IV Simposio

GETHI

Monográfico de Tumores cutáneos infrecuentes

Carcinoma de células de Merkel
Tratamiento de casos avanzados

Organizado por: Grupo Gethi – Grupo Español de Tumores Huérfanos e Infrecuentes

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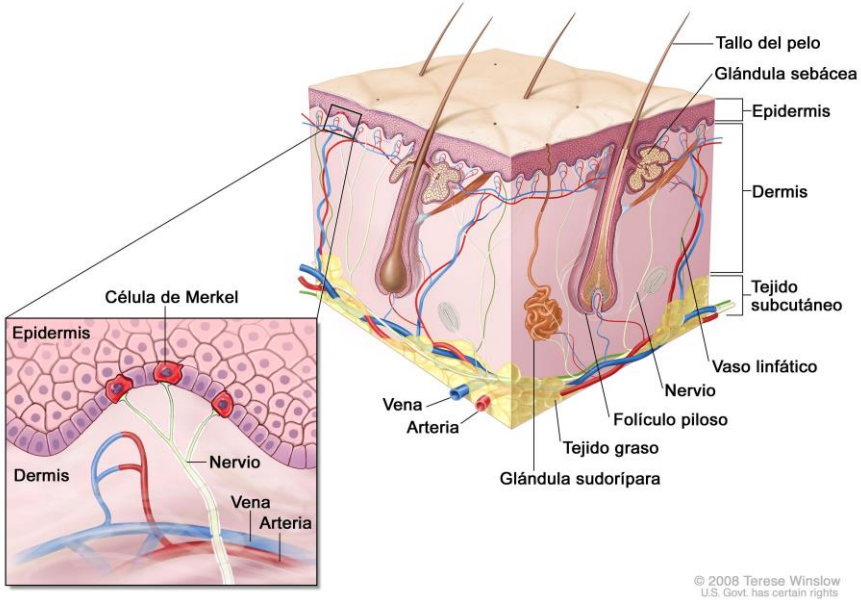
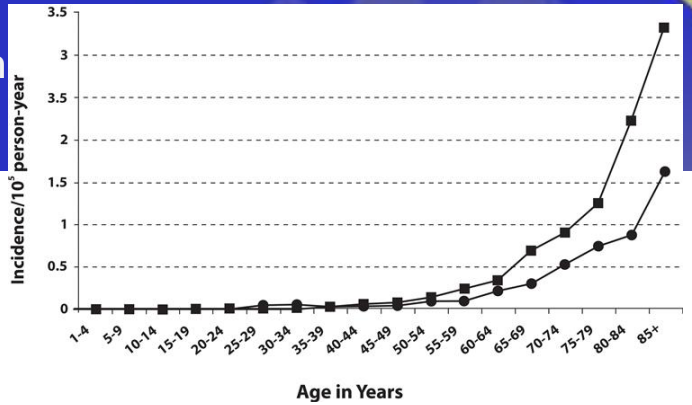
S. Oncología Médica
Hospital Universitario La Paz.
Cátedra UAM-Medicina de Innovación

CÉLULAS DE MERKEL



Células NEUROENDOCRINAS de la PIEL



EPIDEMIOLOGÍA

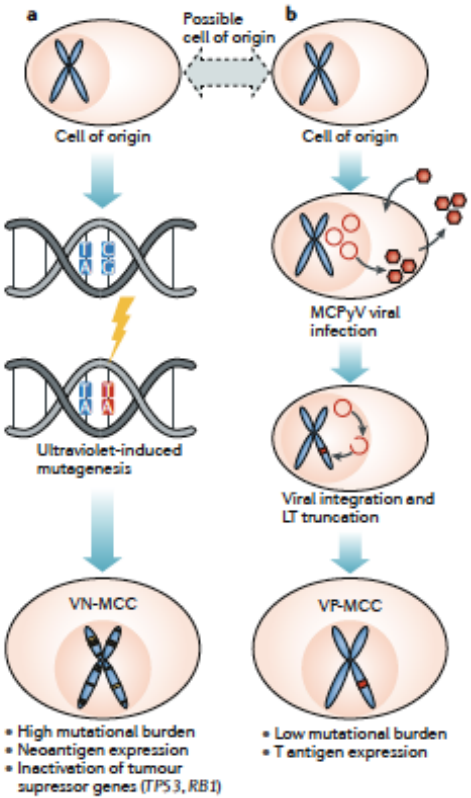
<1% de las neoplasias malignas cutáneas

Europa: 0,2-0,4 / 100000 / año

- Mayor en USA y Australia
- Ha aumentado en los últimos 30 años

FACTORES DE RIESGO

- **UVA (PUVA)**
- Edad
- Raza blanca
- Poliomavirus de Cels. de Merkel
- Inmunodeficiencias
- Irritación crónica



Proposed MCC tumorigenesis pathways in the presence or absence of Merkel cell polyomavirus

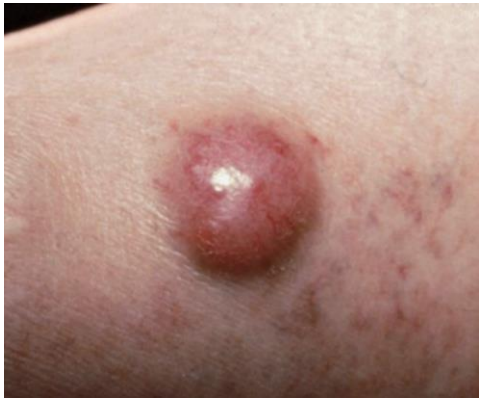
EXPERT CONSENSUS STATEMENT

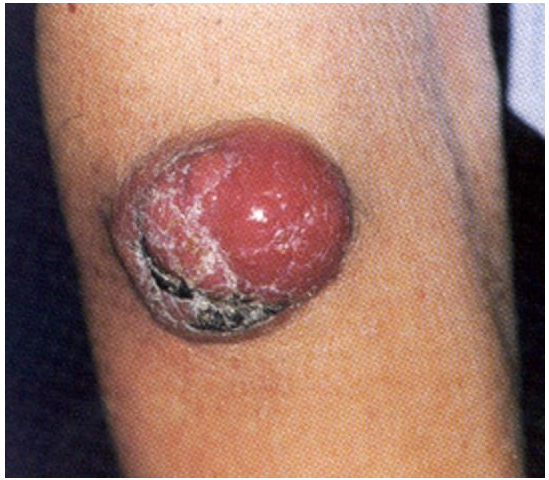
The biology and treatment of Merkel cell carcinoma: current understanding and research priorities

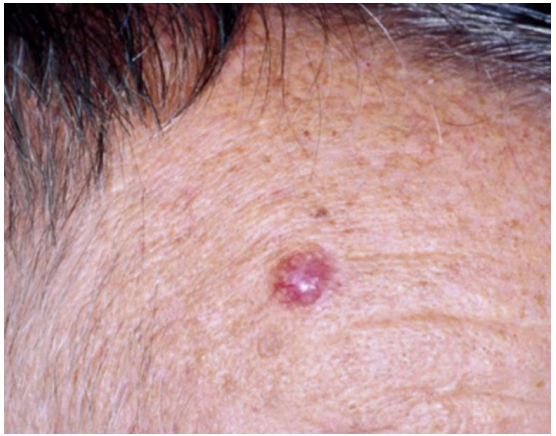
Paul W. Harms[1], Kelly L. Harms[2], Patrick S. Moore[3], James A. DeCaprio[4], Paul Nghiem[5], Michael K. K. Wong[6] and Isaac Brownell[7], on behalf of the International Workshop on Merkel Cell Carcinoma Research (IWMCC) Working Group*

NATURE REVIEWS | CLINICAL ONCOLOGY

https://doi.org/10.1038/s41571-018-0103-2

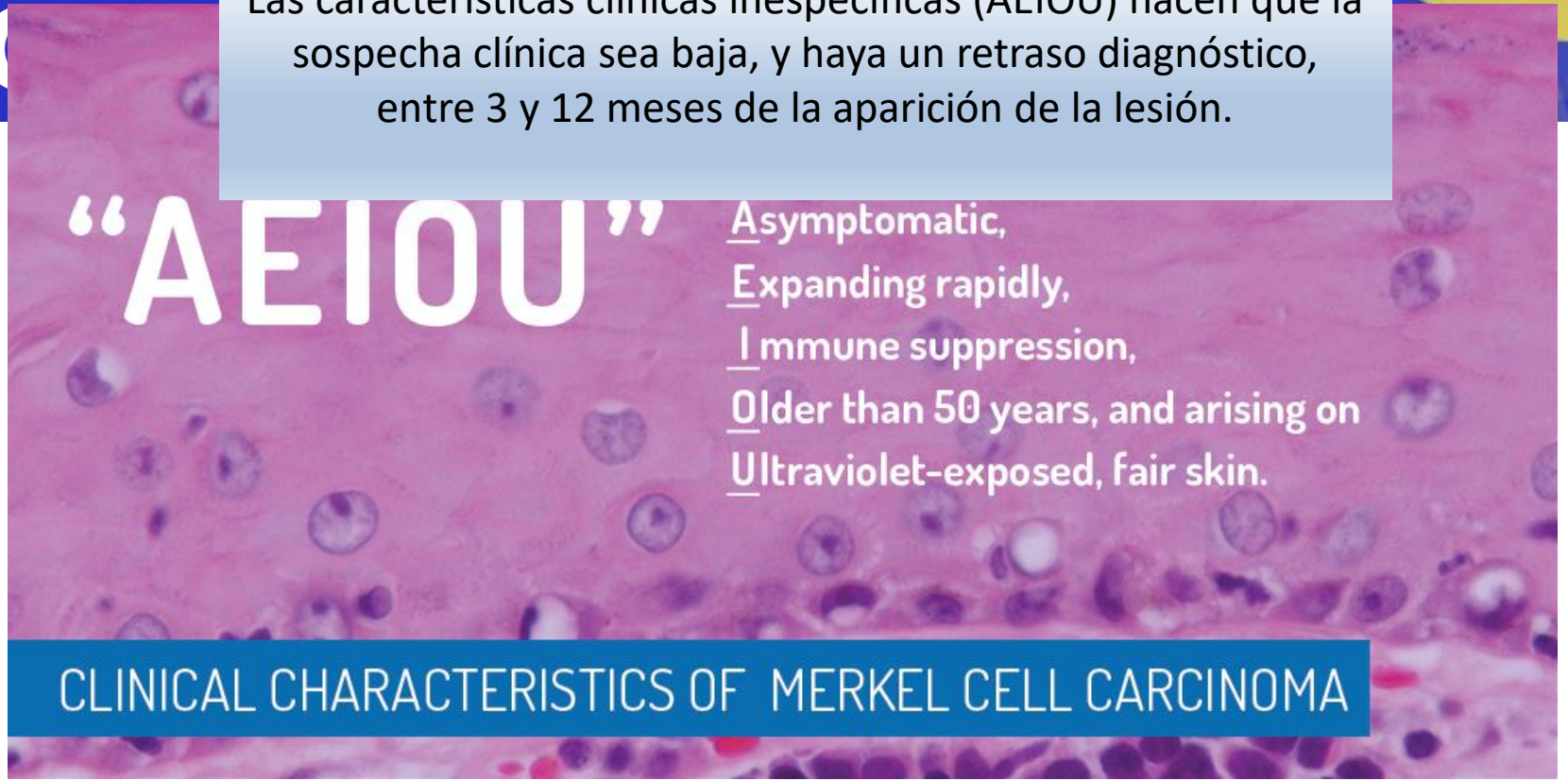






- NÓDULO dérmico
  - Solitario
  - Indoloro
  - Palpable
  - Desde ligeramente eritematoso a violáceo

Las características clínicas inespecíficas (AEIOU) hacen que la sospecha clínica sea baja, y haya un retraso diagnóstico, entre 3 y 12 meses de la aparición de la lesión.



