any treatment-related adverse event, n (%)	94 (81.0)	21 (18.1)
Fatigue	24 (20.7)	1 (0.9)
Asthenia	16 (13.8)	0
Pruritus	15 (12.9)	1 (0.9)
IRR[a]	13 (11.2)	1 (0.9)
Chills	12 (10.3)	0
Lipase increased	6 (5.2)	4 (3.4)
Appetite decreased	6 (5.2)	1 (0.9)
ALT increased	5 (4.3)	1 (0.9)
Amylase increased	3 (2.6)	3 (2.6)
AST increased	2 (1.7)	1 (0.9)
Autoimmune nephritis	1 (0.9)	1 (0.9)
Autoimmune neuropathy	1 (0.9)	1 (0.9)

	N=116	
	Any grade	Grade ≥3
Any treatment-related adverse event, n (%)	94 (81.0)	21 (18.1)
Cholangitis	1 (0.9)	1 (0.9)
Colitis	1 (0.9)	1 (0.9)
Dehydration	1 (0.9)	1 (0.9)
Dermatitis psoriasiform	1 (0.9)	1 (0.9)
Gait disturbance	1 (0.9)	1 (0.9)
Liver function test increased	1 (0.9)	1 (0.9)
Paraneoplastic encephalomyelitis	1 (0.9)	1 (0.9)
Paraneoplastic syndrome	1 (0.9)	1 (0.9)
Polyneuropathy in malignant disease	1 (0.9)	1 (0.9)
Troponin increased	1 (0.9)	1 (0.9)
Tumor lysis syndrome	1 (0.9)	1 (0.9)
Any IRR[b]	34 (29.3)	1 (0.9)

TRAEs of any grade in ≥10% of patients or grade ≥3 in any patient are listed.
[a] Treatment-related IRRs based on the single Medical Dictionary for Regulatory Activities preferred term. [b] Includes adverse events (irrespective of relatedness) categorized as IRR, drug hypersensitivity, or hypersensitivity reaction that occurred on the day of or the day after infusion, in addition to signs/symptoms of IRR that occurred on day of infusion (during or after the infusion) that resolved on the day of onset or the next day.

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **IRR**, infusion-related reaction; **TRAE,** treatment-related adverse event.

D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646.

JAVELIN Merkel 200 (Part B): Subsequent Treatment (In Any Line)

- 48 patients (41.4%) received ≥1 subsequent anticancer drug therapy after discontinuing study treatment with avelumab
- The most common subsequent therapies (any line) were etoposide (20 [17.2%]), carboplatin (18 [15.5%]), and avelumab (14 [12.1%]; all 14 patients received single-agent avelumab outside of a clinical trial)

Subsequent treatment,[a] n (%)	n=48[b]
Etoposide	20 (17.2)
Carboplatin	18 (15.5)
Avelumab	14 (12.1)
Pembrolizumab	9 (7.8)
Paclitaxel	5 (4.3)
Ipilimumab	4 (3.4)
Cisplatin	3 (2.6)
Carboplatin + etoposide	2 (1.7)
Cisplatin + etoposide	2 (1.7)
Nivolumab	2 (1.7)
Temozolomide	2 (1.7)

In 14 patients who received further avelumab after discontinuing from the study:

	n=14
Reason for discontinuation	
PD	6
AE	3
Other[c]	5
Response status when avelumab was discontinued (per investigator assessment)	
CR/PR	6
PD	6
NE	2
Best response to post-study avelumab (per investigator assessment)	
CR	5
SD	1
PD	2
NR	6

Best response to subsequent avelumab	n=6
CR	3
SD	1
Unknown	2

Best response to subsequent avelumab	n=6
CR	1
PD	2
Unknown	3

Best response to subsequent avelumab	n=2
CR	1
Unknown	1

[a]Agents that were used in 2 or more patients. [b] Some patients received >1 subsequent treatment and are subsequently included in more than one row of the table. [c]Other reasons include physician and/or patient decision in 3 instances, complete metabolic remission in 1 instance, and not specified in 1 instance.
AE, adverse event; **CR**, complete response; **NE**, not estimable; **NR** not reported; **PD**, progressive disease; **PR** partial response; **SD**, stable disease.

D'Angelo SP et al. Abstract No. 604. Presented at: SITC 2022. November 8-12, 2022; Boston, MA, USA.

