Emerging Role of Immunotherapy in Metastatic Merkel Cell Carcinoma (MCC)

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Objective

- General Background
  - Epidemiology, Pathogenesis
  - Merkel Cell Polyomavirus
- Management of MCC
  - Surgery, Radiation
  - Chemotherapy, Immunotherapy
- Recent Immunotherapy Trials in MCC
  - Avelumab
  - Pembrolizumab
- Emerging Serologic Testing to Monitor MCC
- MCC Therapeutic Pipeline
- Challenges in MCC
- Case Studies

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Background

https://en.wikipedia.org/wiki/Friedrich_Sigmund_Merkel

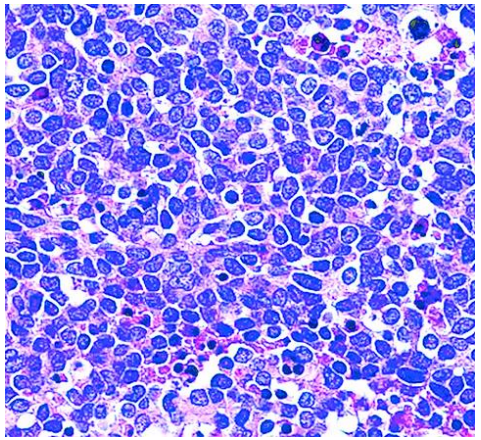
- Originally thought to derive from the Merkel cell, a mechanoreceptor cell type first described by Friedrich Sigmund Merkel (1845-1919).
- Dr. Toker first described a ‘trabecular carcinoma’ of the skin in 1972; he later related this disease to the Merkel cell based on electron microscopy studies demonstrating the presence of dense-core granules.
- More recent studies suggest that Merkel cell carcinoma is derived from a pluripotent stem cell in the skin.

Prieto Muñoz, I. et al. *Cancer Treatment Rev.*

Background

- Aggressive skin cancer composed of small, round, blue cells that stain positive for neuroendocrine markers including synaptophysin, chromogranin A, as well as CK20 in a ‘dot-like’ pattern.

- 70% of patients present with Stage I/II disease, 25% present with palpable LNs, and 5% present with distant metastases.



http://www.pathologyoutlines.com

- Associated with immunosuppression, UV radiation, male gender, and older age (median age of diagnosis at 75).

- ~2000 new cases diagnosed annually in the U.S. based on 2015 census data.

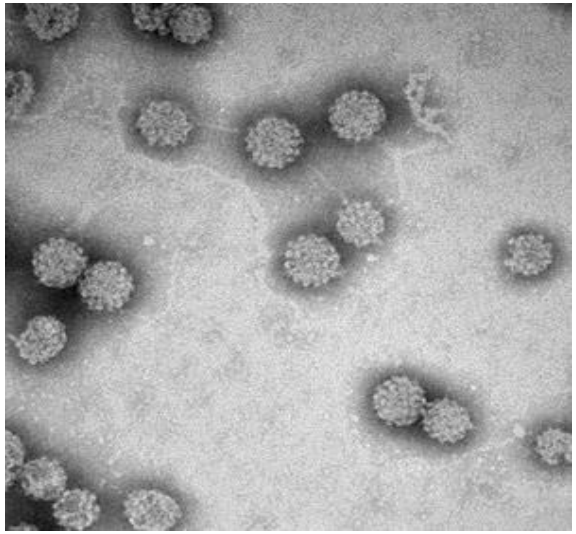
- MCC is a chemosensitive disease associated with a high risk of recurrence.

- Historical retrospective studies have demonstrated 5 year overall survival = 0-18%.

Iyer, J. et al. *Cancer Med.* 2016. 5: 2294.

Tai, P. et al. *J. Clin Oncol.* 2000. 18:2493.

Background



https://ccr.cancer.gov/news/inthejournals/mvc

- ~80% of cases have also been associated with the Merkel Cell Polyomavirus (97% based on PCR).
- Immunosuppression seems to allow for Merkel Cell Polyomavirus oncogenesis.
- MCPyV integrates into the genome of target cells and drives cellular proliferation via expression of the large T antigen and sequestration of the RB protein.
- MCPyV-negative MCCs develop in response to prolonged radiation exposure; associated with higher mutational burden characteristic of a UV damage signature.

Feng, H. et al. *Science.* 2008. 319: 1096.

Banks, et al. *J Oncol Practice*. 2016. 12: 637.