Heath M, et al.: Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 58 (3): 375-81, 2008

Stage		Primary Tumor	Lymph Node	Metastasis
0		In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I	Clinical*	≤ 2 cm maximum tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
I	Pathological**	≤ 2 cm maximum tumor dimension	Nodes negative by pathologic exam	No distant metastasis
IIA	Clinical	> 2 cm tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIA	Pathological	> 2 cm tumor dimension	Nodes negative by pathological exam	No distant metastasis
IIB	Clinical	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIB	Pathological	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by pathologic exam	No distant metastasis
III	Clinical	Any size / depth tumor	Nodes positive by clinical exam (no pathological exam performed)	No distant metastasis
IIIA	Pathological	Any size / depth tumor	Nodes positive by pathological exam only (nodal disease not apparent on clinical exam)	No distant metastasis
		Not detected ("unknown primary")	Nodes positive by clinical exam, and confirmed via pathological exam	No distant metastasis
IIIB	Pathological	Any size / depth tumor	Nodes positive by clinical exam, and confirmed via pathological exam OR in-transit metastasis***	No distant metastasis
IV	Clinical	Any	+/- regional nodal involvement	Distant metastasis detected via clinical exam
IV	Pathological	Any	+/- regional nodal involvement	Distant metastasis confirmed via pathological exam

* Clinical detection of nodal or metastatic disease may be via inspection, palpation, and/or imaging

**Pathological detection/confirmation of nodal disease may be via sentinel lymph node biopsy, lymphadenectomy, or fine needle biopsy; and pathological confirmation of metastatic disease may be via biopsy of the suspected metastasis

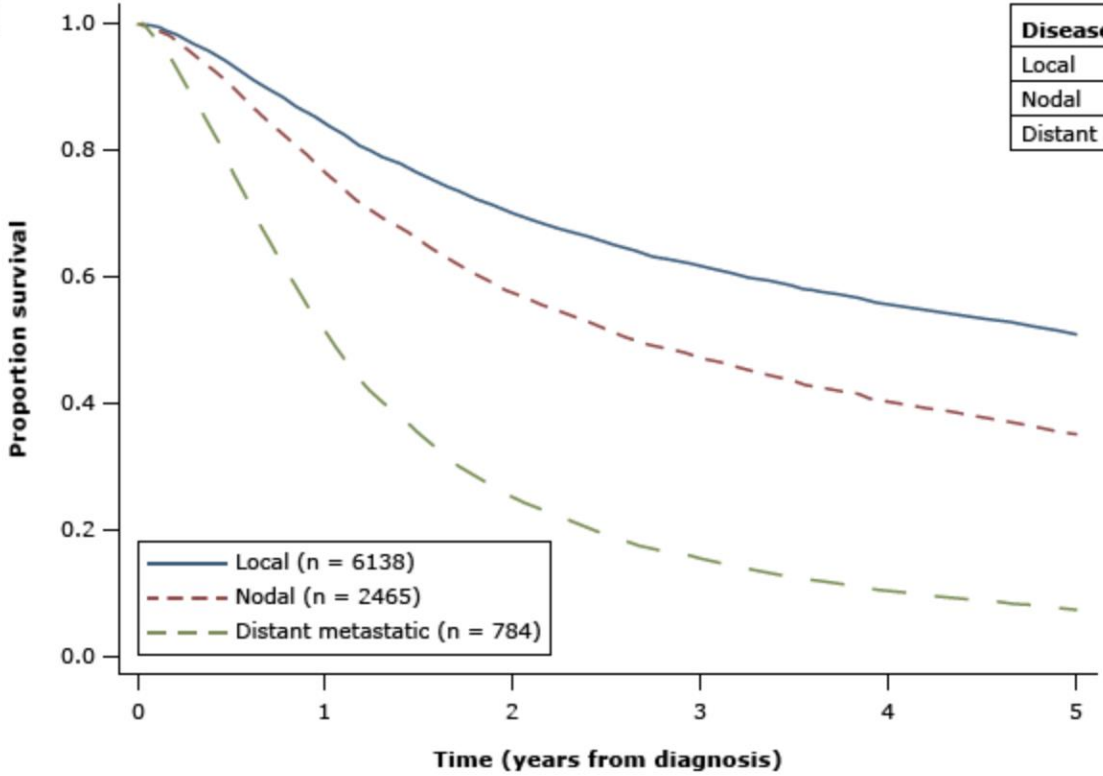
***In transit metastasis: a tumor distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion

American College of Surgeons, Chicago, Illinois. *The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017)*

IV Sim

GE

Merkel cell carcinoma overall survival based upon extent of disease



Disease extent	5-year OS
Local	50.6%
Nodal	35.4%
Distant metastatic	13.5%

American College of Surgeons, Chicago, Illinois. *The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017)*

Sólo el 2% se diagnostican como enfermedad diseminada

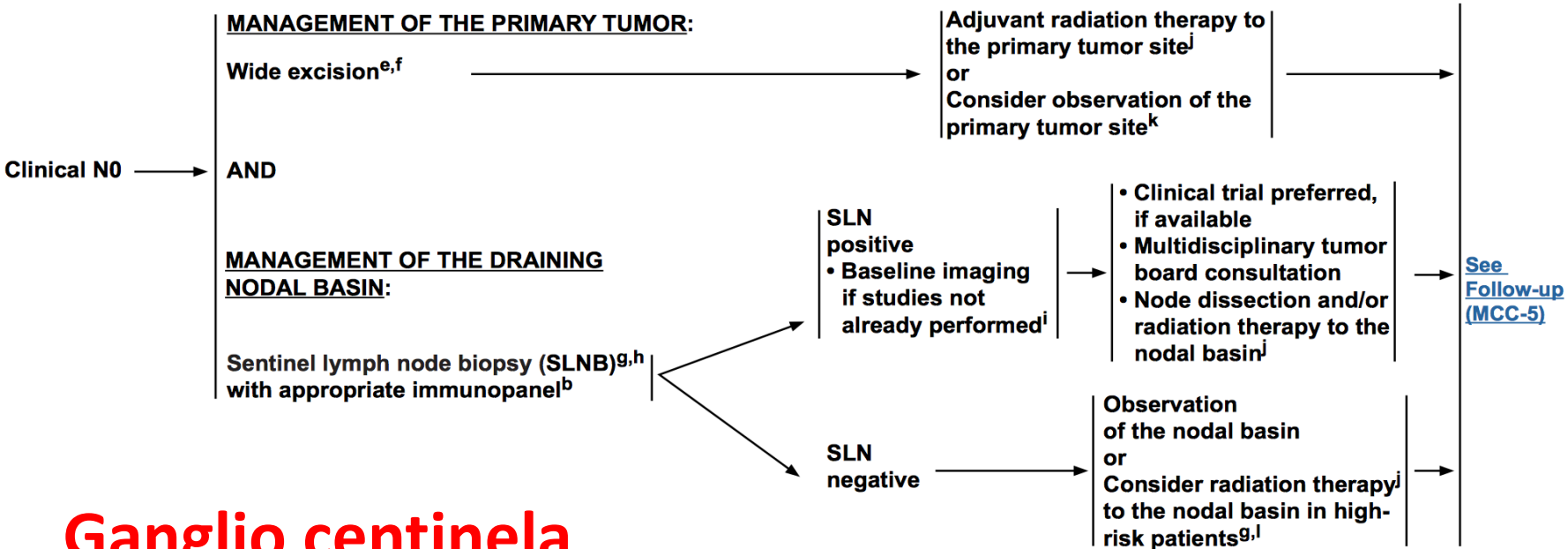
Tai PTH et al. *Chemotherapy in neuroendocrine/Merkel Cell Carcinoma of the skin:* Case series and review of 204 cases. J Clin Oncol 2000; 18(12):2493-2499

Un tercio desarrollarán metástasis

Raaf J. Trabecullar-Merkel Carcinoma of the skin. Treatment of primary, recurrent and metastatic disease. Cancer 1986; 57: 178-182.

