



Updates in Merkel Cell Carcinoma

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Massachusetts General Cancer Center

Pennsylvania Academy of Dermatology and Dermatologic Surgery
September 22nd, 2023

1

Disclosures

- I have received honoraria from Pfizer, Merck Sharpe & Dome, EMD Serono, Checkpoint Therapeutics, Bristol Myers Squibb, Incyte, Castle Biosciences, Regeneron and Sanofi Genzyme for participation on advisory boards. I have stock options in Checkpoint Therapeutics and Avstera.
- We will be discussing off-label use of therapies

2

Learning Objectives

- Brief overview of the clinical features and pathophysiology of MCC
- Recognize the use of **Imaging, Lymph Node Evaluation** and **blood-based tests (AMERK & liquid biopsies)** in clinical practice
- Discuss approved therapeutic strategies in MCC, including the use of **ICIs as primary treatment**, as well as emerging strategies in the **neo-adjuvant** and **adjuvant** setting

MGH-MEEI Center for Merkel Cell Carcinoma

Tuesday Morning – MEEI

Head and Neck Surgical Oncology



Kevin Emerick M.D.

Radiation Oncology



Chirayu Patel M.D., MPH

Medical Oncology
Dermatology



David Miller M.D., Ph.D.

Medical/Surgical Oncology



Howard Kaufman MD

Tuesday Afternoon – MGH Cancer Center

Surgical Oncology



James Cusack M.D.

Radiation Oncology



Chirayu Patel M.D., MPH

Medical Oncology
Dermatology



David Miller M.D., Ph.D., FAAD

Interactivity Question



Raise your hand if you have diagnosed
Merkel cell carcinoma in the last 5 years



Interactivity Question



Raise your hand if you have diagnosed
Merkel cell carcinoma in the last 1 year

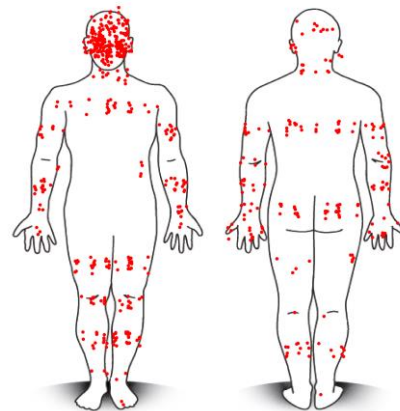


Overview

- **Clinical Features of MCC**
- Overview of Pathophysiology
- Work Up
- Management

Clinical Features MCC

- 80-90% of these arise on **UV-exposed skin**
- The tumor favors the head and neck region, followed by the extremities & the buttocks
 - About 50% of cases present on the head & neck
 - Roughly another 40% present on the extremities
 - Only about 10% are on the trunk & buttock area
 - And roughly another 10-20% present with no primary on the skin and only nodal metastases



Miller, DM unpublished data

Clinical Features MCC

- Protean in appearance and non-specific
- Can be skin-toned
- Can look like a lipoma
- Classically presents as a pink–red to violaceous, firm, dome-shaped, solitary nodule that has grown rapidly
 - Can double within a couple of months
- Rarely on a clinician’s differential diagnosis

MCC Rarely Suspected

- We evaluated a cohort of 232 patients with MCC at MGB for pre-biopsy clinical impressions
- 83% of cases (192/232) had at least one pre-biopsy DDx available within the clinician note or clinical history section of the pathology report

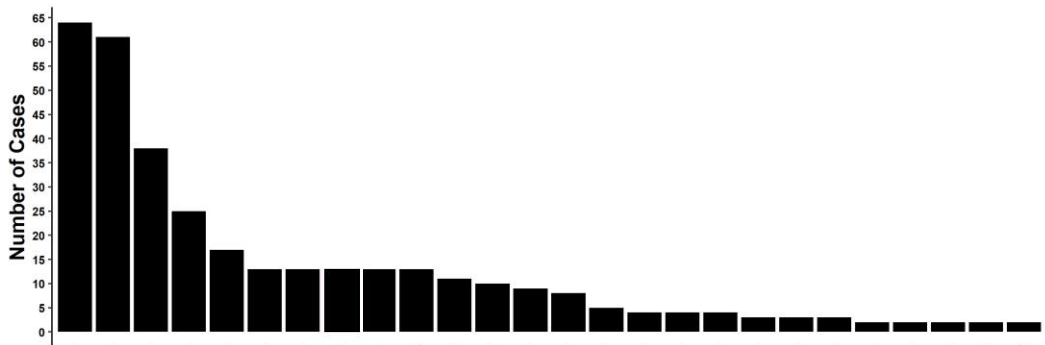
Clinical Impressions of Primary Cutaneous MCC



Saqlain et al. DOJ. 2021

11

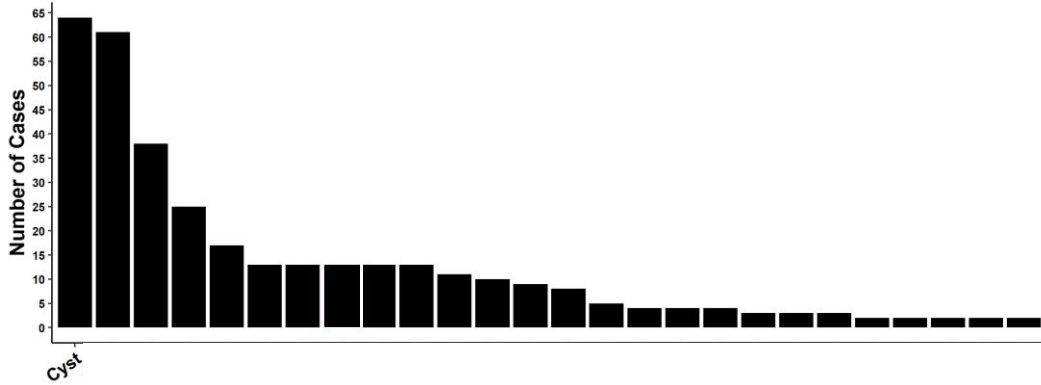
Clinical Impressions of Primary Cutaneous MCC



Saqlain et al. DOJ. 2021

12

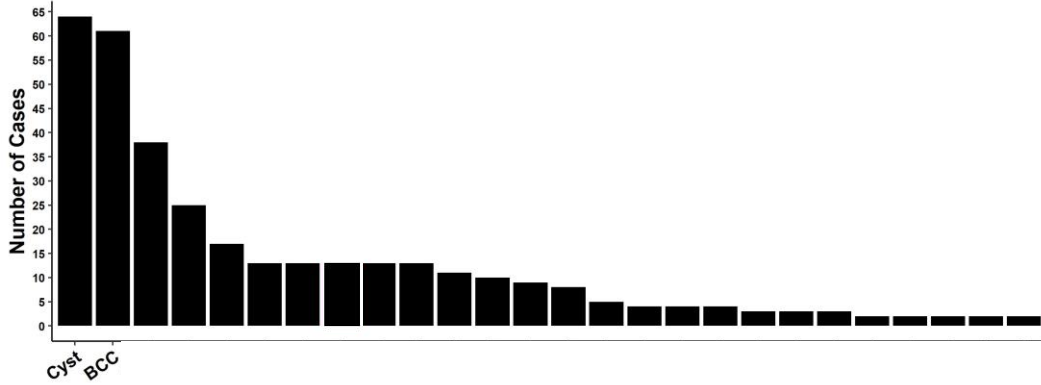
Clinical Impressions of Primary Cutaneous MCC



Saqlain et al. DOJ. 2021

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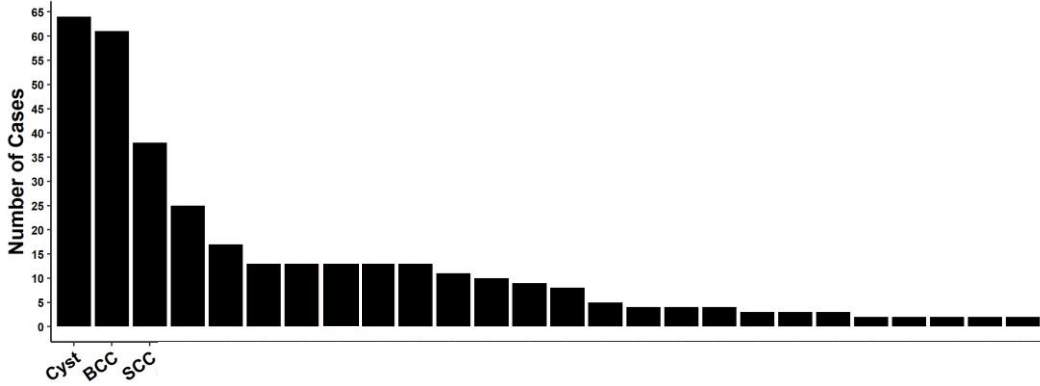
Clinical Impressions of Primary Cutaneous MCC