Staging

- Stage I – Primary tumors ≤ 2 cm
- Stage II – Primary tumors > 2 cm or a primary tumor with invasion into bone, cartilage, muscle, or fascia
- Stage III – Any primary tumor with regional lymph node involvement
- Stage IV – Metastasis beyond the regional lymph nodes

Management of MCC

- **Stage I and II MCC**
  - Wide local excision with ≥ 1 cm margin
  - Sentinel Lymph Node Biopsy (SLNBx)
    - ~20% of T1 MCC, ~50% of T2 MCC exhibit nodal metastases[1]
    - Node-positive MCC patients exhibit inferior clinical outcomes
    - Completes pathologic staging, informs prognosis, and guides clinical trial referral
    - Provides therapeutic benefit by surgically removing the involved node; risk of disease recurrence is 3.5x lower in patients who undergo SLN biopsy compared to those who do not
    - **All clinically node negative patients, including those with small primary lesions, should undergo a SLNBx[2]**
  - False-negative rate of SLNBx in MCC is estimated to be ~15-20% → high-risk patients with negative SLNBx should be considered for adjuvant radiotherapy to the lymph node bed[3]

[1]Angeles, C. Wong, S. *J Oncol Practice*. 2016. 12: 647. [2]2017 NCCN Guidelines. Merkel Cell Carcinoma. [3]Howle, J. et al. Australas J Dermatol. 2012. 53: 26.

Management of MCC

- **Stage III MCC**
  - 1/3 of MCC patients present with node-positive disease
  - Complete LN dissection recommended when feasible[1]
  - Patients with clinically positive nodes have a 5 year disease-specific survival of ~50%[2]
  - Adjuvant radiation therapy is recommended in the presence of extra-capsular extension or multiple node involvement
  - Concurrent chemoradiation found to be beneficial in the setting of high-risk head & neck disease based on a retrospective review of 4,815 patients[3]
    - Positive margins, male gender, primary tumor size ≥ 3 cm
  - Clinical trial referral

[1]2017 NCCN Guidelines. Merkel Cell Carcinoma. [2]Allen, P. et al. *J Clin Oncol.* 2005.23: 2300 [3]Chen, M. et al. *JAMA Otolaryngol*. 2015. 141: 137.

Management of MCC

- **Stage IV MCC**
  - Chemotherapy
    - Carboplatin/etoposide regimen
    - First line setting response rates between 53-61%; however, these responses lack durability (median duration of response of 85 days)
    - Second line setting response rates reported at ~23%
    - Alternative regimens: carboplatin, topotecan, CAV
  - Immunotherapy

JAVELIN Phase II Clinical Trial

- Multicenter, open-label, single group, phase II clinical trial enrolled patients with Stage IV Merkel cell carcinoma refractory to at least one line of chemotherapy.
- Patients with HIV, immunosuppression, or previous solid organ transplants were excluded.
- Patients received avelumab, a human anti-PD-L1 IgG1 monoclonal antibody, at 10 mg/mL by 1 hr infusion once every 2 weeks.
- Radiological assessment performed every 6 weeks per RECIST version 1.1.
- Confirmation of progression was confirmed by a repeat 6 week scan.

Kaufmann, H. et al. *Lancet Oncol.* 2016. 17:

JAVELIN Phase II Clinical Trial

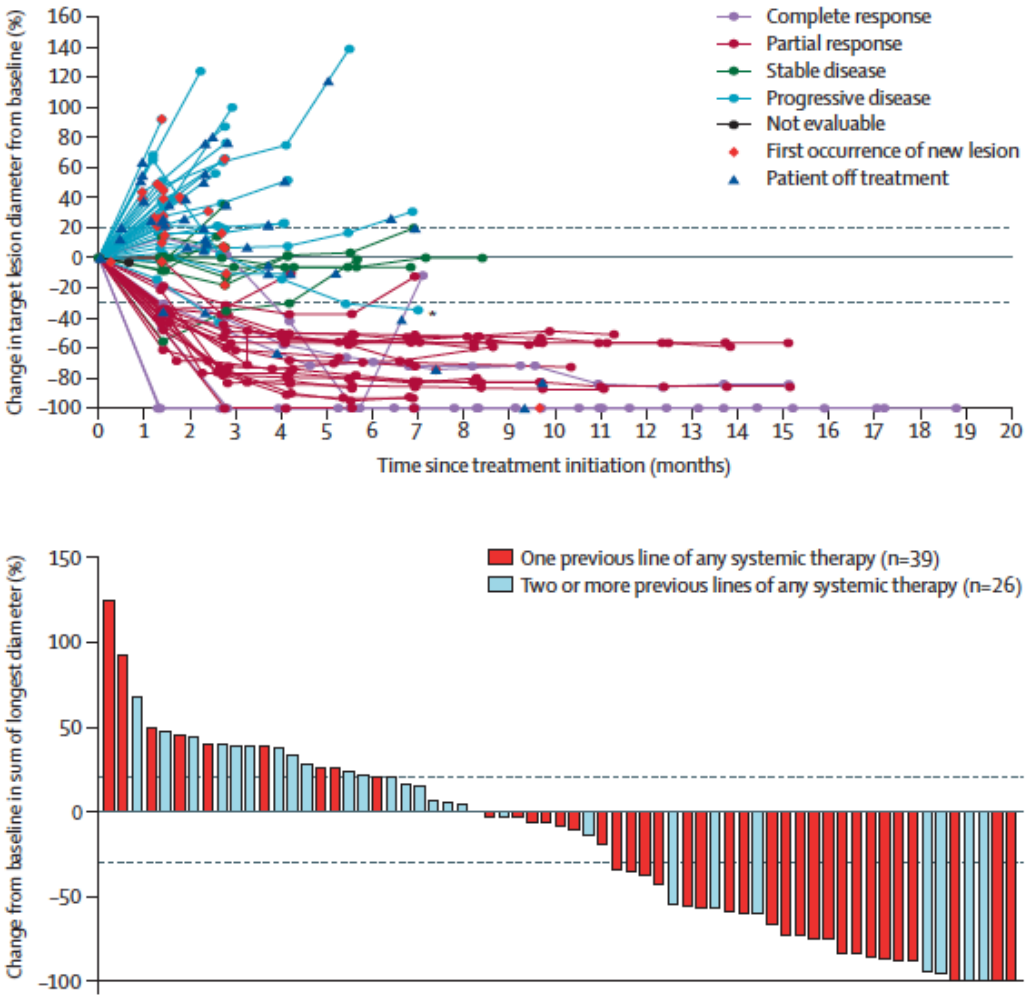
- 88 patients were enrolled and treated with avelumab between July 25, 2014, and September 3, 2015
  - 41% had received two or more previous lines of therapy
  - 53% had visceral metastases
- Median follow-up was 10.4 months
- 79% were PD-L1-positive (>1% positive tumor cells)
- 60% were Merkel cell polyomavirus-positive

	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)

- Response duration lasting at least 6-months: 29%
- 6.7% 6-month durable response rate to chemotherapy in refractory MCC patients

Kaufmann, H. et al. *Lancet Oncol.* 2016. 17: 1374.

JAVELIN Phase II Clinical Trial



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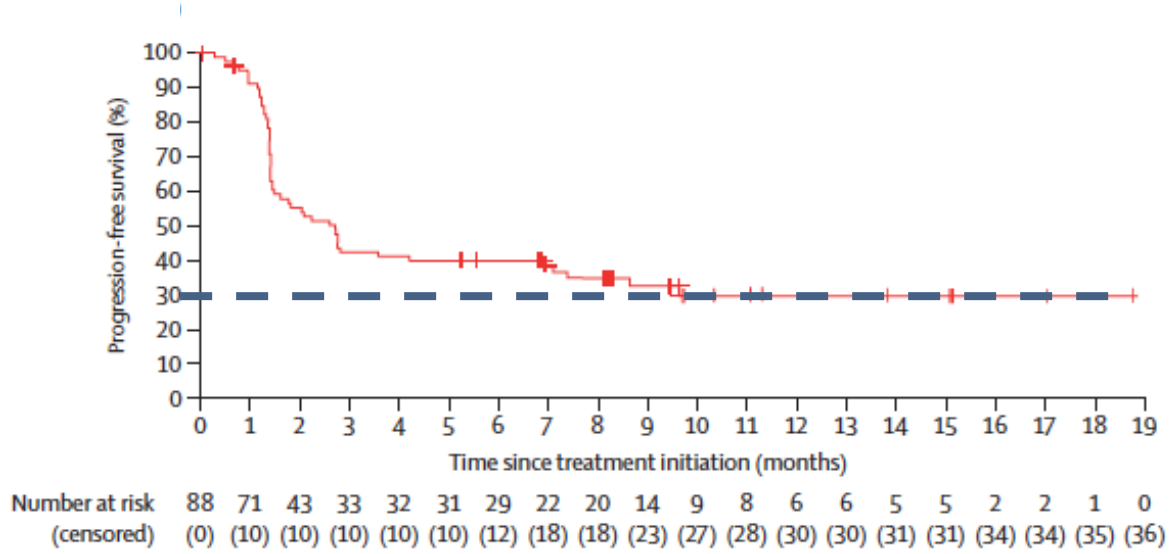
JAVELIN Phase II Clinical Trial



- Median PFS = 2.6 months
- Median OS = 11.3 months
- 6 month survival = 69%
- 18 month survival = 30%
- Median time of response = 6 weeks

- PD-L1-positive: 34.5% ORR
- PD-L1-negative: 18.8% ORR
- MCPyV-positive: 26.1% ORR
- MCPyV-negative: 35.5% ORR

Kaufmann, H. et al. *Lancet Oncol.* 2016. 17: 1374.