Cirugía

Radioterapia



Ganglio centinela

I. Prieto et al. / Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

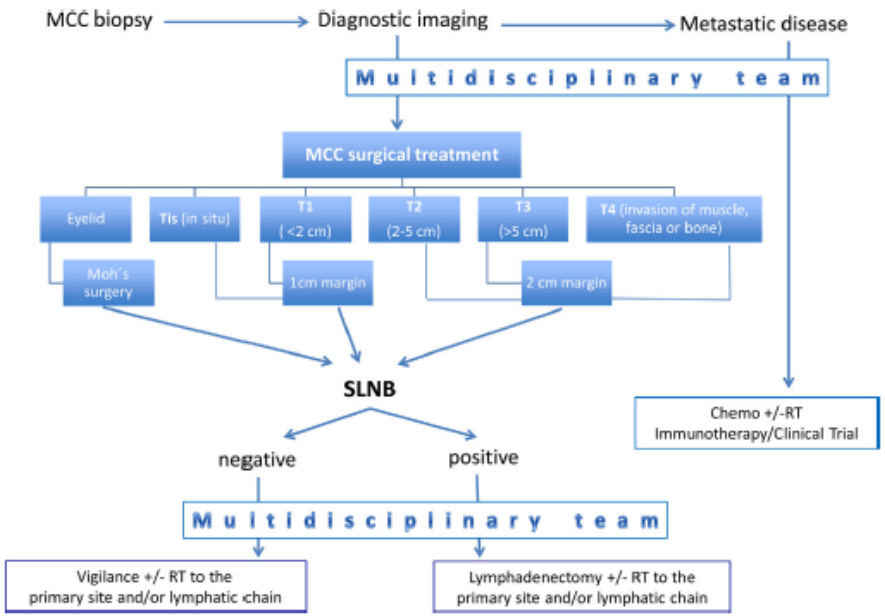


Fig. 4. MCC decision algorithm. Recommended surgical margins, sentinel lymph node biopsy (SLNB) timing and multidisciplinary team interventions.

Contents lists available at ScienceDirect

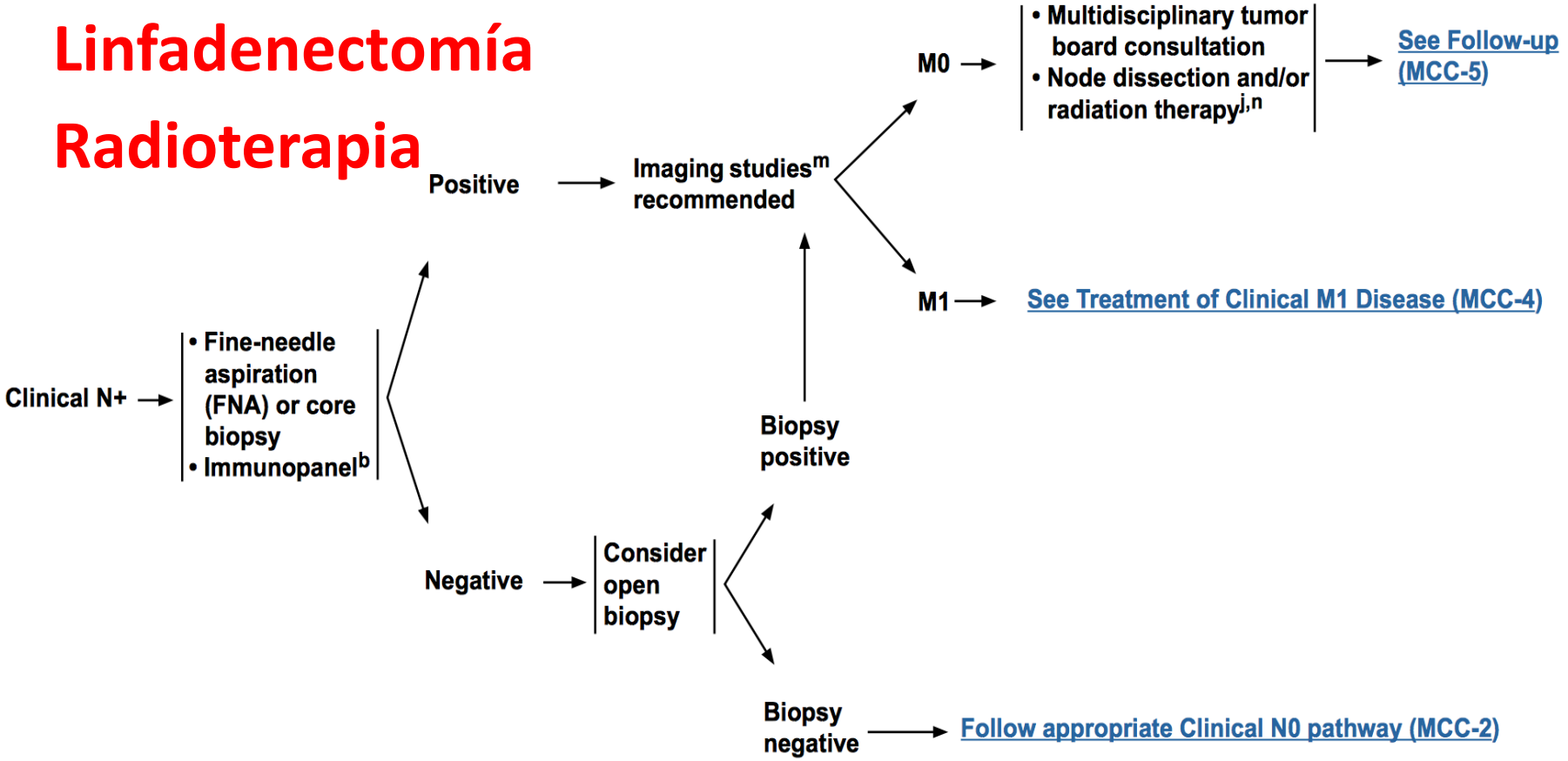
Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Merkel cell carcinoma: An algorithm for multidisciplinary management and decision-making

Isabel Prieto[a,*], Teresa Pérez de la Fuente[b], Susana Medina[c], Beatriz Castelo[d], Beatriz Sobrino[e], Jose R. Fortes[f], David Esteban[g], Fernando Cassinello[h], Raquel Jover[i], Nuria Rodríguez[j]

Linfadenectomía
Radioterapia



Quimioterapia

Clinical M1 → **Multidisciplinary tumor board consultation** →

Clinical trial preferred if available
or
Consider any of the following therapies or combinations of:
- **Systemic therapy[o]**
- **Radiation therapy[j]**
- **Surgery[p,q]**

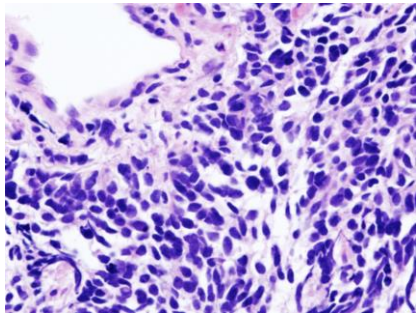
or
Best supportive care

Inmunoterapia

Estudios retrospectivos

QT adyuvante y QT/RT.

Enfermedad locorregional y metastásica



Pautas extrapoladas del Ca. microcítico de pulmón

Carboplatino-etopósido

Ciclofosfamida/adriamicina/vincristina

Carboplatino AUC 2

-Pilsen M et al. Weekly carboplatin reduces toxicity during synchronous chemoradiotherapy for Merkel cell carcinoma of skin. Int J Radiat Oncol Biol Phys. 2008;72(4):1070

-Travis, W. D. 2010. *Advances in neuroendocrine lung tumors*. Ann. Oncol. 21(Suppl 7): vii65–vii71.

QUIMIOSENSIBLE

- **1ª línea:**

  Tasas de respuesta: 53-61%

  Las respuestas no son duraderas: SLP: 3 meses (94 días)

  Sin beneficio sobre la supervivencia global: SG: 9,5 meses

- **2ª línea:**

  Tasa de respuesta: 23%

  SLP: 2 meses (61 días)

-J Clin Oncol 2000; 18: 2493–99.
-Cancer 1999; 85: 2589–95.
-Cancer Med 2016; published online July 19. DOI:10.1002
-Am J Clin Oncol 1991; 14: 166–69.
-Proc Am Soc Clin 2014; 32 (suppl 5S): abstr 9049
-J Skin Cancer 2013; 2013: 327150

OncoTargets and Therapy

Dovepress
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Open Access Full Text Article

REVIEW

Is this the end of cytotoxic chemotherapy in Merkel cell carcinoma?

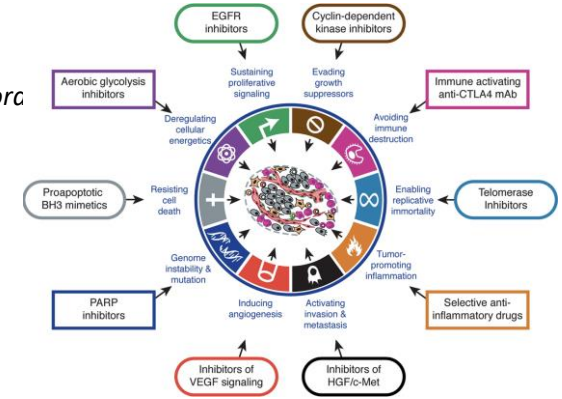
This article was published in the following Dove Press journal:
OncoTargets and Therapy
28 September 2017
Number of times this article has been viewed

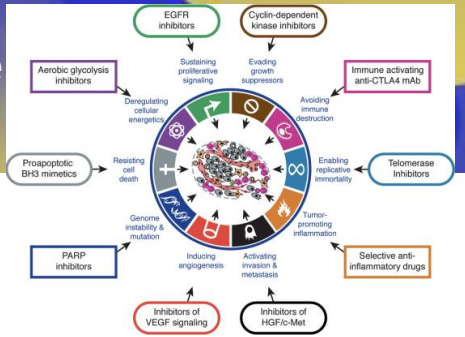
Peor pronóstico en pacientes inmunodeprimidos

Liang E et al. *Merkel Cell Carcinoma Analysis of Outcomes: A 30- Year Experience*. PLoS One. 2015;10(6):e012947.

Mejor pronóstico si infiltrados intratumorales TCD8+.

Paulson KG et al. *Transcriptome-wide studies of merkel cell carcinoma and validation of intratumoral independent predictor of survival.* J Clin Oncol. 2011 Apr;29(12):1539-46.





PD-L1

Expresado en células tumorales
Expresado por células del MCC y por infiltrados inmunes adyancentes

Lipson EJ, Vincent JG, Loyo M, et al. PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. Cancer Immunol Res 2013; 1: 54–63.

Diana terapéutica para la reactivación del sistema inmune

Iwai Y et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade Proc Natl Acad Sci USA 2002; 99: 12293

Alta concentración: pronóstico y predictivo: No está clara su utilidad como biomarcador

atel SP, Kurzrock R. *PD-L1 expression as a predictive biomarker in cancer immunotherapy*. Mol Cancer Ther 2015; 14: 847–56.