Saqlain et al. DOJ. 2021

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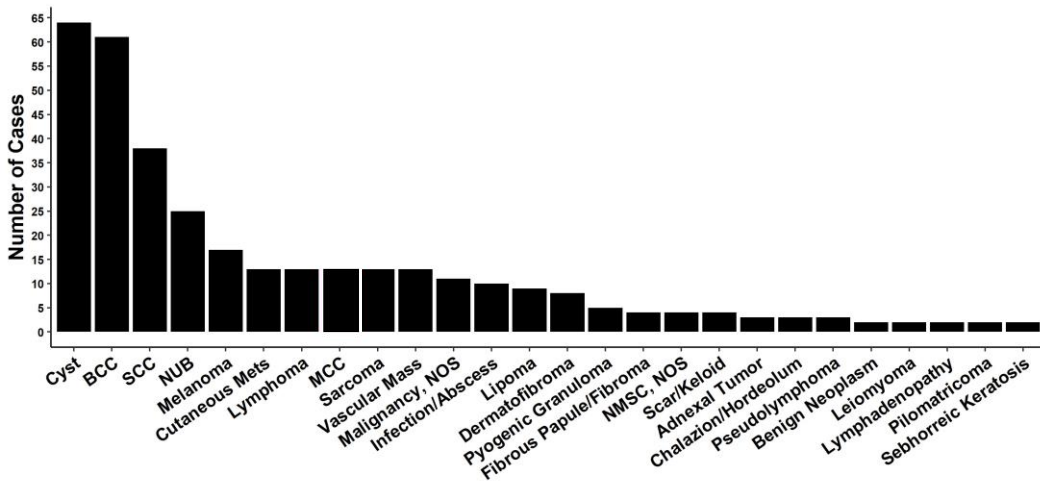
Clinical Impressions of Primary Cutaneous MCC



Saqlain et al. DOJ. 2021

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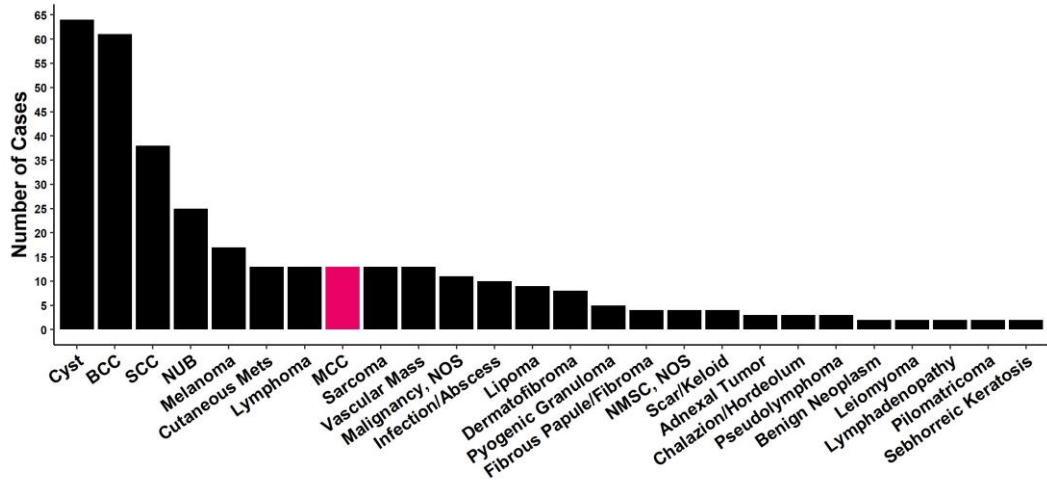
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Saqlain et al. DOJ. 2021

16

Clinical Impressions of Primary Cutaneous MCC



Saqlain et al. DOJ. 2021

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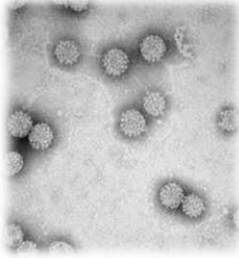
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- Clinical Features of MCC
- **Overview of Pathophysiology**
- Work Up
- Management

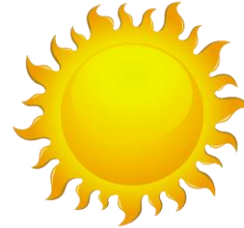
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Pathogenesis **Two Distinct Mechanisms**

Merkel Cell Polyomavirus

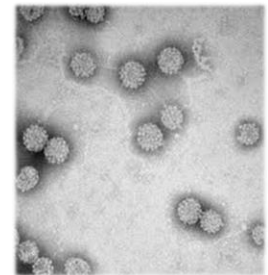


UV-Induced Damage

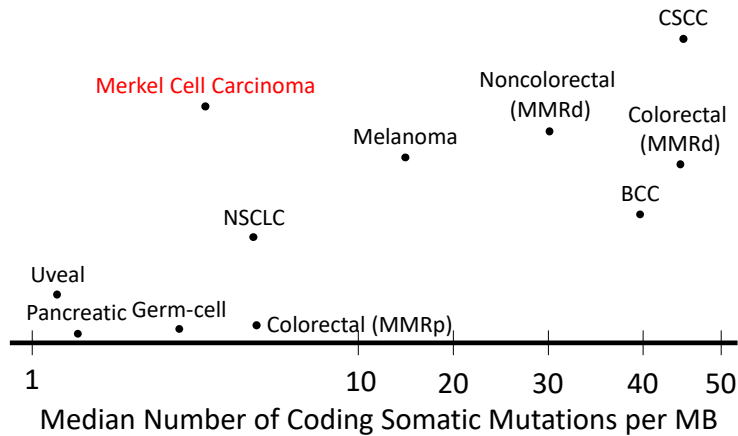


Merkel Cell Polyoma Virus **Discovery**

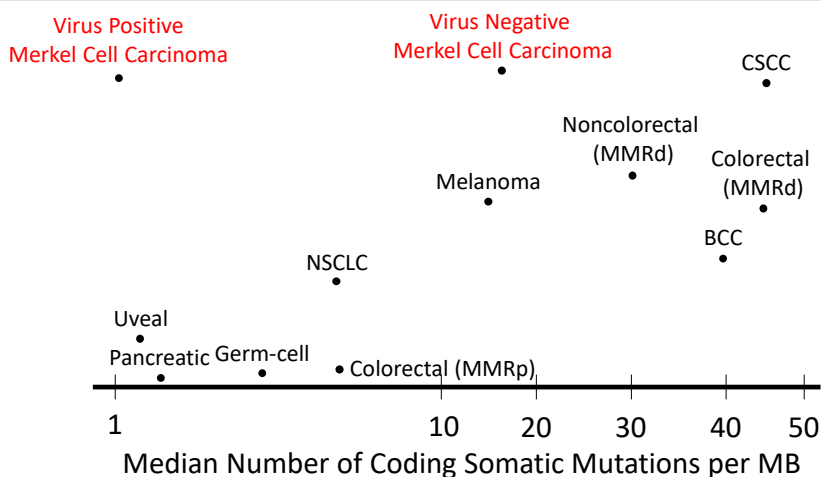
- A watershed finding regarding the etiology of MCC was the discovery in 2008 of the **Merkel cell polyomavirus** by the Moore-Chang group
- They demonstrated that in most MCCs the viral DNA was **clonally integrated** into the host cell DNA
- MCC is associated with clonal integration of the Merkel cell polyoma virus in about **60-80% of cases**