JAVELIN Phase II Clinical Trial

	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

- Treatment-related adverse events occurred in 70% of patients
- Grade 3 AEs in 5%; no deaths on study
- 2/88 patients discontinued therapy

Kaufmann, H. et al. *Lancet Oncol.* 2016. 17: 1374.

CITN-09 Phase II Clinical Trial

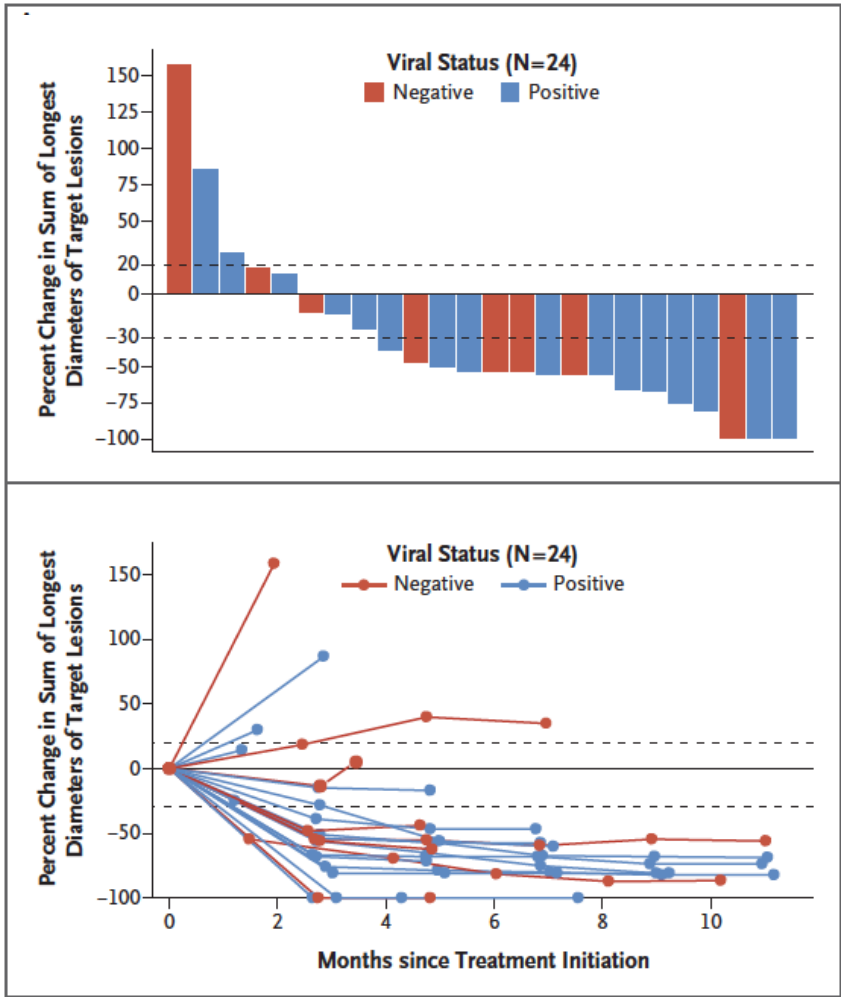
- Multicenter, open-label, single group, phase II clinical trial enrolled untreated patients with either Stage IV or recurrent locoregional Merkel cell carcinoma that is not amenable to surgery.
- Patients with an immunodeficiency or undergoing treatment with systemic immunosuppressive therapy were excluded.
- Patients received pembrolizumab, a humanized anti-PD-1 IgG4 monoclonal antibody, at 2 mg/kg IV every 3 weeks.
- Radiological assessment performed at 12 weeks and then every 9 weeks per RECIST version 1.1.

Nghiem, P. et al. *NEJM.* 2016. 374: 26.