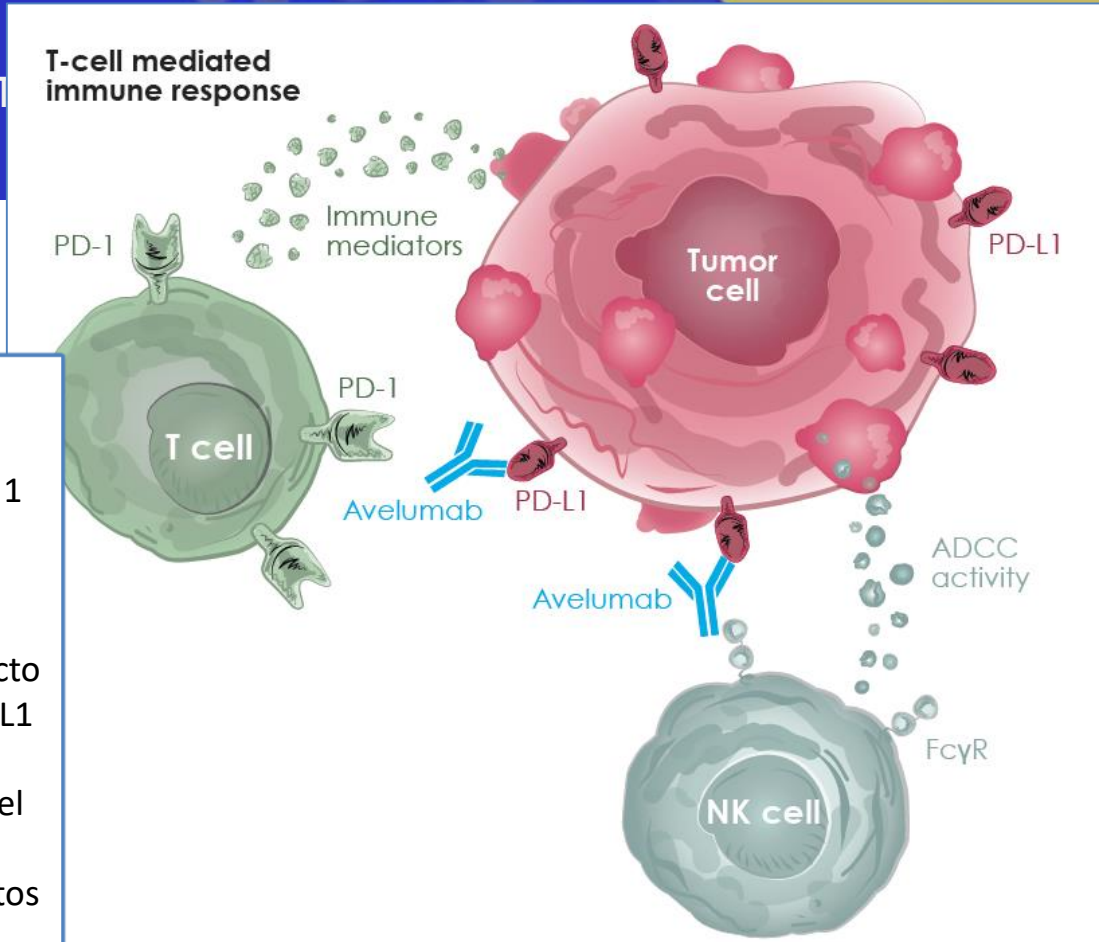
Aguiar PN Jr, Santoro IL, Tadokoro H, et al. *The role of PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: a network meta-analysis.* Immunotherapy 2016; 8: 479–88.

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Céleste Lebbé, Gerald P Linette, Michele Milella, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie Cuillerot, Paul Nghiem

AVELUMAB

- Anticuerpo monoclonal humano, de clase IgG1, dirigido contra el ligando de muerte programada 1 (anti PDL1)
- Doble acción
  - - Inhibe la interacción PDL1 (célula tumoral) – PD1 (linfocito T). Elimina el efecto supresor de la célula tumoral mediante PDL1 sobre el linfocito citotóxico TCD8+: restauración de la respuesta antitumoral del linfocito TCD8+.
  - - Inducción de lisis directa por los linfocitos NK mediante Citotoxicidad Celular Dependiente de Anticuerpos (CCDA)



Study design: JAVELIN Merkel 200

Phase 2, prospective, open-label, international, multicenter trial

Patients: key eligibility criteria

- Histologically confirmed stage IV MCC
  - Disease progression following ≥1 prior line of chemotherapy in the metastatic setting
- Immune-competent status
  - Patients with HIV infection, immunosuppression, hematologic malignancies, or organ transplants excluded
- Unselected for PD-L1 expression or MCPyV status
- ECOG PS 0-1 and adequate end-organ function

Dosing

Avelumab
10 mg/kg IV Q2W
until confirmed PD,* unacceptable toxicity, or other criteria for withdrawal were met

Key assessments

Primary endpoint: best overall response by RECIST v1.1 per independent review committee

Duration of response

Progression-free survival

Overall survival

Safety and tolerability

Objective of this presentation

- Report post hoc analyses of efficacy in subgroups based on baseline patient and disease characteristics

Data cut-off: March 3, 2016 (minimum follow-up of ≥6 months in all patients) **NCT02155647**

ECOG PS, Eastern Cooperative Oncology Group performance status; **HIV**, human immunodeficiency virus; **IV**, intravenous; **PD**, progressive disease; **RECIST**, Response Evaluation Criteria In Solid Tumors.

* Patients may continue avelumab beyond radiological disease progression in the absence of significant clinical deterioration and based on investigator assessment of potential benefit from continued treatment.

Baseline characteristics

Characteristic (N=88)	n (%)
Age	
<65 years	22 (25.0)
≥65 years	66 (75.0)
Median, years (range)	72.5 (33-88)
Sex	
Male	65 (73.9)
Female	23 (26.1)
ECOG PS	
0	49 (55.7)
1	39 (44.3)
Site of primary tumor	
Skin	67 (76.1)
Lymph node	12 (13.6)
Other	2 (2.3)
Missing	7 (8.0)
Number of prior systemic anticancer treatments	
1	52 (59.1)
2	26 (29.5)
≥3	10 (11.4)

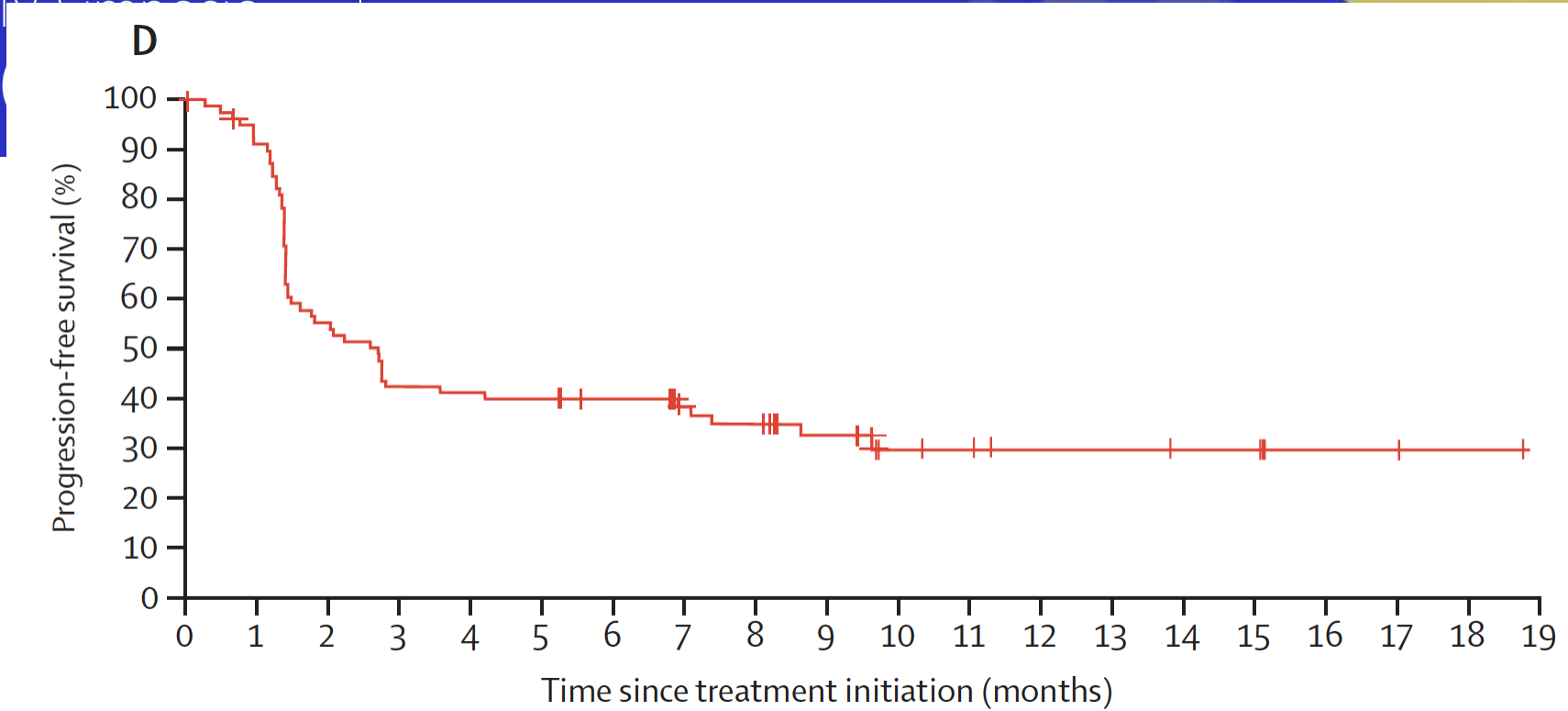
Characteristic (N=88)	n (%)
Visceral disease at study entry*	
Yes	47 (53.4)
No	41 (46.6)
Lymph node disease only	
Yes	19 (21.6)
No	69 (78.4)
Sum of target lesion diameters (SLD) at baseline	39 (44.3)
≤Median SLD	38 (43.2)
>Median SLD	11 (12.5)
Not evaluable	79.0 (16-404)
Median SLD, mm (range)	
Tumor PD-L1 expression (5% cutoff)†	
Positive	19 (21.6)
Negative	55 (62.5)
Not evaluable	14 (15.9)
Tumor MCPyV status‡	
Positive	46 (52.3)
Negative	31 (35.2)
Not evaluable	11 (12.5)

* Metastases not isolated to lymph nodes, skin, or soft tissue. † PD-L1 positivity was defined by a threshold level of ≥5% positive tumor cells of any intensity detected by immunohistochemistry (IHC) using a proprietary assay (Dako, Carpinteria, CA, USA) based on anti–PD-L1 monoclonal antibody clone 73-10 (Merck KGaA, Darmstadt, Germany). ‡ MCPyV large T-antigen expression was assessed by IHC using a specific monoclonal antibody clone CM2B4 (Santa Cruz Biotechnology, Santa Cruz, CA, USA).