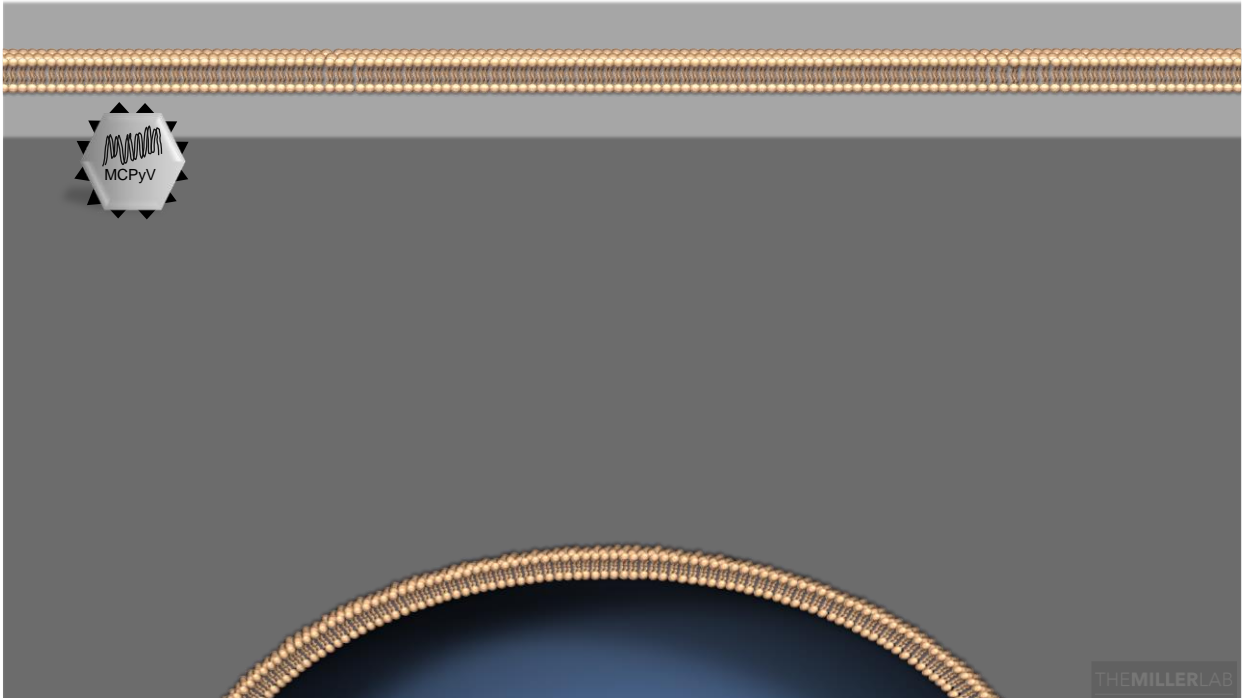


Pathogenesis Mutational Landscape

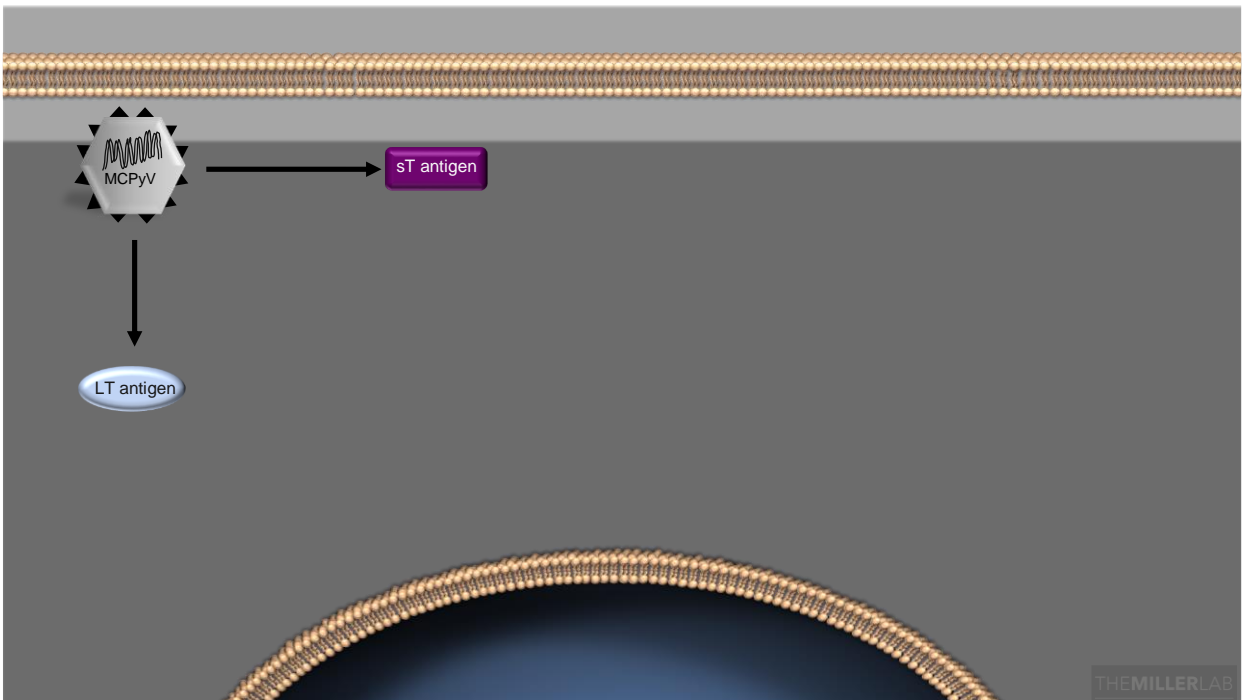


Pathogenesis Mutational Landscape

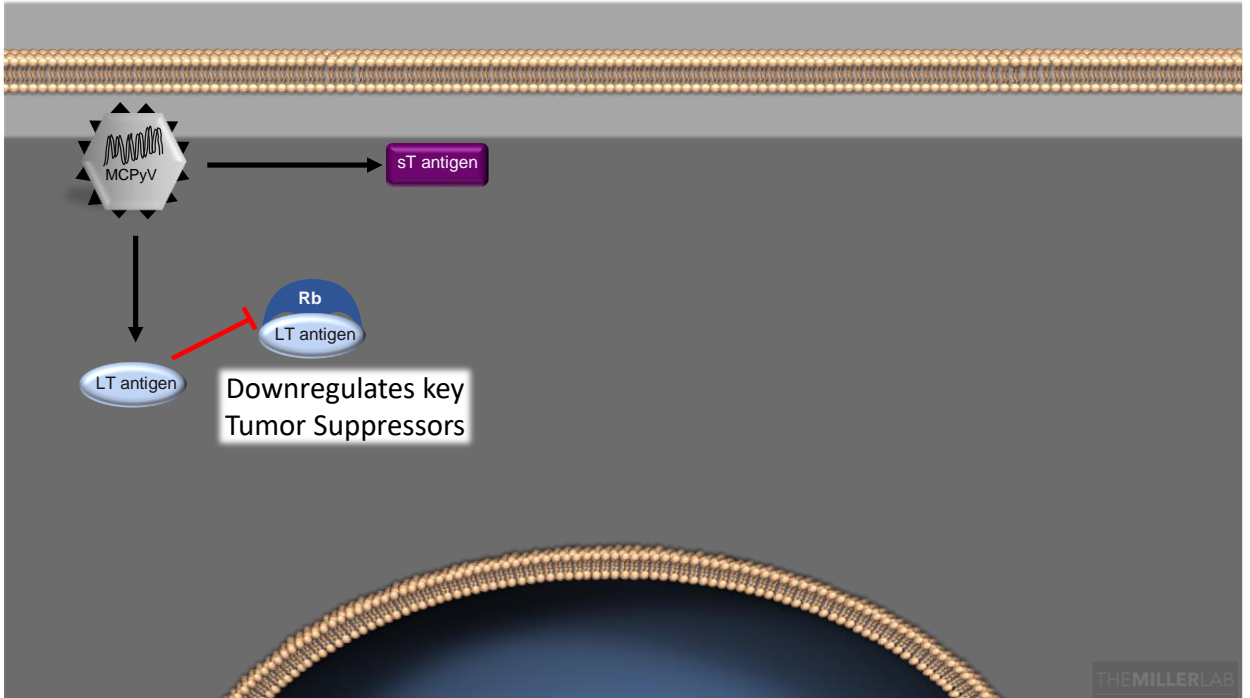




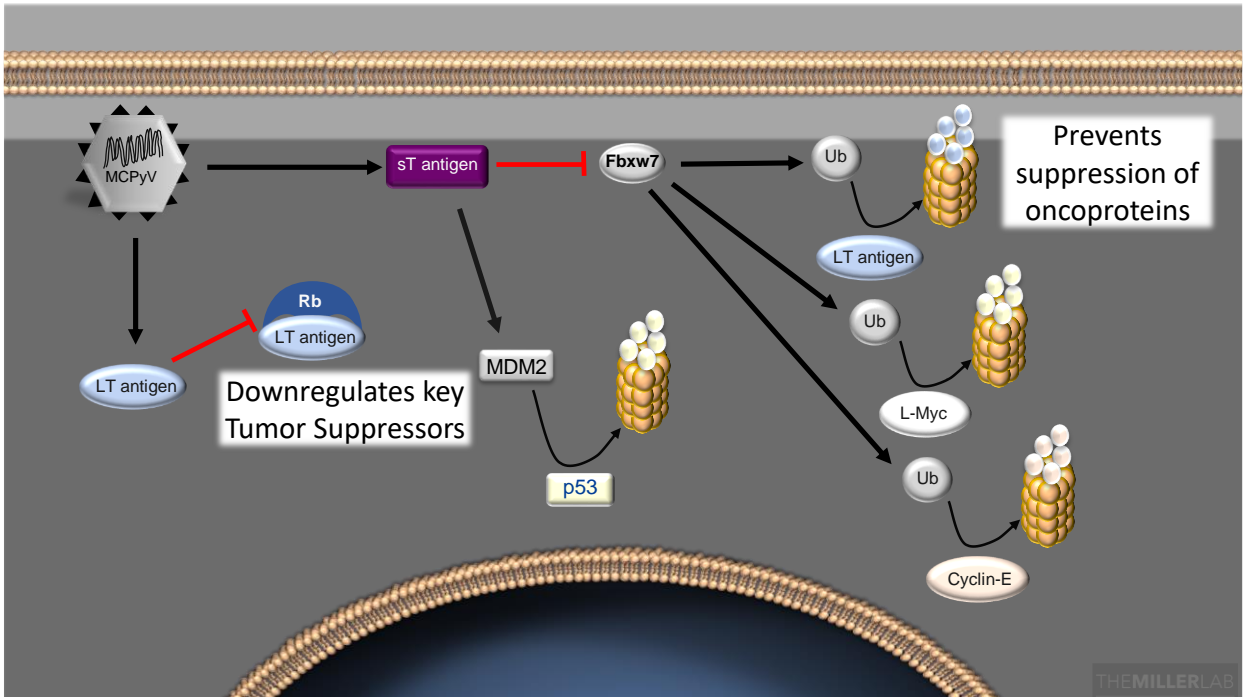
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26