CITN-09 Phase II Clinical Trial

- 26 patients with either Stage IIIB (8%) or IV (92%) MCC were enrolled between January 2015 and December 2015
- Median follow-up was 33 weeks
- 65% were Merkel cell polyomavirus-positive

- 56% ORR (4 CR, 10 PR)
- 12/14 responses ongoing

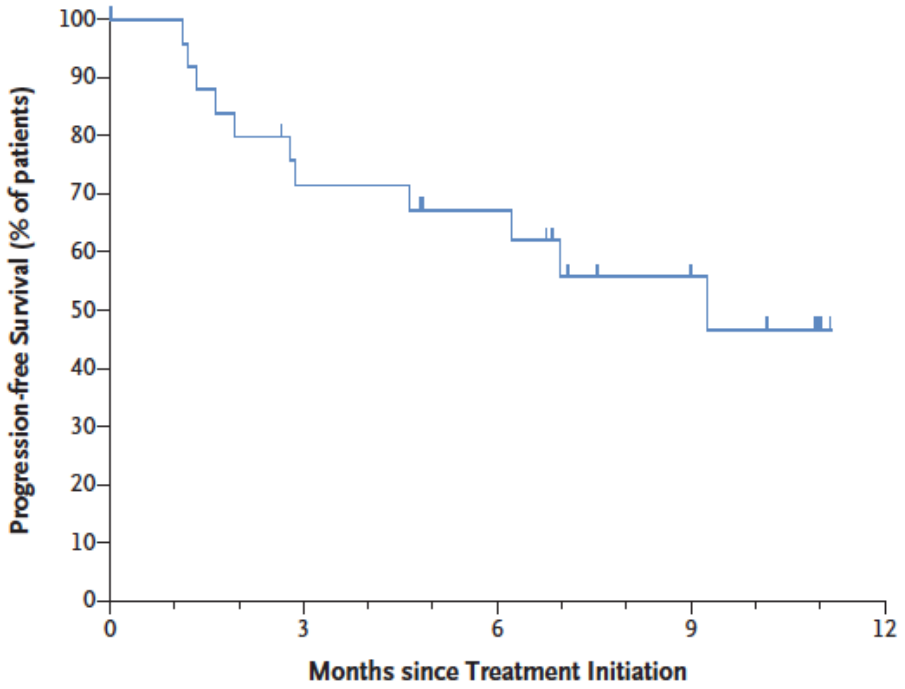


Nghiem, P. et al. *NEJM.* 2016. 374: 26.

CITN-09 Phase II Clinical Trial

- Median PFS = 9 months
- PFS at 6 months = 67%

- MCPyV-positive: 62% ORR
- MCPyV-negative: 44% ORR
- Treatment-related adverse events occurred in 77%
- Grade 3/4 AEs in 15%
- 2/26 patients discontinued therapy



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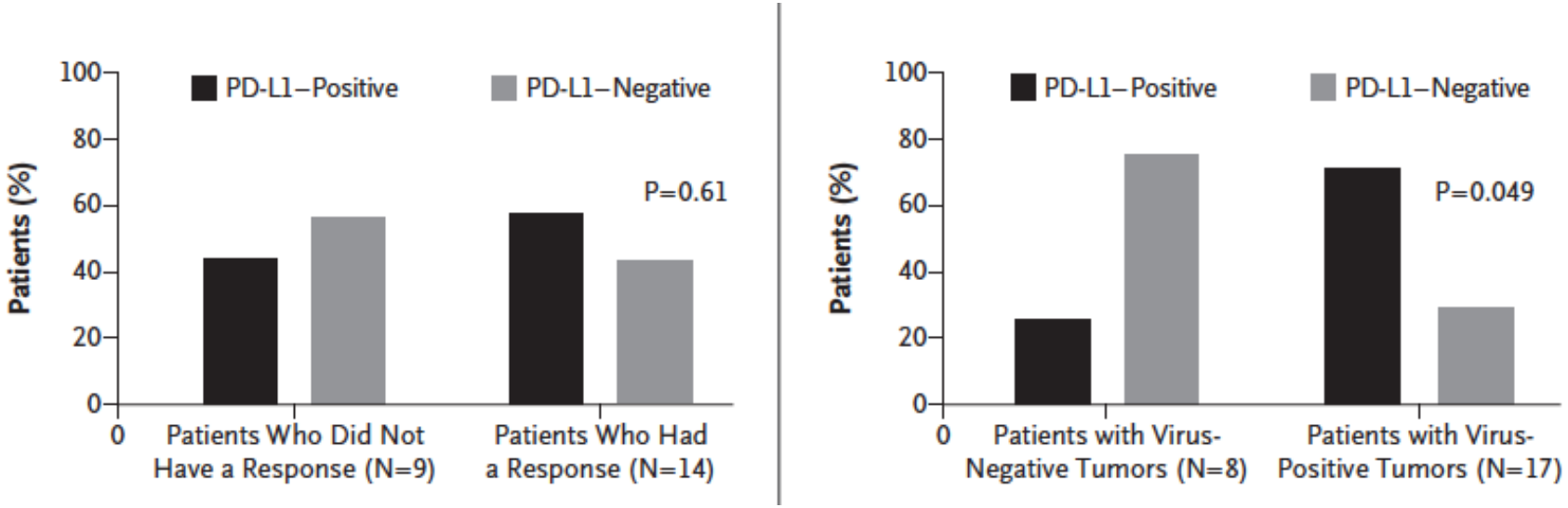
CITN-09 Phase II Clinical Trial



- No association between pre-treatment PD-L1 expression levels and responses to pembrolizumab
- MCPyV status correlates with PD-L1 expression status

Nghiem, P. et al. *NEJM.* 2016. 374: 26.