Kaufman HL, et al. Lancet Oncol. 2016;17(10):1374-85.

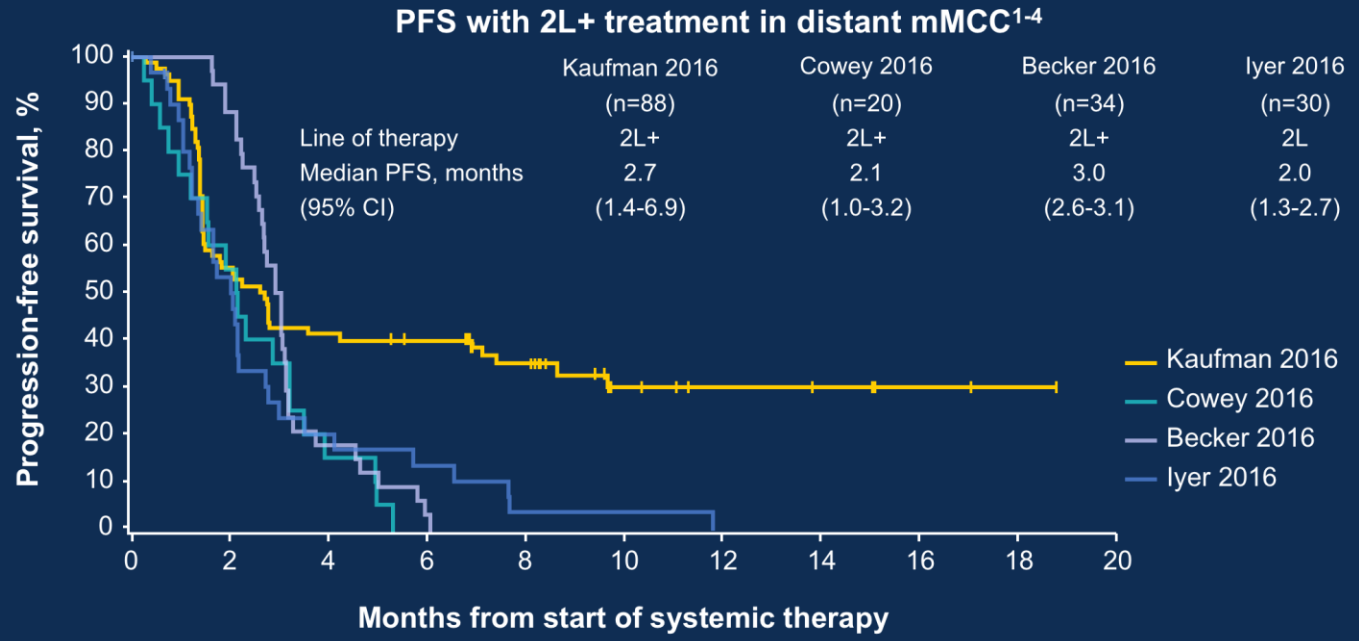
	Confirmed best overall response* (n=88)
Complete response	8 (9%)
Partial response	20 (23%)
Stable disease	9 (10%)
Progressive disease	32 (36%)
Non-complete response/ non-progressive disease†	1 (1%)
Non-assessable‡	18 (20%)
Objective response§	31·8% (21·9–43·1)

Duración de la respuesta (DR)[a]	
Mediana, meses	NA
(IC del 95%)	(18, no estimable)
Mínima, máxima	2,8, 24,9+
≥ 6 meses mediante K-M (IC del 95%)	93% (75, 98)
≥ 12 meses mediante K-M (IC del 95%)	71% (51, 85)
Supervivencia libre de progresión (SLP)	
Mediana de la SLP, meses	2,7
(IC del 95%)	(1,4, 6,9)
Tasa de SLP a los 6 meses por K-M (IC del 95%)	40% (29, 50)
Tasa de SLP a los 12 meses por K-M (IC del 95%)	29% (19, 39)



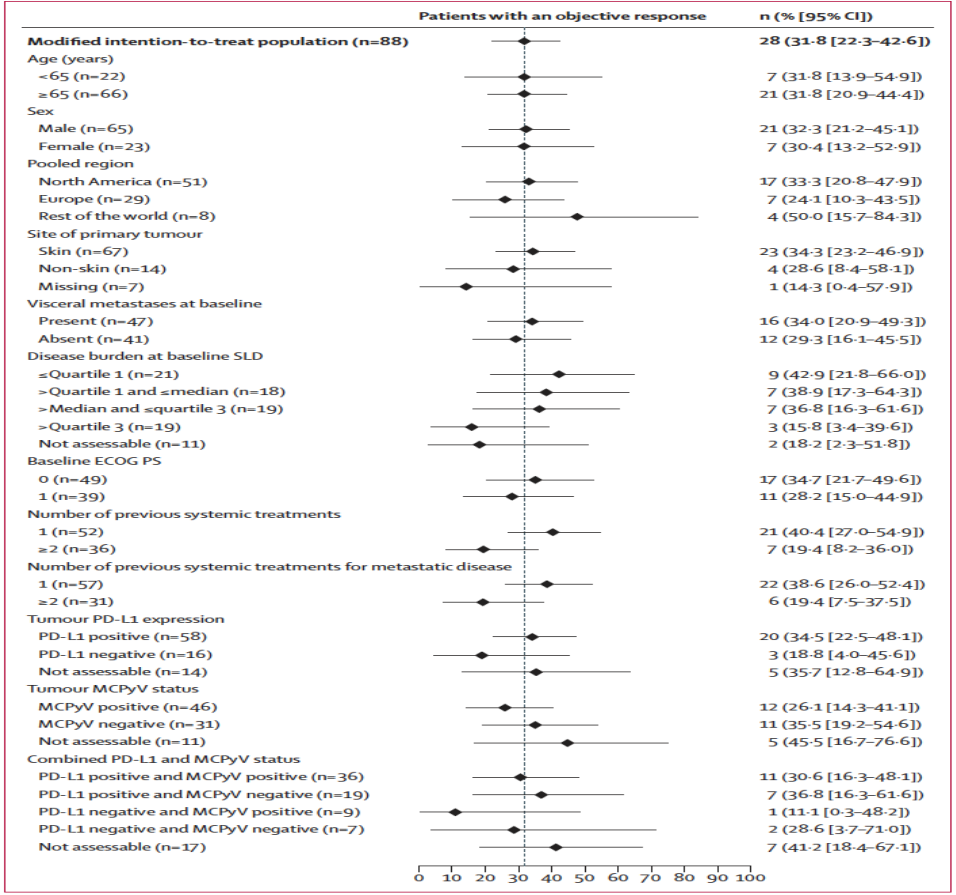
Mediana de seguimiento: 10,4 meses.

Progression-free survival of avelumab compared with historical chemotherapy*



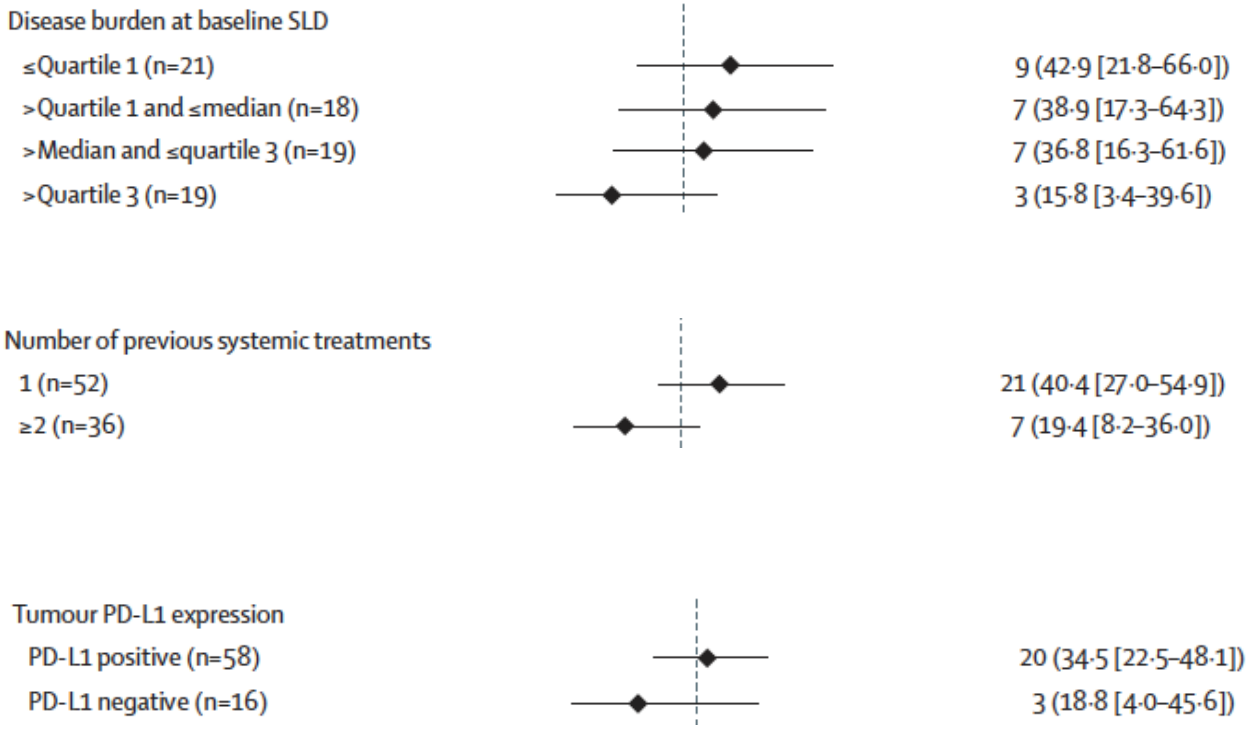
* This figure is for illustrative purposes only and is not a direct head-to-head comparison.