Merkel Cell Carcinoma Prognosis

Criterion	Stage	5-year Survival
Primary lesion \leq 2 cm (SLNBx Neg)	Pathological Stage I	62.8
Primary lesion $>$ 2 cm, no invasion (SLNBx Neg)	Pathological Stage IIA	54.6
Primary lesion with tissue invasion (SLBx Neg)	Pathological Stage IIB	34.8

Merkel Cell Carcinoma Prognosis

Criterion	Stage	5-year Survival
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Primary lesion $>$ 2 cm, no invasion (SLNBx Neg)	Pathological Stage IIA	54.6
Primary lesion with tissue invasion (SLBx Neg)	Pathological Stage IIB	34.8
Clinical Occult Node, +SLNBx (T _{any} pN1a)	Pathological Stage IIIA	40.3
Clinical Positive Node	Pathological Stage IIIB	26.8
Distant Metastasis	Pathological Stage IV	13.5

Merkel Cell Carcinoma Prognosis

Criterion	Stage	5-year OS
Primary lesion \leq 2 cm (SLNBx Neg)	Pathological Stage I	88
Primary lesion >2 cm, no invasion (SLNBx Neg)	Pathological Stage IIA	66
Primary lesion with tissue invasion (SLBx Neg)	Pathological Stage IIB	66
Clinical Occult Node, +SLNBx (T_{any} pN1a)	Pathological Stage IIIA	68
Clinical Positive Node	Pathological Stage IIIB	54
Distant Metastasis	Pathological Stage IV	NA

Merkel Cell Carcinoma Prognosis

Criterion	Stage	5-year MSS
Primary lesion \leq 2 cm (SLNBx Neg)	Pathological Stage I	95
Primary lesion >2 cm, no invasion (SLNBx Neg) Primary lesion with tissue invasion (SLBx Neg)	Pathological Stage IIA/B	80
Clinical Occult Node, +SLNBx (T_{any} pN1a)	Pathological Stage IIIA	78
Clinical Positive Node	Pathological Stage IIIB	56
Distant Metastasis	Pathological Stage IV	NA

Overview

- Clinical Features of MCC
- Overview of Pathophysiology
- **Workup: Imaging, AMERK and ctDNA**
- Management

Interactivity Question



Interactivity Question



Raise your hand if you have ordered a PET-CT in the last 5 years



MCC Work Up **Imaging**

- NCCN Guidelines: Imaging is encouraged in **most cases of MCC**
- Singh et al demonstrated that occult metastatic disease has been detected in 12%–20% of patients who presented without suspicious findings on history and physical examinations¹
- We use **PET-CT** as our baseline cross-sectional imaging modality in all patients

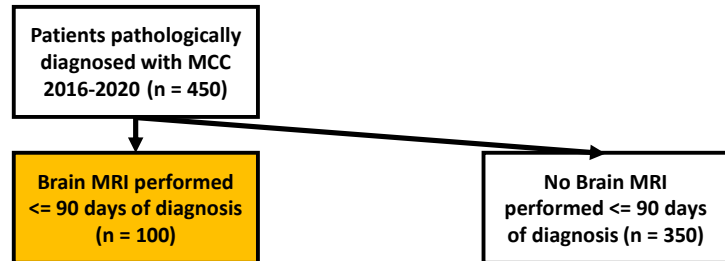
MCC Work Up Imaging

- Use of brain MRI as initial work up – as clinically indicated

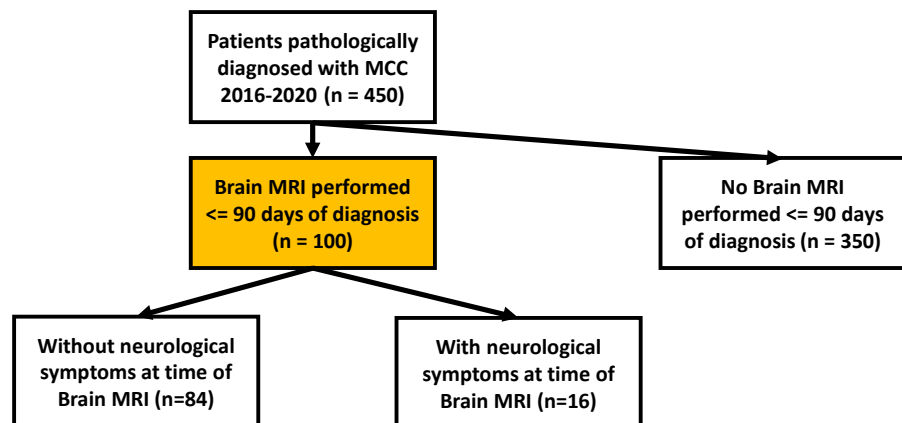
MCC Work Up Imaging

Patients pathologically
diagnosed with MCC
2016-2020 (n = 450)

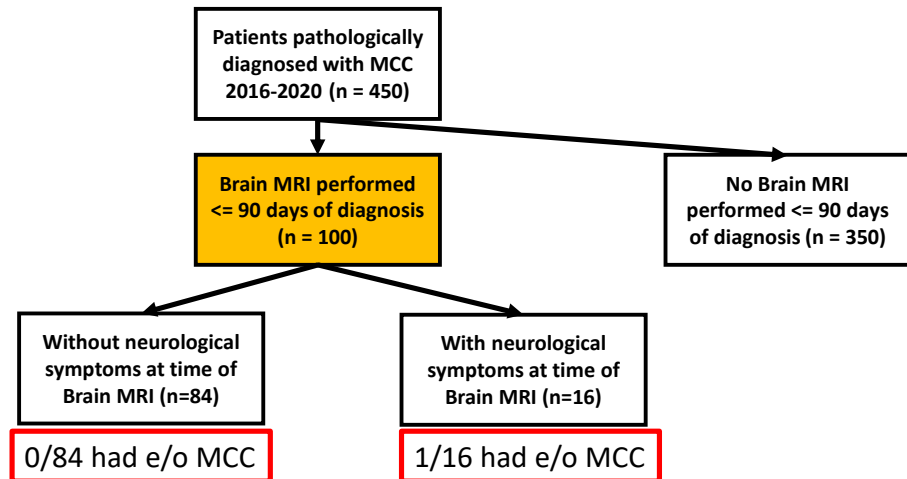
MCC Work Up Imaging



MCC Work Up Imaging



MCC Work Up Imaging



MCC Work Up Lymph Node Evaluation

- If regional disease is evident on physical exam or scans
 - FNA/Core Biopsy

MCC Work Up Lymph Node Evaluation

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- If distant disease is detected on imaging
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MCC Work Up Lymph Node Evaluation

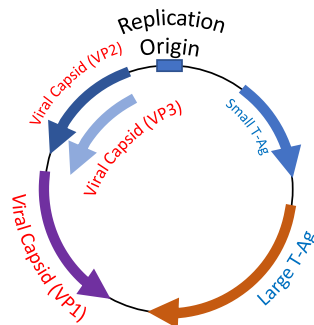
- If regional disease is evident on physical exam or scans
 - FNA/Core Biopsy
- If distant disease is detected on imaging
 - FNA/Core Biopsy
- If no evidence of regional or distant disease
 - Sentinel Lymph Node Biopsy in all suitable patients
 - Even in the absence of metastatic disease on exam/imaging 30% of patients may have MCC on SLNBx¹

MCC Work Up **AMERK**

Viral Oncoprotein Antibodies as a Marker for Recurrence of Merkel Cell Carcinoma: A Prospective Validation Study

Kelly G. Paulson, MD, PhD^{1,2,5}; Christopher W. Lewis, BS¹; Mary W. Redman, PhD⁴; William T. Simonson, MD, PhD³; Aaron Lisberg, MD¹; Deborah Ritter, MS³; Chihiro Morishima, MD³; Kathleen Hutchinson, MS³; Lola Mudgistratova, BA¹; Astrid Blom, MD¹; Jayasri Iyer, MD¹; Ata S. Moshiri, MD, MPH¹; Erica S. Tarabdkar, MD¹; Joseph J. Carter, PhD⁶; Shailender Bhatia, MD^{2,5}; Masaoki Kawasumi, MD, PhD¹; Denise A. Galloway, PhD⁶; Mark H. Wener, MD³; and Paul Nghiem, MD, PhD^{1,5}
Cancer April 15, 2017