Serologic Testing to Monitor MCC

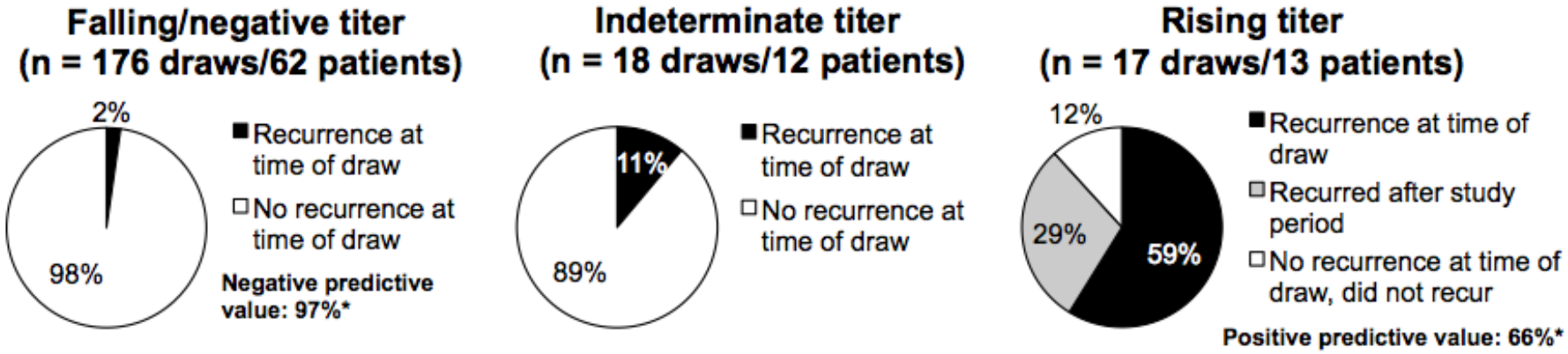
- Overall recurrence rate of MCC is >40%.
- Serologic testing for MCC is based on the development of antibodies to a Merkel Cell Polyomavirus (MCPyV) large T antigen oncoprotein (6 cc blood sample required).
- ~50% of patients with a new diagnosis of MCC exhibit evidence of this antibody (higher rates in patients with occult primary lesions).
- <1% in patients without MCC.
- Patients with detectable MCPyV antibodies exhibit a 42% lower risk of disease recurrence.

https://www.merkelcell.org/testing-and-diagnosis/serology/

Paulson, K. et al. *Cancer Res.* 2010. 70:

Serologic Testing to Monitor MCC

- Patients with detectable MCPyV antibodies exhibit a 42% lower risk of disease recurrence.
- Falling titers have a 97% negative predictive value for disease recurrence.