1. Kaufman HL, et al. Lancet Oncol. 2016;17(10):1374-85. 2. Cowey CL, et al. Value Health. 2016;19(7):Abstract A717. 3. Becker J, et al. Ann Oncol. 2016;27(Suppl):Abstract 1154P. 4. Iyer JG, et al. Cancer Med. 2016;5(9):2294-301.



En el análisis posterior entre subgrupos, no se encontraron diferencias estadísticamente significativas entre los diferentes subgrupos.

- Tendencia a una mayor SLP en los subgrupos:
  - Menor carga tumoral
  - Menor número de líneas previas
  - PDL1 positivo (5%)



Adverse events

	Grade 1–2	Grade 3
Fatigue	21 (24%)	0
Infusion-related reaction*	15 (17%)	0
Diarrhoea	8 (9%)	0
Nausea	8 (9%)	0
Asthenia	7 (8%)	0
Rash	6 (7%)	0
Decreased appetite	5 (6%)	0
Maculopapular rash	5 (6%)	0
Blood creatine phosphokinase increase	1 (1%)	1 (1%)
Lymphopenia	0	2 (2%)
Blood cholesterol increase	0	1 (1%)
Aminotransferase increase	0	1 (1%)
Potential immune-mediated treatment-related adverse event†		
Hypothyroidism	3 (3%)	0
Hyperthyroidism	2 (2%)	0
Pneumonitis	1 (1%)	0
Type 1 diabetes mellitus	1 (1%)	0

Conclusions

- Avelumab monotherapy showed durable antitumor activity across all evaluable subgroups of patients with mMCC that progressed after chemotherapy
- In this analysis, no predictive biomarker with clear clinical utility was identified, although there was a trend of higher response in patients with PD-L1–positive vs PD-L1–negative tumors
- Avelumab may be a new therapeutic option for patients with mMCC
- This ongoing multicenter trial is currently evaluating first-line avelumab treatment in patients with mMCC

LIMITACIONES

This study does have limitations, which include the non-randomised study design and the small sample size.

1. Fase II
2. No aleatorizado
3. Tamaño muestral pequeño (n=88)

FDA News Release

FDA approves first treatment for rare form of skin cancer

For Immediate Release March 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to Bavencio (avelumab) for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC), including those who have not received prior chemotherapy. This is the first FDA-approved treatment for metastatic MCC, a rare, aggressive form of skin cancer.

Two-year efficacy and safety update from JAVELIN Merkel 200 part A: a registrational study of avelumab in metastatic Merkel cell carcinoma progressed on chemotherapy

Version 6/3/18

Paul Nghiem[1], Shailender Bhatia[2], Andrew S. Brohl[3], Omid Hamid[4], Janice M. Mehnert[5], Patrick Terheyden[6], Kent C. Shih[7], Isaac Brownell[8], Celeste Lebbé[9], Karl D. Lewis[10], Gerald P. Linette[11], Michele Milella[12], Meliessa Hennessy[13], Marcis Bajars[13], Christine Hicking[14], Sandra P. D'Angelo[15]

[1]University of Washington Medical Center at South Lake Union, Seattle, WA, USA; [2]University of Washington Medical Center, Seattle, WA, USA; [3]Moffitt Cancer Center, Tampa, FL, USA; [4]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [5]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [6]University of Lübeck, Lübeck, Germany; [7]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [8]National Cancer Institute, Bethesda, MD, USA; [9]CIC and Dermatology, Saint-Louis Hospital, Paris, France; [10]University of Colorado Denver, School of Medicine, Aurora, CO, USA; [11]University of Pennsylvania, Philadelphia, PA, USA; [12]IRCCS Regina Elena National Cancer Institute, Rome, Italy; [13]EMD Serono, Inc, Billerica, MA, USA; [14]Merck KGaA, Darmstadt, Germany; [15]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA

Abstract No. 9507

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Paul Nghiem, MD, PhD

Presented By Paul Nghiem at 2018 ASCO Annual Meeting

Study status

- Median follow-up, 29.2 mo (range, 24.8-38.1 mo)
- Median duration of treatment, 3.9 mo (range, 0.5-36.4 mo)
- Treatment ongoing in 9 patients (10.2%)
- Treatment discontinued in 79 patients (89.8%)

Reason	n (%)
Progressive disease	42 (47.7)
Death	10 (11.4)
Adverse event	9 (10.2)
Consent withdrawal	7 (8.0)
Other	11 (12.5)

n=4 (4.5%) with CR stopped treatment per protocol

CR, complete response

Response to avelumab

Response parameter	N=88
ORR (95% CI), %	33.0 (23.3-43.8)
Confirmed BOR, n (%)	
CR	10 (11.4)
PR	19 (21.6)
SD	9 (10.2)
PD	32 (36.4)
Not evaluable*	18 (20.5)
DCR, %	43.2

Patient responses remain unchanged from the 1-y analysis[1]

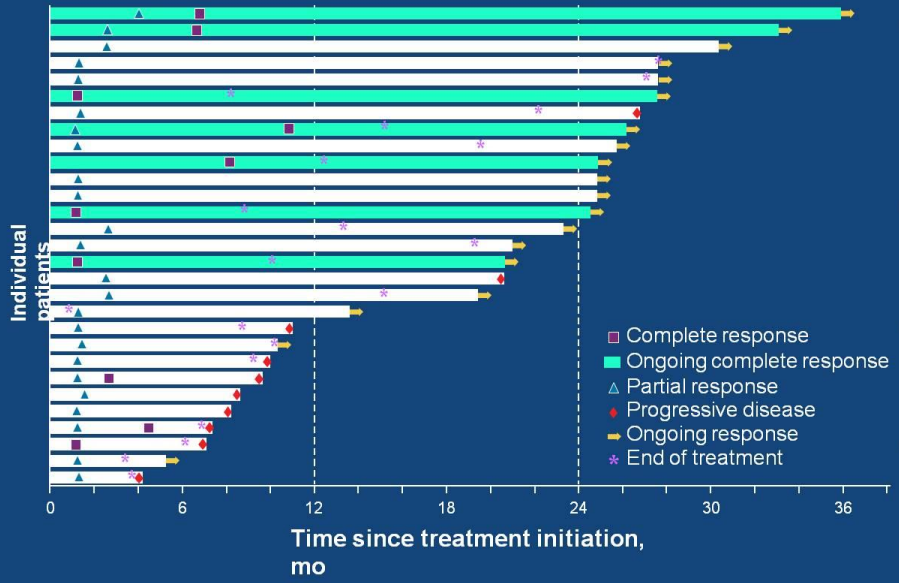
DCR, disease control rate; **ORR**, objective response rate; **PR**, partial response; **SD**, stable disease

* Patients not evaluable for a confirmed BOR had no baseline lesions identified by independent review (n=4), baseline but no postbaseline assessments (n=10), all nonassessable postbaseline assessments (n=2), no postbaseline tumor assessment before the start of new anticancer therapy (n=1), or SD of insufficient duration (n=1)

1. Kaufman HL, et al. *J Immunother Cancer*. 2018;6(1):7.

Presented By Paul Nghiem at 2018 ASCO Annual Meeting

Time to and duration of response (n=29)



- Median DOR not yet reached
  - Lower bound 95% CI: 18.0 mo
  - Range, 2.8 to 31.8+ mo
- Of 10 patients with CR, 7 are ongoing
- Estimated 67% DOR ≥2 y (95% CI, 46%-81%)*
- PD in 10 responders (most between 6-12 mo; no predictors)

*Based on Kaplan-Meier estimate

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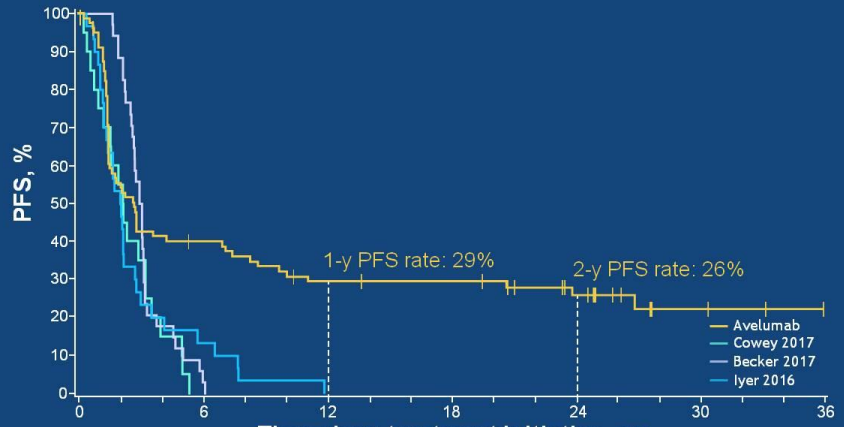
Progression-free survival with avelumab and retrospective chemotherapy data[1-3,*]



Number at risk																			
Avelumab	88	43	32	30	27	24	21	20	20	20	19	16	13	8	3	3	2	1	0
Cowey 2017	20	11	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Becker 2017	34	30	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iyer 2016	30	15	6	4	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

*This figure is for illustrative purposes only and is not a direct head-to-head comparison; it incorporates multiple different data sets and is not from a randomized clinical trial

1. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 2. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41. 3. Iyer JG, et al. *Cancer Med*. 2016;5(9):2294-301.

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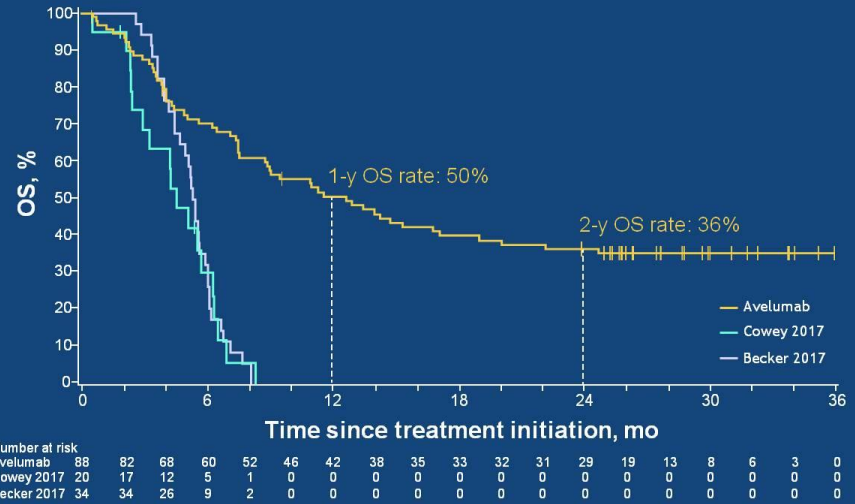
Overall survival with avelumab and retrospective chemotherapy data[1,2,*]



Number at risk

Avelumab	88	82	68	60	52	46	42	38	35	33	32	31	29	19	13	8	6	3	0
Cowey 2017	20	17	12	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Becker 2017	34	34	26	9	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

OS, overall survival

* This figure is for illustrative purposes only and is not a direct head-to-head comparison; it incorporates multiple different data sets and is not from a randomized clinical trial

1. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 2. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41.