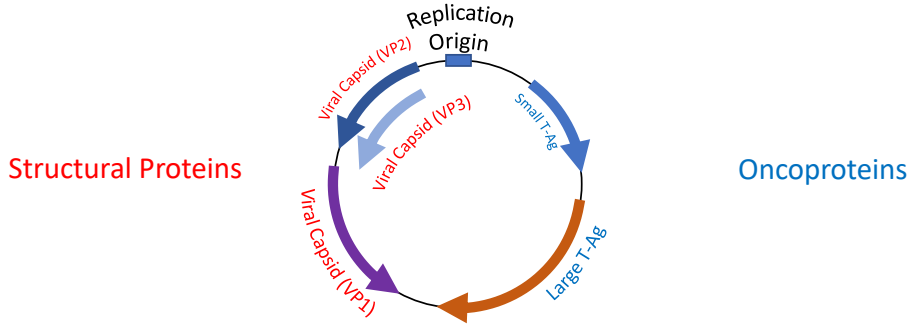
MCC Serum Oncoprotein Antibody Test **Overview**



Merkel Cell Polyomavirus Genome

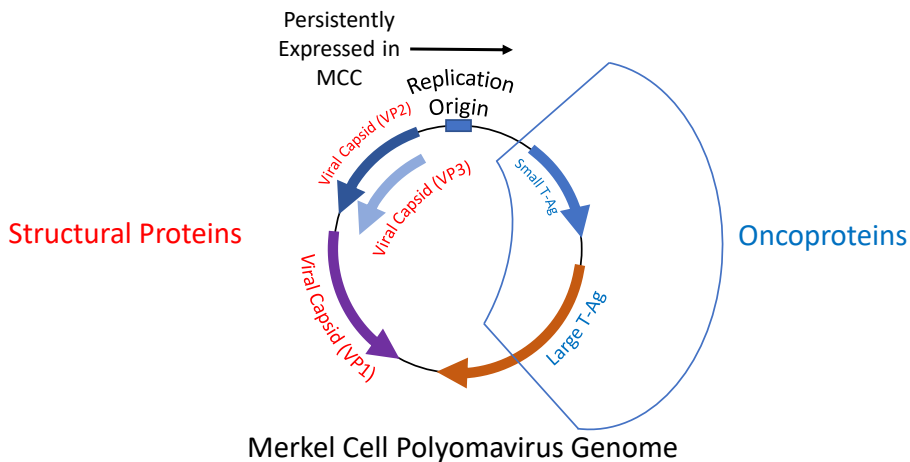
Adapted from Paulson et al. *Cancer*. 2017;123(8):1464-1474

MCC Serum Oncoprotein Antibody Test Overview



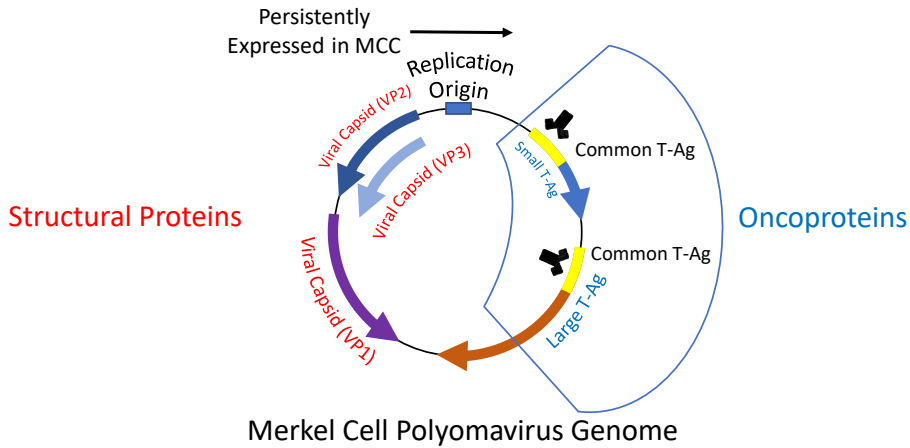
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MCC Serum Oncoprotein Antibody Test Overview



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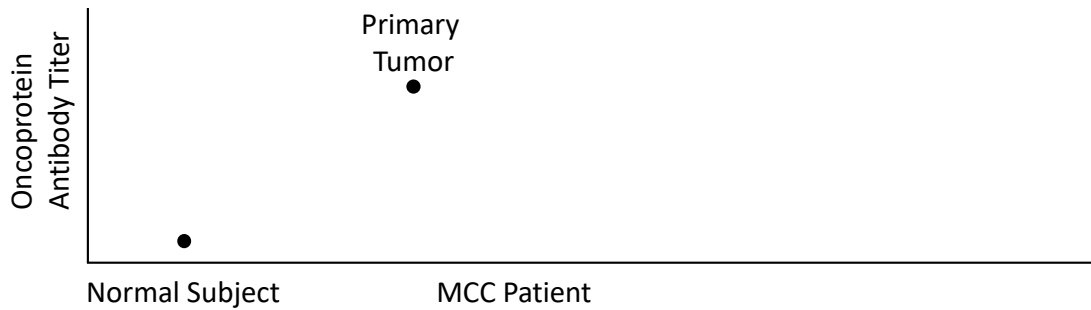


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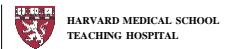
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MCC Serum Oncoprotein Antibody Test Overview

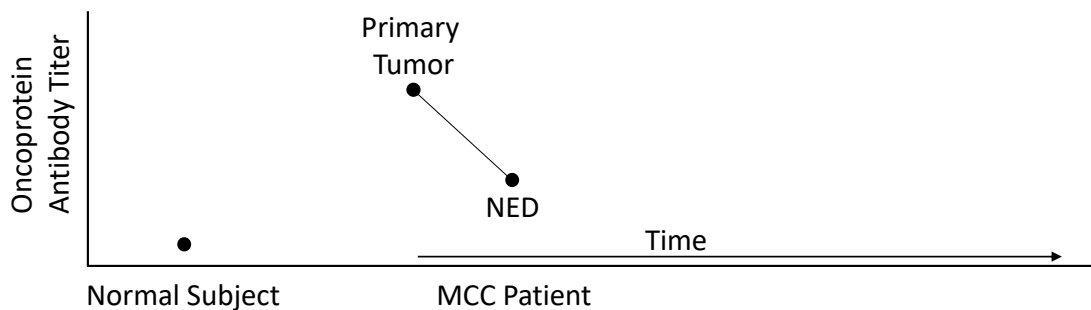


Mass General Brigham
Mass General Cancer Center Figure Adapted from Paulson et al. *Cancer*. 2017;123(8):1464-1474

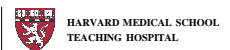


49

MCC Serum Oncoprotein Antibody Test Overview

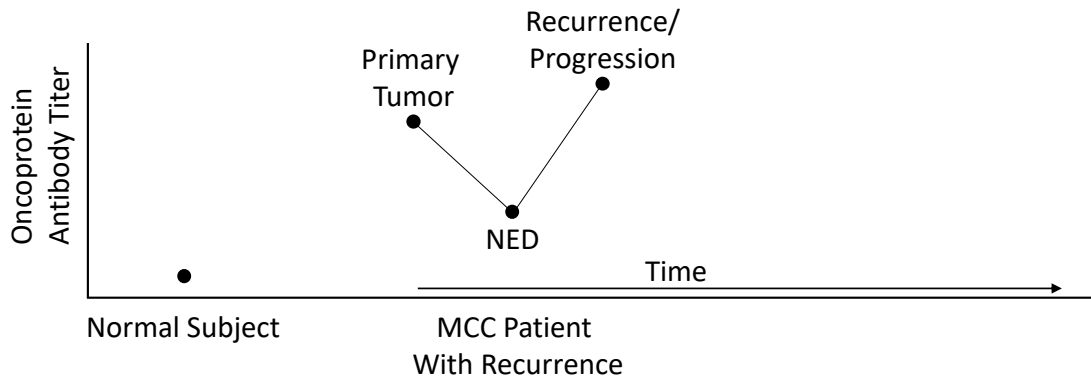


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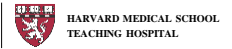


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MCC Serum Oncoprotein Antibody Test Overview

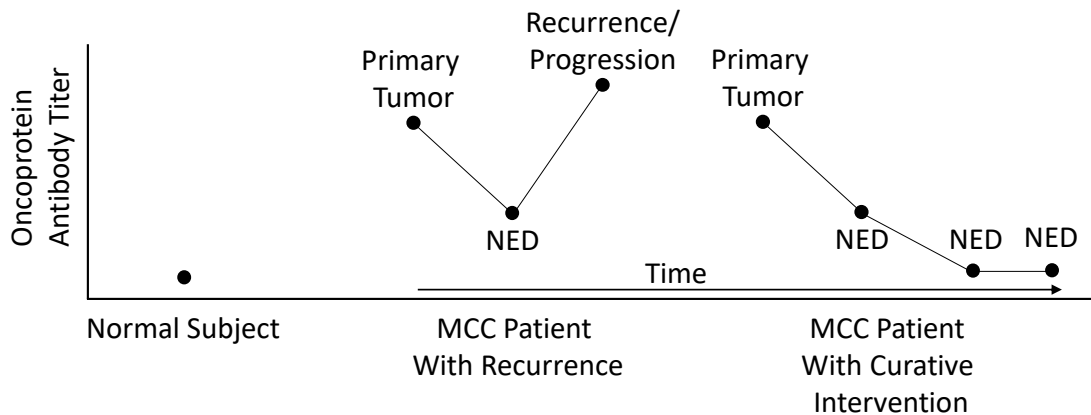


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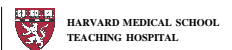