JAVELIN Merkel 200 (Part B): Summary

1L avelumab ORR was 40% and DRR was 30%[1]

With 1L avelumab, median OS was 20.3 months[1] and 4-year OS rate was 38%[2]

PD-L1

Most patients in the study population had PD-L1− tumors (75.0% vs 18.1% with PD-L1+ tumors)[1]

- Responses occurred in patients with both PD-L1+ and PD-L1− tumors, with a trend for higher response rates in patients with PD-L1+ tumors

This study does have limitations, including its single-arm, phase 2 design and the small sample size[1]

- Study was not designed or powered to show statistical significance. Long-term analyses reported are limited to OS

Safety results were consistent with results from previous studies of avelumab monotherapy in mMCC and other tumors[1]

DOR, duration of response; **DRR**, durable response rate; **mMCC**, metastatic Merkel cell carcinoma; **ORR**, overall response rate; **OS**, overall survival; **PD-L1**, programmed death ligand 1.

1. D'Angelo SP et al. J Immunother Cancer 2021;9(7):e002646; 2. D'Angelo SP et al. Abstract No. 604. Presented at: SITC 2022. November 8-12, 2022; Boston, MA, USA.

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JAVELIN Merkel 200 Clinical Trial Pooled Safety Data per Prescribing Information

JAVELIN Merkel 200: Adverse Reactions

Adverse Reactions in ≥10% of Patients With Metastatic MCC Receiving Avelumab (N=204)

Adverse reactions	Avelumab (N=204)	
	All Grades %	Grade 3-4 %
Fatigue[a]	47	2.9
Musculoskeletal pain[b]	29	1.5
Infusion-related reaction[c]	26	0.5
Rash[d]	25	0
Nausea	23	0
Constipation	22	0.5
Cough	22	0
Diarrhea[e]	21	1
Decreased appetite	18	3.4
Edema[f]	17	0

Adverse reactions	Avelumab (N=204)	
	All Grades %	Grade 3-4 %
Abdominal pain[g]	16	3.4
Decreased weight	16	0.5
Pruritus[h]	16	0.5
Dyspnea[i]	15	1
Arthralgia	13	0.5
Vomiting	12	1
Hypertension	11	6

- **The median duration of exposure to avelumab was 4.1 months (range: 2 weeks to 48 months).**
- **Serious adverse reactions occurred in 52% of patients receiving avelumab. The most frequent serious adverse reactions (≥2% of patients) were general physical health deterioration, anemia, abdominal pain, acute kidney injury, sepsis, hyponatremia, and infusion-related reaction.**

a Fatigue is a composite term that includes fatigue and asthenia. b Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, neck pain, and pain in extremity. c Infusion-related reaction is a composite term that includes drug hypersensitivity, flushing, hypersensitivity, chills, pyrexia, back pain, infusion-related reaction, dyspnea, and hypotension. d Rash is a composite term that includes rash, rash macular, rash maculo-papular, erythema, rash erythematous, rash pruritic, and dermatitis bullous. e Diarrhea is a composite term that includes diarrhea and colitis. f Peripheral edema is a composite term that includes peripheral edema, genital edema and peripheral swelling. g Abdominal pain is a composite term that includes abdominal pain, abdominal pain lower and abdominal pain upper. h Pruritus is a composite term that includes pruritus and pruritus generalized. i Dyspnea is a composite term that includes dyspnea and dyspnea exertional.

BAVENCIO® (avelumab) Prescribing Information. Rockland, MA: EMD Serono Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf

JAVELIN Merkel 200: Laboratory Abnormalities

Lab Abnormalities Worsening From Baseline Occurring in ≥20% of Patients With Metastatic MCC Receiving Avelumab

Laboratory tests	Any grade (%)[a]	Grade 3-4 (%)[a]
Chemistry		
AST increased	31	3
ALT increased	22	3.5
Lipase increased	21	5
Hematology		
Lymphocyte count decreased	51	16
Hemoglobin decreased	40	6
Platelet count decreased	23	1.5

- Avelumab was permanently discontinued for adverse reactions in 27% of patients
  - The most frequent adverse reactions (>1% of patients) that resulted in permanent discontinuation were infusion-related reaction, anemia, increased ALT, and increased AST
- Dose interruptions due to an adverse reaction, excluding temporary interruptions due to infusion-related reactions, occurred in 29% of patients
  - The most frequent adverse reactions (>1% of patients) that required dosage interruption were nasopharyngitis, anemia, diarrhea, lung infection and increased ALT

ALT, Alanine aminotransferase; **AST**, Aspartate aminotransferase.

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 185 to 199 patients).
BAVENCIO® (avelumab) Prescribing Information. Rockland, MA: EMD Serono Inc https://www.emdserono.com/us-en/pi/bavencio-pi.pdf