Presented By Paul Nghiem at 2018 ASCO Annual Meeting

Conclusions: avelumab in mMCC

- With ≥2 y of treatment, no new or delayed safety signals
- Neither MCPyV nor PD-L1 predicted response or durability
- ORR in 2L+ remains 33% (ORR in 1L reported as 62%)[1]
- DOR and OS exceeded that observed with chemotherapy[2-4]
  - Estimated 67% of responders had DOR ≥2 y*
  - Estimated 36% of all patients alive at ≥2 y*

*Based on Kaplan-Meier estimate

1. D'Angelo SP, et al. *JAMA Oncol*. 2018. [Epub ahead of print]. Pre-planned interim analysis. 2. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 3. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41. 4. Iyer JG, et al. *Cancer Med*. 2016;5(9):2294-301.

Presented By Paul Nghiem at 2018 ASCO Annual Meeting

First-line avelumab treatment in patients with metastatic Merkel cell carcinoma (mMCC): preliminary data from an ongoing study

S. P. D'Angelo[1], J. S. Russell[2], J. Hassel[3], C. Lebbé[4], B. Chmielowski[5], G. Rabinowits[6], P. Terheyden[7], I. Brownell[8], I. Zwiener[9], M. Bajars[10], M. Hennessy[11], H. L. Kaufman[12]

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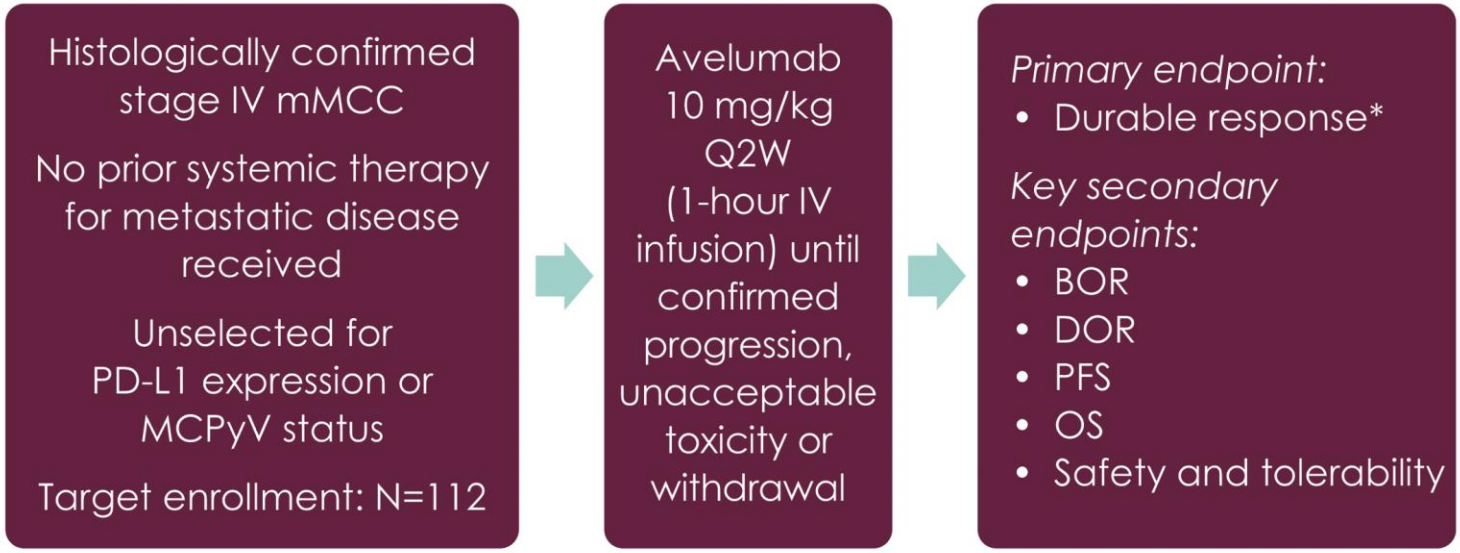
Poster presentation at the 53rd ASCO Annual Meeting, June 2-6, 2017; Chicago, IL, USA.

JAVELIN Merkel 200 (part B) study design



* Defined as objective response according to RECIST v1.1 per IERC with a duration of ≥6 months.

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Characteristic	N=29
Age, n (%)	
<65 years	7 (24.1)
≥65 years	22 (75.9)
Median age, years (range)	75.0 (47-87)
Sex, n (%)	
Male	21 (72.4)
Female	8 (27.6)
ECOG PS, n (%)	
0	23 (79.3)
1	6 (20.7)
Site of primary tumor, n (%)	
Skin	28 (96.6)
Lymph node	1 (3.4)
Tumor size, cm	
Median	3.0
Range	1.3-8.0
Time from initial diagnosis to study entry, months	
Median	13.0
Range	0.7-120.9

Efficacy outcomes by RECIST v1.1 per IERC

	Confirmed response in patients with ≥3 months of follow-up (n=29)	Confirmed response in patients with ≥6 months of follow-up (n=14)
ORR (95% CI), %	62.1 (42.3–79.3)	71.4 (41.9–91.6)
BOR, n (%) CR PR Stable disease Progressive disease Non-evaluable*	 4 (13.8) 14 (48.3) 3 (10.3) 7 (24.1) 1 (3.4)	 4 (28.6) 6 (42.9) 1 (7.1) 2 (14.3) 1 (7.1)
Response durability	**n=18**	**n=10**
Median DOR (95% CI), months	NE (4.0–NE)	NE (4.0–NE)
Responses with ≥3 months' duration (95% CI), %	93 (61–99)	100 (NE–NE)
Responses with ≥6 months' duration (95% CI), %	83 (46–96)	89 (43–98)

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Incidence of TRAEs (n=39)

Adverse event (any grade ≥7.5% or any grade ≥3)	Any grade, n (%)	Grade ≥3, n (%)
Any TRAE	28 (71.8)	8 (20.5)
Fatigue	9 (23.1)	0
IRR*	9 (23.1)	1 (2.6)
Asthenia	3 (7.7)	0
Lipase increased	3 (7.7)	1 (2.6)
Elevated ALT	3 (7.7)	1 (2.6)
Blood CPK increased	2 (5.1)	1 (2.6)
Autoimmune nephritis	1 (2.6)	1 (2.6)
Cholangitis	1 (2.6)	1 (2.6)
Elevated AST	1 (2.6)	1 (2.6)
Gait disturbance	1 (2.6)	1 (2.6)
Paraneoplastic encephalomyelitis	1 (2.6)	1 (2.6)
Polyneuropathy in malignant disease	1 (2.6)	1 (2.6)
Paraneoplastic syndrome	1 (2.6)	1 (2.6)
Troponin increased	1 (2.6)	1 (2.6)

ORR: 62,1%

SLP 3m: 67%

CONCLUSIONS

- In this interim analysis of patients with mMCC with no prior therapy for metastatic disease, avelumab treatment was associated with early responses and a confirmed ORR of 62.1% (95% CI: 42.3–79.3)
  - These findings corroborate prior evidence from part A of this study, which suggested that ORR is higher in patients with 1 vs ≥2 prior lines of therapy (40.4% vs 22.2%)[15]
- First-line treatment with avelumab shows early signals of durable response, consistent with previous results in patients with prior treatment[14,15]
  - Of 18 patients in this analysis with ≥3 months of follow-up who achieved an objective response, 83% were estimated to have a response lasting ≥6 months
- The safety profile of avelumab was generally manageable and tolerable
- Avelumab is the first and only approved treatment in the United States for adults and pediatric patients 12 years and older with mMCC

JAMA Oncology | Brief Report

Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma

A Preplanned Interim Analysis of a Clinical Trial

Sandra P. D'Angelo, MD; Jeffery Russell, MD, PhD; Céleste Lebbé, MD, PhD; Bartosz Chmielowski, MD, PhD; Thilo Gambichler, MD; Jean-Jacques Grob, MD; Felix Kiecker, MD; Guilherme Rabinowits, MD; Patrick Terheyden, MD; Isabella Zwiener, PhD; Marcis Bajars, MD; Meliessa Hennessy, MPH; Howard L. Kaufman, MD

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Second-line avelumab treatment of patients with metastatic Merkel cell carcinoma: experience from a global expanded access program

J. W. Walker[1], V. Kasturi[2], C. Lebbé[3], S. Sandhu[4], G. Grignani[5], M. Hennessy[2], S. Hildemann[6], J. Reed[2], S. Hariharan[7]