51

MCC Serum Oncoprotein Antibody Test Overview



Mass General Brigham
Mass General Cancer Center Figure Adapted from Paulson et al. *Cancer*. 2017;123(8):1464-1474



52

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

PT NO. NAME (Last, First) DOA SSN XXXXX-XX-XXXX		CLINICAL LAB REQUEST UW MEDICINE CLINICAL IMMUNOLOGY LAB AMERK Requisition University of Washington Medical Center 1959 NE Pacific St., NW 2225 Seattle, WA, 98195 (206) 550-4600 How to Order/Send samples, Billing (206) 556-1449 Technical Questions		ORDERED BY: PROCESSED BY:																																					
ORDERING PHYSICIAN TYPE: <input type="checkbox"/> Serology SPECIMEN TYPE: <input type="checkbox"/> AM <input type="checkbox"/> PM DATE TIME COLLECTED ORDER SPECIMEN # UR HOSPITAL # ICD / Diagnosis Code SEND REPORT TO (Physician, Clinic, Physician)		REQUIRED ICD codes: ICD codes are provided only for informational or educational purposes. The decision as to which ICD code to use rests solely with the ordering health care provider. The ordering health care provider should assign the most accurate code possible whether included in the table of ICD codes or not.		AMERK Anti-Merkel Cell Panel (Serum, 2 mL, min. 0.5 mL)																																					
ADDRESS CITY STATE ZIP TELEPHONE FAX FAX Results Yes No SUBSCRIBER NUMBER SUBSCRIBER ID # UROLINK Medicare (answer required to question below) Is this a hospital outpatient or inpatient? Yes No (see response to additional information)		Merkel Virus Oncoprotein Serology: Oncoprotein antibodies are present in the blood of 50% of patients when they have clinically detectable MCC. In patients who make oncoprotein antibodies, titers are expected to decrease significantly within 3 months of successful treatment of MCC. Changes in oncoprotein titer of less than 25% may not be biologically significant. A significant rise in titer or stabilization of titer above 2000 STU may be associated with persistent or recurrent MCC. Questions? See www.merkelcell.org/sero		Table of ICD codes: <table border="1"> <tr> <td>C4A Unspecified</td> <td>MCC of the Trunk</td> </tr> <tr> <td>MCC of the Face</td> <td>C4A.5 Trunk, unspecified</td> </tr> <tr> <td>C4A.0 Lip</td> <td>C4A.51 Anal or perianal skin</td> </tr> <tr> <td>C4A.1 Eyelid (incl. Canthus)</td> <td>C4A.52 Skin of breast</td> </tr> <tr> <td>C4A.10 Eyelid, unspecified</td> <td>C4A.59 Trunk, other part</td> </tr> <tr> <td>C4A.11 Eyelid, right</td> <td>MCC of the Limb</td> </tr> <tr> <td>C4A.12 Eyelid, left</td> <td>C4A.6 Upper limb (incl. shoulder)</td> </tr> <tr> <td>C4A.2 Ear (and ext, auricular canal)</td> <td>C4A.60 Upper limb, unspecified</td> </tr> <tr> <td>C4A.20 Ear, Unspecified</td> <td>C4A.61 Upper limb, right</td> </tr> <tr> <td>C4A.21 Ear, right</td> <td>C4A.62 Upper limb, left</td> </tr> <tr> <td>C4A.22 Ear, left</td> <td>C4A.7 Lower limb, (incl hip)</td> </tr> <tr> <td>C4A.3 Face, other parts</td> <td>C4A.70 Lower limb, unspecified</td> </tr> <tr> <td>C4A.30 Face, unspecified</td> <td>C4A.71 Lower limb, right</td> </tr> <tr> <td>C4A.31 Nose</td> <td>C4A.72 Lower limb, left</td> </tr> <tr> <td>C4A.4 Scalp and Neck</td> <td>Other</td> </tr> <tr> <td>Nodeal and Metastatic MCC</td> <td>C4A.8 Overlapping Sites</td> </tr> <tr> <td>C7B.1 Secondary MCC</td> <td>C4A.9 Unspecified Sites</td> </tr> <tr> <td>Z85.821 History of MCC on the skin</td> <td></td> </tr> </table>		C4A Unspecified	MCC of the Trunk	MCC of the Face	C4A.5 Trunk, unspecified	C4A.0 Lip	C4A.51 Anal or perianal skin	C4A.1 Eyelid (incl. Canthus)	C4A.52 Skin of breast	C4A.10 Eyelid, unspecified	C4A.59 Trunk, other part	C4A.11 Eyelid, right	MCC of the Limb	C4A.12 Eyelid, left	C4A.6 Upper limb (incl. shoulder)	C4A.2 Ear (and ext, auricular canal)	C4A.60 Upper limb, unspecified	C4A.20 Ear, Unspecified	C4A.61 Upper limb, right	C4A.21 Ear, right	C4A.62 Upper limb, left	C4A.22 Ear, left	C4A.7 Lower limb, (incl hip)	C4A.3 Face, other parts	C4A.70 Lower limb, unspecified	C4A.30 Face, unspecified	C4A.71 Lower limb, right	C4A.31 Nose	C4A.72 Lower limb, left	C4A.4 Scalp and Neck	Other	Nodeal and Metastatic MCC	C4A.8 Overlapping Sites	C7B.1 Secondary MCC	C4A.9 Unspecified Sites	Z85.821 History of MCC on the skin	
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OTHER RESOURCE WEBSITES: Revised 03/17		Relevant Reference: Paulson, et al. Cancer Research 2010, 70:5389-97 http://www.ncbi.nlm.nih.gov/pubmed/20559476		MEDICARE BILLING INFORMATION Medicare billing policies are from submitting a Medicare claim for laboratory testing ordered to use on hospital inpatients or hospital outpatients. For these services, we bill the originating provider.																																					

53

MCPyV Antibody Test Clinical Utility

- Oncoprotein Ab Test can identify two populations of patients
 - Seronegative group, that may benefit from closer imaging
 - Seropositive group, who may benefit from serial titer assessment
 - Paul Nghiem’s group at University of Washington has studied a cohort of patients over 10 years and reported NPV and PPV of 99%
- Limitations
 - Not applicable for patients with virus negative tumors

Interactivity Question



Raise your hand if you have ordered a liquid biopsy before



Liquid Biopsy

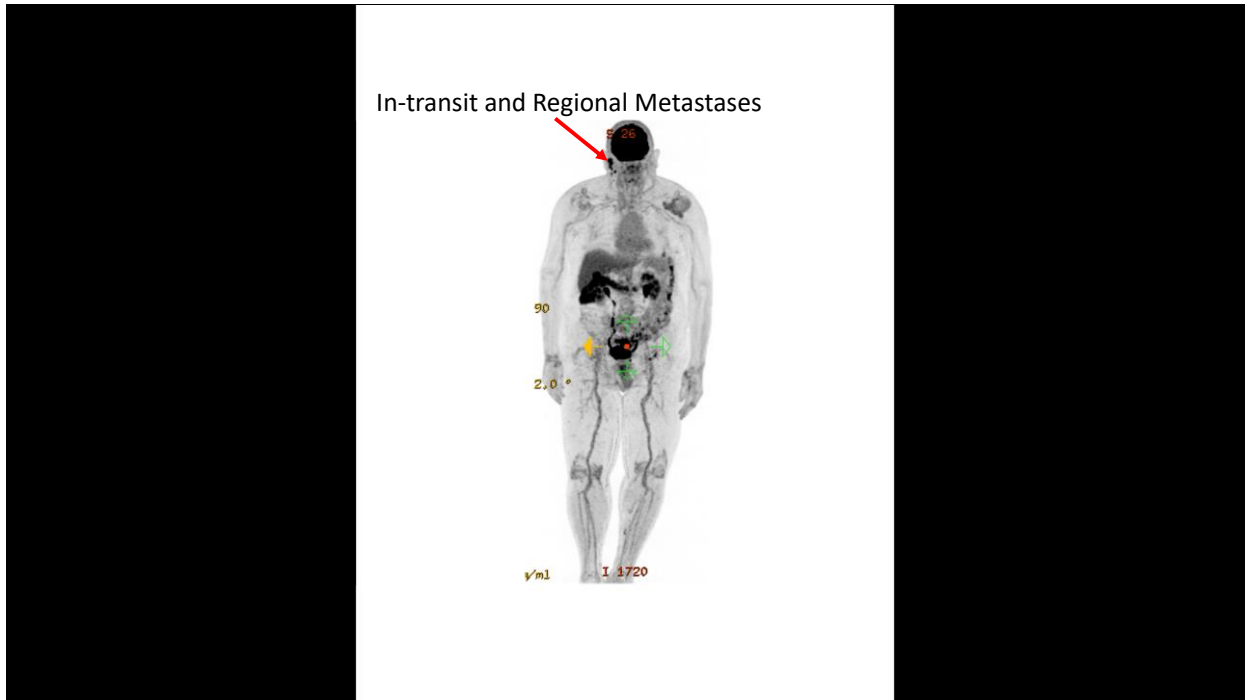
- Allows for the sequential analysis of
 - circulating tumor cells (CTCs) or
 - cell-free DNA (cfDNA)/circulating tumor DNA (ctDNA)
- Potential non-invasive approach for:
 - Surveillance
 - Prognosis
 - Guidance for therapeutic options in several cancers