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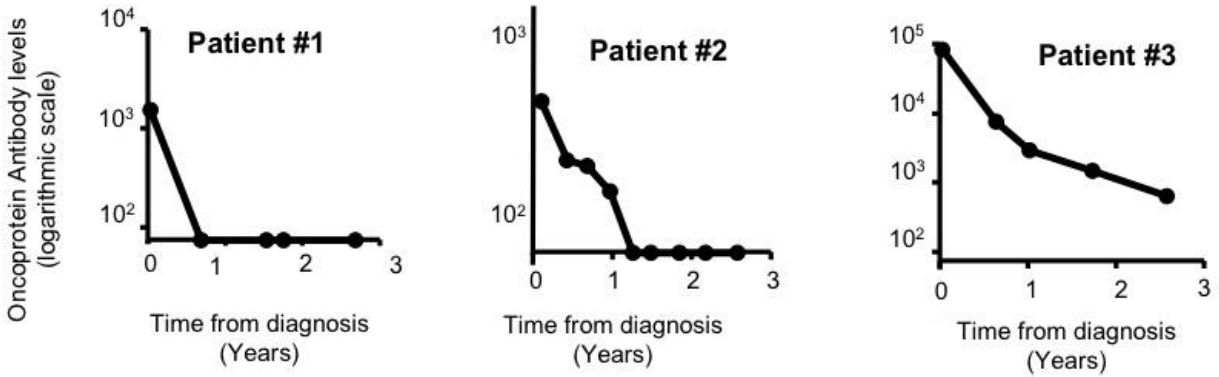
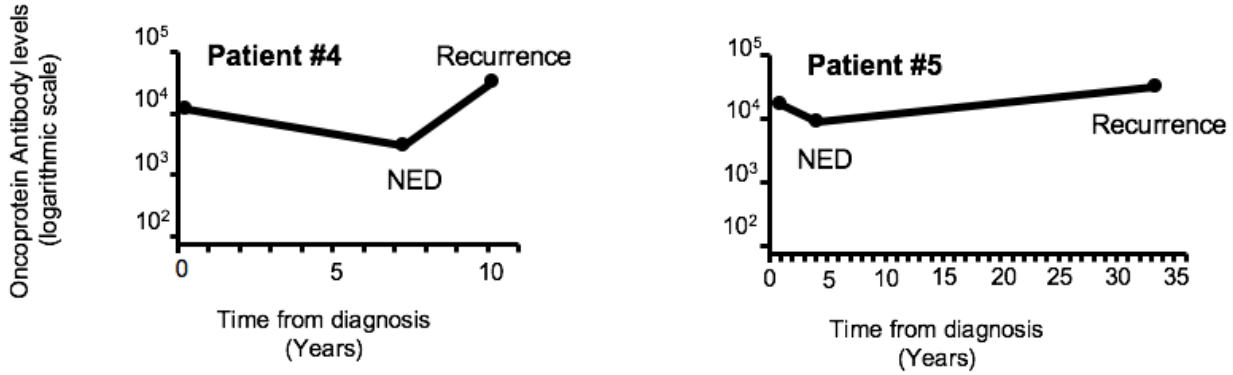
Paulson, K. et al. *Cancer Res.* 2010. 70:

Serologic Testing to Monitor MCC



Patients with No Disease Recurrence

- Ab levels typically decrease by >90% within one year after Tx



Patients with Disease Recurrence

https://www.merkelcell.org/testing-and-diagnosis/serology/

Paulson, K. et al. *Cancer.* 2016.

Serologic Testing to Monitor MCC

- Recommended to obtain MCPyV serologies within 2-3 months of initial diagnosis as a baseline measurement

- No detectable MCPyV antibody:
  - 40% higher risk of disease recurrence
  - Suggests that more frequent imaging is necessary to monitor disease

- Detectable MCPyV antibody:
  - Can track disease recurrence using serologic testing
  - Suggests that imaging can be less frequent when monitoring this disease

MCC Therapeutic Pipeline

- Avelumab 10 mg/kg IV every 2 weeks + local radiation vs IT IFN-α + MCPyV TAg-specific $CD8^+$ T cells in patients with Stage IV MCC (phase I/II study, NCT02584829)
- Ipilimumab 1 mg/kg IV every 6 weeks + nivolumab 240 mg IV every 2 weeks ± SBRT in patients with Stage IV MCC (randomized phase II study, NCT03071406)
- TVEC ± local radiation for patients with unresectable Stage III or IV MCC (randomized phase II study, NCT02819843)
- Activated NK cell (NK-92) infusion + IL-15 (ALT-803) in patients with unresectable Stage IIIB or IV MCC (phase II study, NCT02465957)
- Adjuvant ipilimumab 3 mg/kg therapy x 4 doses vs observation for previously resected MCC (randomized phase II study, NCT02196961)

Current Challenges

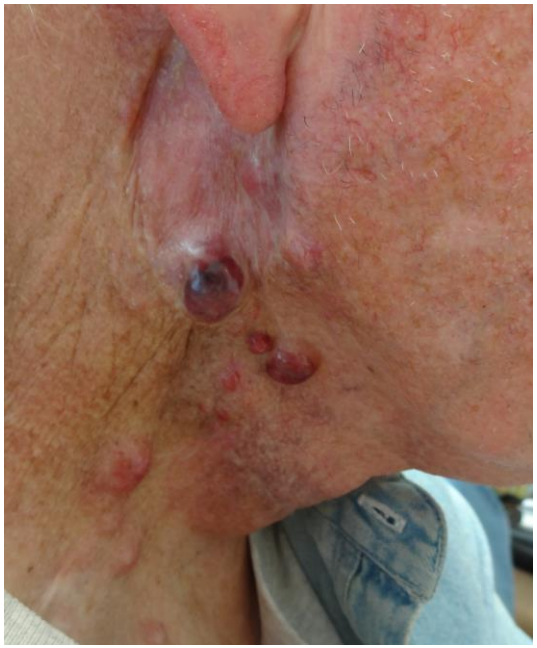
- anti-PD-1/PD-L1 antibody-refractory MCC patients
  - Intra-lesional therapeutic strategies to induce MCC antigen-specific $CD8^+$ T cell clones
  - Combination immunotherapy regimens may be difficult in this patient population
- Immunosuppressed patients
  - Alternative treatment strategies may be necessary
- Patients with comorbid autoimmune diseases
  - Anti-PD-1/PD-L1 antibody therapy should be considered
  - Vaccine/tumor antigen-directed therapies reasonable to consider
- Intra-cranial metastases