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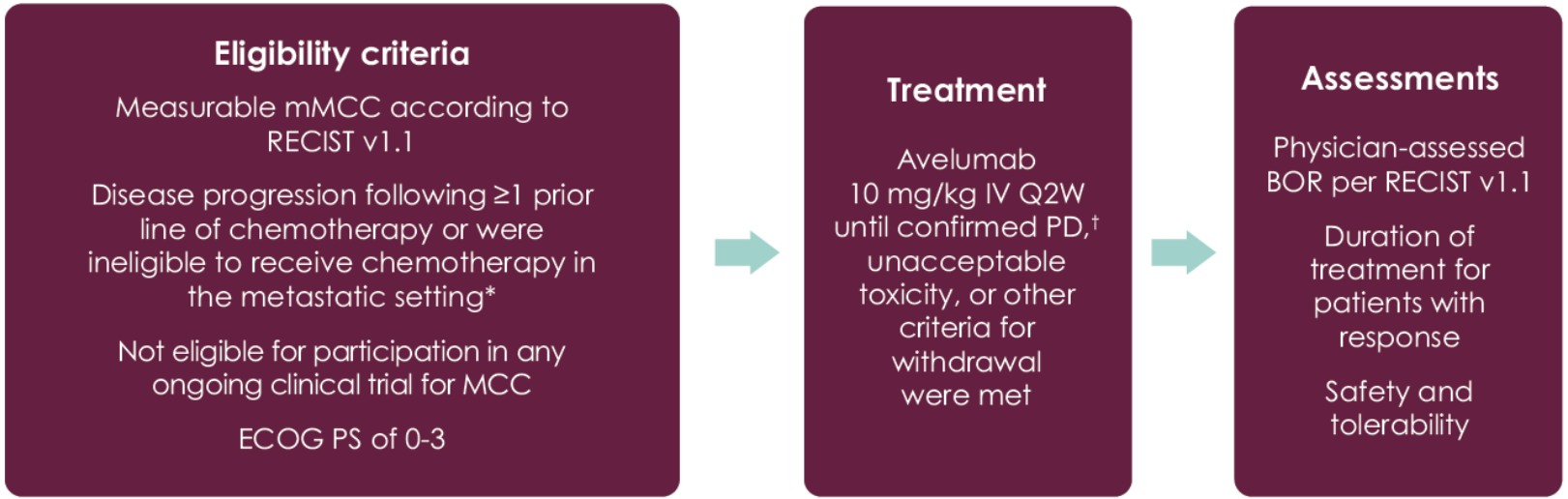
Poster presentation at the 2018 ASCO Annual Meeting, June 1–5, 2018; Chicago, IL, USA

METHODS

- Patients participating in the EAP (NCT03089658) had stage IV mMCC and PD on or after chemotherapy or were ineligible for either participation in clinical trials or chemotherapy
- Patients with clinically significant comorbidities (eg, renal dysfunction) may have been ineligible to receive chemotherapy
  - Patients with unresectable stage III MCC were ineligible for participation
- In contrast to JAVELIN Merkel 200, patients in the EAP could have ECOG performance status (PS) of ≥2, treated brain metastases, or immunosuppressive conditions



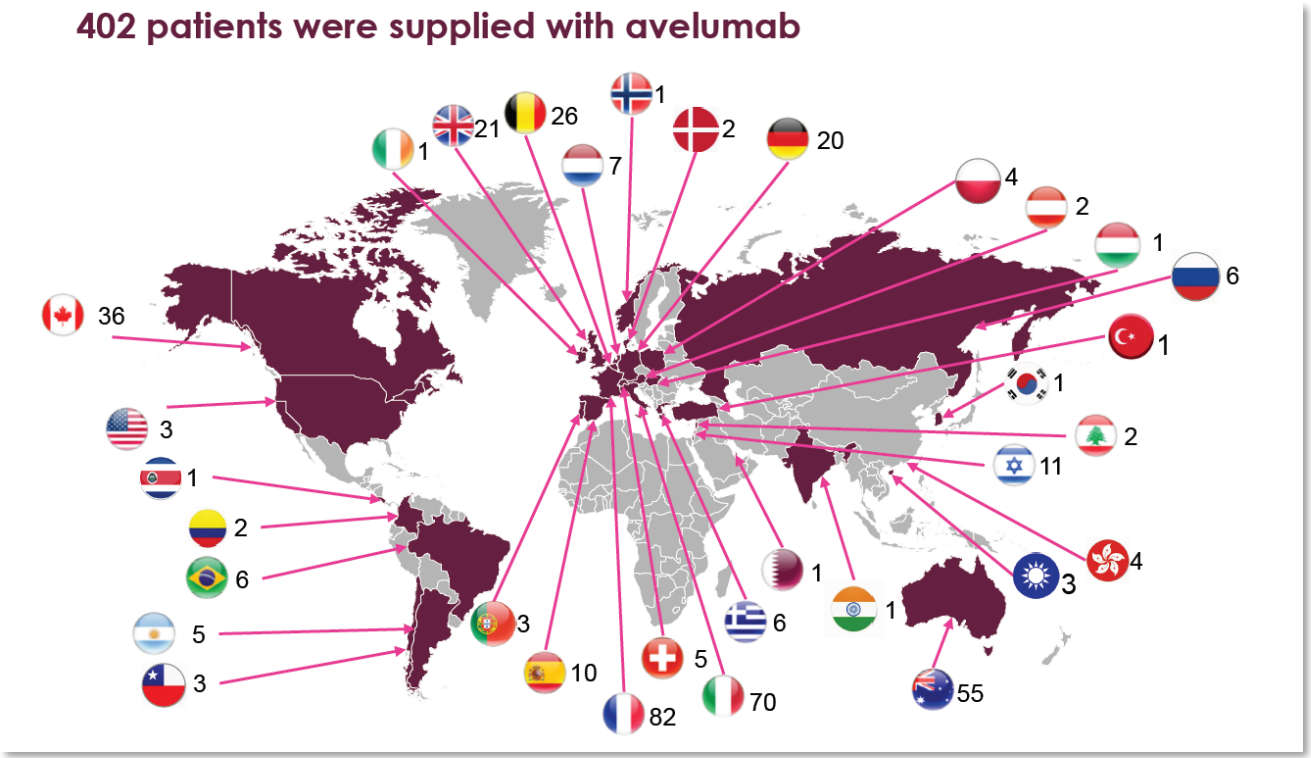
BOR, best overall response
* Patients may have received first-line avelumab if they were ineligible for chemotherapy
† Patients may have continued avelumab beyond radiological disease progression in the absence of significant clinical deterioration and based on physician assessment of potential benefit from continued treatment

RESULTS

- Between January 2016 and April 30, 2018 (data cutoff date), 521 requests for avelumab were received from 37 countries
- 462 were approved, 48 were medically rejected for various reasons (eg, incorrect diagnosis, lack of appropriate prior therapy, incomplete information), and 11 were withdrawn
  - Most requests were from France (n=96), Italy (n=87), and Australia (n=68)
- Median age was 74 years (range, 28-95 years), and 67% of patients were male

- Of the 402 patients supplied with avelumab:
  - 88 predated the EAP portal (implemented in May 2017) and did not have outcome data, regardless of response or resupply
  - 42 were approved ≤90 days prior to the data cutoff date and were therefore too early to evaluate
  - 272 were potentially evaluable for outcomes, with 157 (57.7%) patient outcomes provided

MCC EAP enrollment



Cutoff date: April 30, 2018

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Baseline characteristics

Characteristic	n=512
Age, n (%)	
<65 years	99 (19.3)
≥65 years	413 (80.7)
Median (range), years	74 (28-95)
Sex, n (%)	
Male	343 (67.0)
Female	169 (33.0)
Weight, n (%)*	
<80 kg	202 (52.7)
≥80 kg	181 (47.3)
Median (range), kg	78 (41-150)
ECOG PS, n (%)*	
0	154 (40.2)
1	192 (50.1)
2	29 (7.6)
3	8 (2.1)

* Weight and ECOG PS at baseline are available only for the 383 patients enrolled via the portal.

RESULTS

- In 157 response-evaluable patients, the ORR was 51.6%, including CR in 24.8% (n=39; including 3 immunocompromised patients) and PR in 26.8% (n=42; including 1 immunocompromised patient)
  - Durable responses were observed in immune-competent and immunocompromised patients
- The EAP is ongoing but will close in 2018 with regulatory approval in multiple countries

Response in patients participating in avelumab MCC EAP

Response parameter*	All evaluable patients n=157	Immunocompromised patients n=8
ORR, %	51.6	50.0
DCR, %	71.3	62.5
Confirmed BOR, n (%)		
CR	39 (24.8)	3 (37.5)
PR	42 (26.8)	1 (12.5)
SD	31 (19.7)	1 (12.5)
PD	45 (28.7)†	3 (37.5)
Duration of treatment for patients with response		
Median (range), days	195 (30-570)‡	113 (90-420)

DCR, disease control rate

* Response was reported according to treating-physician assessment of follow-up scans at the time of resupply

† Patients with PD or AEs that required treatment discontinuation within the first 90 days were never resupplied and did not have a follow-up response evaluation; thus, these values may be underreported

‡ As of April 2018: 33 patients with response remain on treatment in the EAP; 20 patients with response were transferred to commercial supply and no longer followed for outcomes

Physician-reported safety profile of avelumab in MCC EAP

TRAEs*	Nonserious events, n	Serious events, n	Total events, n
Infusion-related reaction	6	2	8
Fatigue	5	0	5
Dyspnea	0	4	4
Pyrexia	3	1	4
Asthenia	2	1	3
Chills	1	2	3
Rash	3	0	3

* Preferred terms, all TRAEs observed in ≥3 patients in EAP extracted from the safety database for study 100070-CU (n=402); unsolicited cumulative events provided by treating physicians; overall safety events may have been underreported in this ad hoc program

CONCLUSIONS

- The MCC EAP answered an urgent, **unmet medical need** in patients with mMCC and limited treatment options
- No new safety signals were identified in the EAP population
  - Infusion-related reaction, fatigue, and rash were among the most frequently occurring TRAEs observed in both the EAP and JAVELIN Merkel 200[15]
- In the EAP population, avelumab showed **clinical benefit** in both immunocompromised and immune-competent patients
  - ORR (as evaluated by treating physician) was 51.6%, including 3 immunocompromised patients who achieved CR and 1 who achieved PR
- In a real-world setting, avelumab showed safety and efficacy consistent with the JAVELIN Merkel 200 clinical trial[15]

1. NOMBRE DEL MEDICAMENTO

Bavencio 20 mg/ml concentrado para solución para perfusión

2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA

Cada ml de concentrado contiene 20 mg de avelumab.
Un vial de 10 ml contiene 200 mg de avelumab.

El avelumab es un anticuerpo monoclonal humano de clase IgG1 dirigido contra el ligando proteico inmunomodulador de la superficie celular PD-L1 y producido en células de ovario de hámster chino mediante tecnología de DNA recombinante.

4. DATOS CLÍNICOS

4.1 Indicaciones terapéuticas

Bavencio está indicado como monoterapia para el tratamiento de los pacientes adultos con carcinoma de células de Merkel (CCM) metastásico.

4.2 Posología y forma de administración

El tratamiento debe iniciarlo y supervisarlo un médico experimentado en el tratamiento del cáncer.

Posología
La dosis recomendada de Bavencio es de 10 mg/kg de peso corporal, administrados por vía intravenosa durante 60 minutos, cada 2 semanas.

GRACIAS