Liquid Biopsy ctDNA

- Currently, a variety of sources of ctDNA exist
 - Commercial Vendors
 - Guardant
 - Natera
 - Foundation Medicine
 - Institutional molecular pathology departments
- Limited data in MCC

ctDNA Vignette

- Male in 9th decade of life
- MCC right temple
- In-transit metastases and parotid metastases appreciated on physical exam



59

ctDNA Vignette Stage IIIB

60

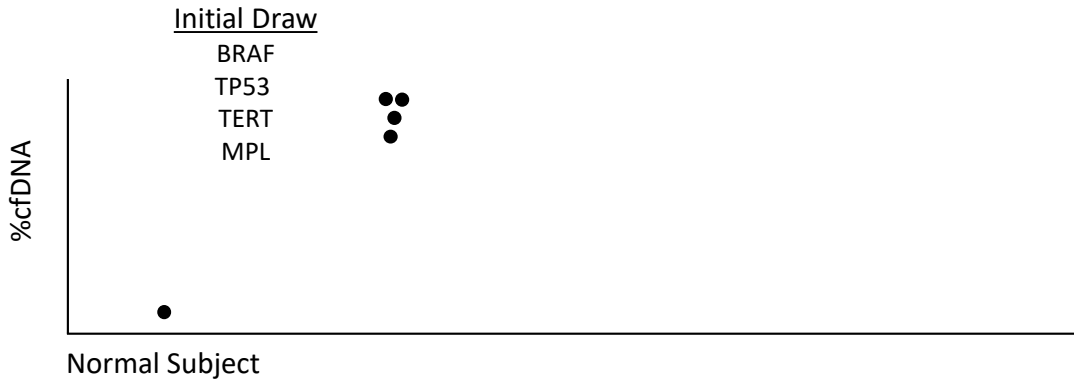
ctDNA Vignette Stage IIIB



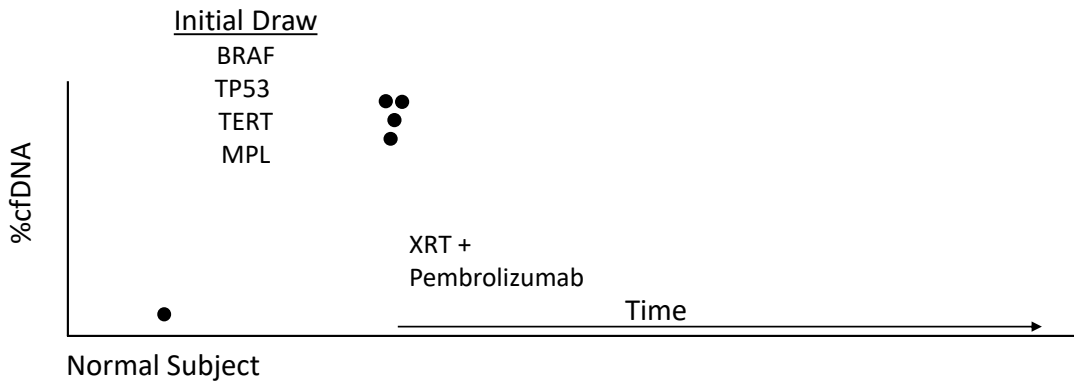
ctDNA Vignette Stage IIIB

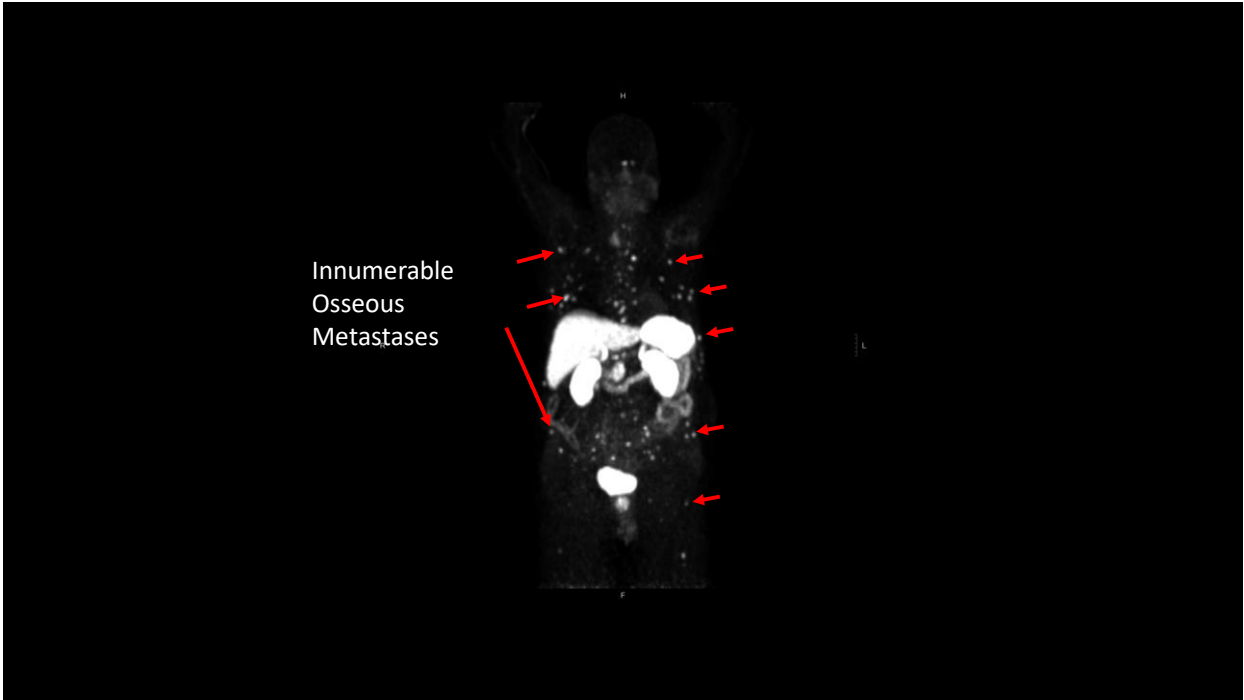


ctDNA Vignette Stage IIIB

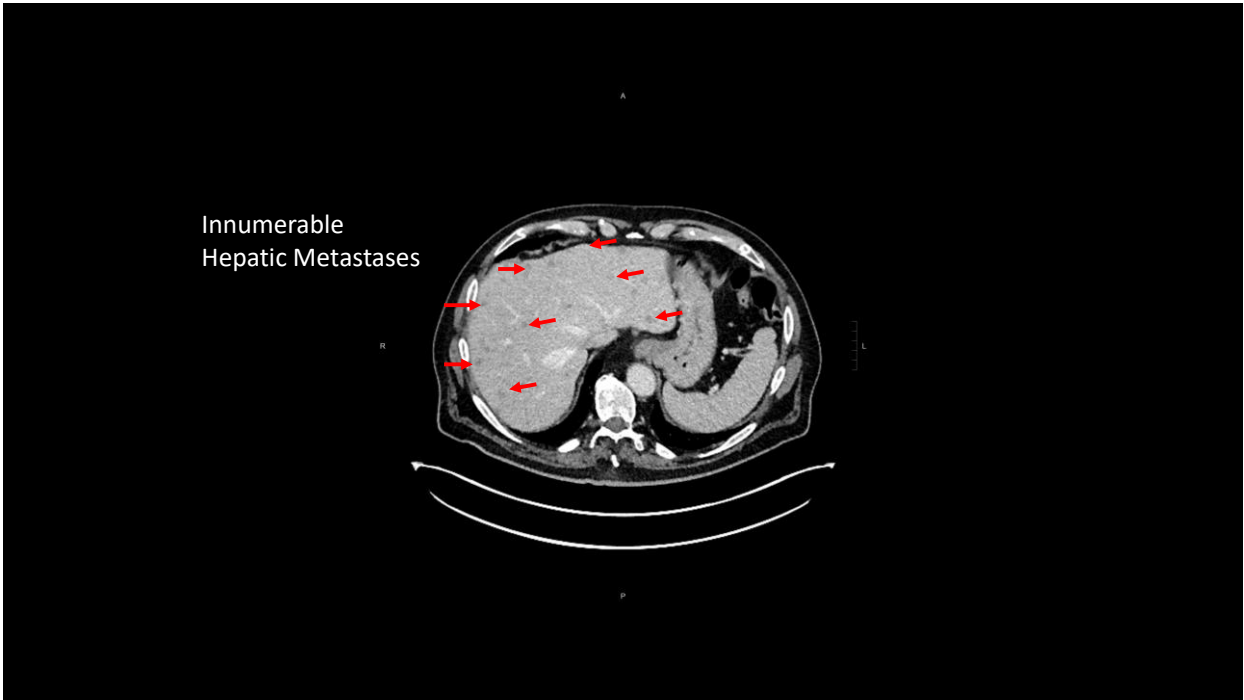


ctDNA Vignette Stage IIIB





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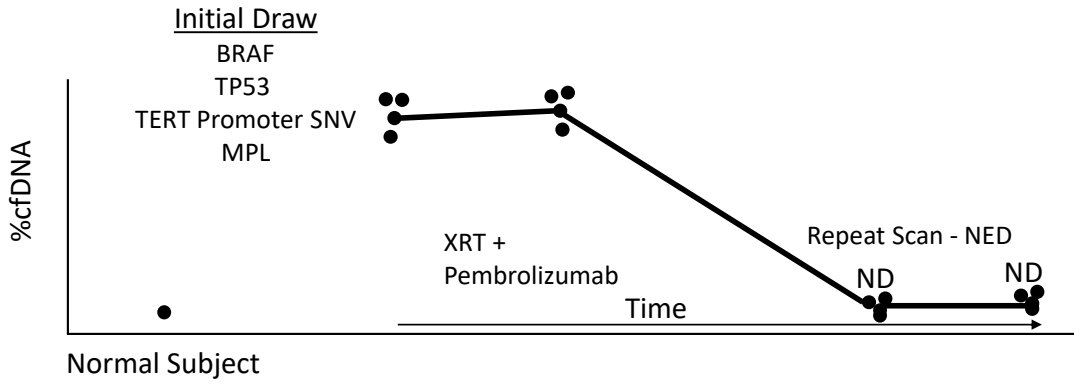


68



69

ctDNA Vignette



70

ctDNA Clinical Utility

- Potential biomarker for rapid progressor phenotype
- Potential utility in assessing treatment response
 - Identify true progression vs. pseudo-progression

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Clinical utility of cell-free DNA liquid biopsies in Merkel cell carcinoma

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Overview

- Overview of Pathophysiology
- Workup: Imaging, AMERK and ctDNA
- **Management**

Management Overview

- Stage I
- Stage II
- Stage III
- Stage IV