Case Study #1

80 yo male with a h/o SCC of the head & neck treated with neoadjuvant chemoradiation and surgical excision, presenting with a new right-sided neck nodule

- Tissue biopsy showed a 0.7 cm small, round, blue cell tumor staining positive for synaptophysin, CD56, and CK20 (TTF-1 negative) with positive margins; interpreted to be c/w MCC
- PCR negative for MCPyV
- PET CT showed right-sided parotid nodule with no mild FDG uptake and no evidence of distant disease
- ENT noting a 3 cm right-sided cervical mass on exam; underwent a radical excision of the soft tissue mass and a right-sided parotidectomy
  - Gross evidence of intra-dermal and intra-lymphatic disease noted
- Initiated on carboplatin/etoposide chemotherapy; completed 4 cycles (was not eligible for additional radiation therapy)

Case Study #1



- PET CT imaging showing evidence of local disease recurrence
- Initiated on avelumab 10 mg/kg IV every 2 weeks on the phase II JAVELIN 200 clinical trial
- Noted to have near complete gross response after 3 doses of avelumab
- Completed regimen with no gross or pathologic evidence of disease
- PET CT imaging 2 years later showing continued CR

Case Study #2

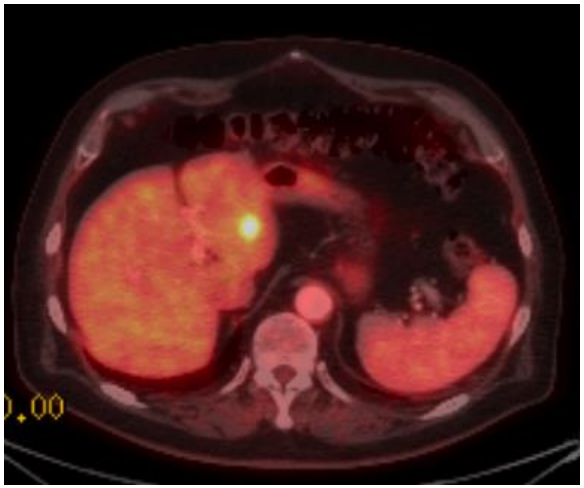
75 yo male diagnosed with MCC over his right calf in March 2011. Primary lesion was chromogranin and synaptophysin positive but CK20 and TTF-1 negative. Underwent WLE and SLNbx which was negative. Underwent local radiation therapy at the tumor bed.

- Presented with AMS and disorientation in March 2017; brain MRI showing multiple enhancing supratentorial lesions with surrounding vasogenic edema
- IC lesion biopsy c/w a neuroendocrine carcinoma positive for synaptophysin, enolase, CD56 (CK20, TTF-1 negative)
- Treated with WBRT – 3 Gy x 10 fractions

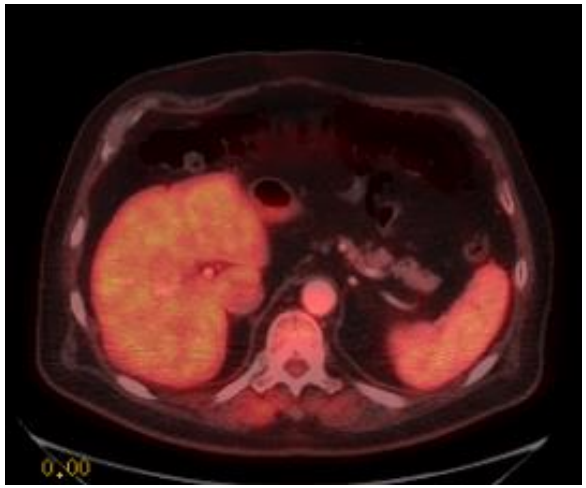
Case Study #2

- Repeat PET CT showing enlarging right apical pulmonary nodule, now FDG avid, along with a new 1 cm FDG avid lesion in the caudate lobe of the liver
- Initiated on avelumab 10 mg/kg IV every 2 weeks
- After 4 doses, clinically asymptomatic with improved energy and no neurologic complications; brain MRI showing no evidence of disease recurrence and significant improvement in vasogenic edema; PET CT demonstrating complete hepatic response with stable right apical lung nodule

Before Treatment



After 4th Cycle



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