Management Overview

- Stage I
- Stage II
- Stage III
- Stage IV

Management Stage I

- Excision
 - 1-2 cm margins*
- Adjuvant XRT (~50 Gy)

*smaller margins may be reasonable if aXRT is planned

Management Adjuvant XRT in Stage I Disease

- Reasonable to Omit aXRT if all of the following are met

Diameter \leq 1-2 cm ✓

No LVI ✓

Margins Clear ✓

Immunocompetent ✓

Management Surgical Margins

- If adjuvant radiotherapy is planned, then a narrow margin excision may be reasonable
- Otherwise excision with 1-2 cm margins

1. Tarabdkar ES et al. *J Am Acad Dermatol.* 2021;84(2):340-347.
2. Harrington C et al. *Ann Surg Oncol.* 2016;23(2):573-578.
3. Perez MC *Ann Surg Oncol.* 2018;25(11):3334-3340.
4. Andruska N et al. *JAMA Dermatol.* 2021.

Management Stage II

- Excision
 - 1-2 cm margins*
- Adjuvant XRT (~50 Gray)

*smaller margins may be reasonable if aXRT is planned

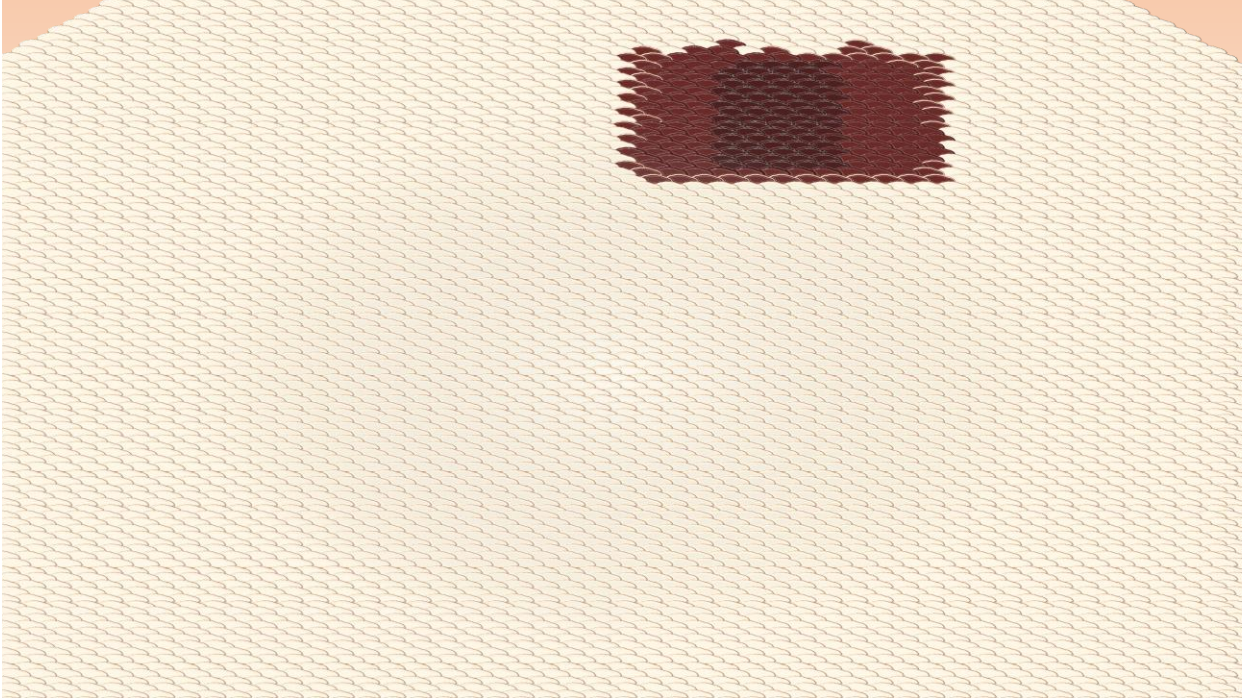
Management Stage III

- Clinically Node Negative
 - Excision
 - 1-2 cm margins to primary site*
 - LN removed at SLNBx
 - Adjuvant XRT to primary and regional basin (~50 Gray)
- Clinically Positive Stage III
 - Excision/Nodal dissection with aXRT
 - Clinical trial

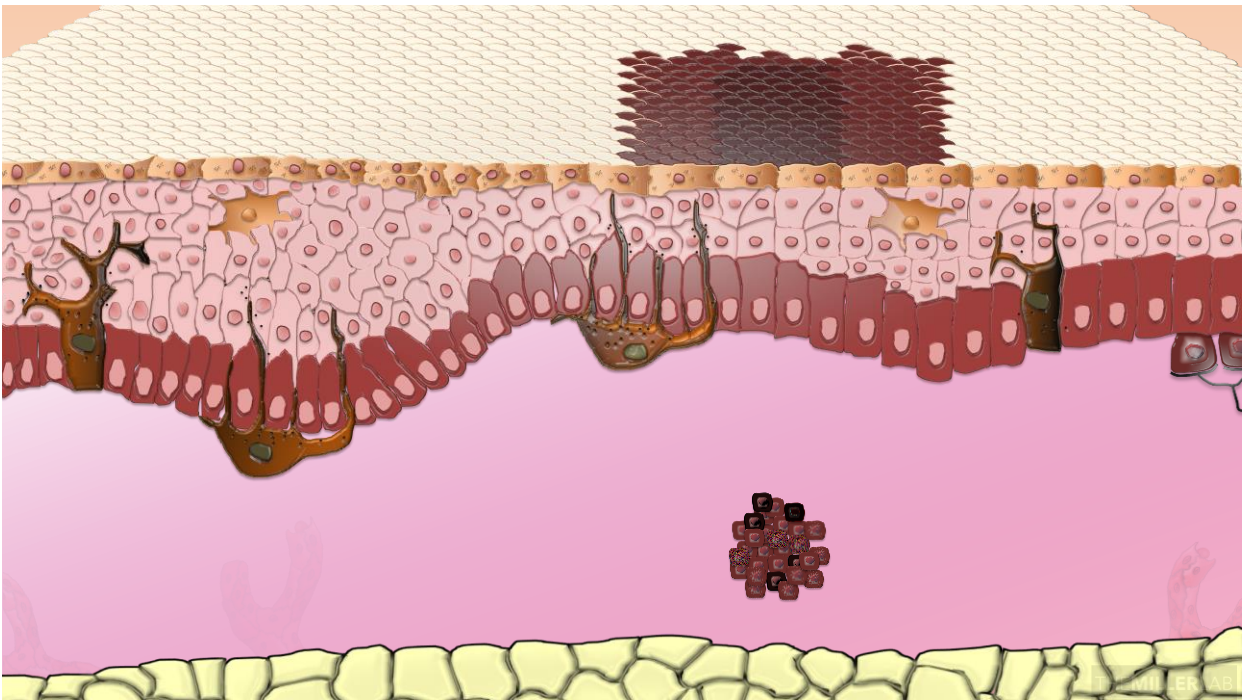
*smaller margins may be reasonable if aXRT is planned

Management Stage IV and Unresectable Dz

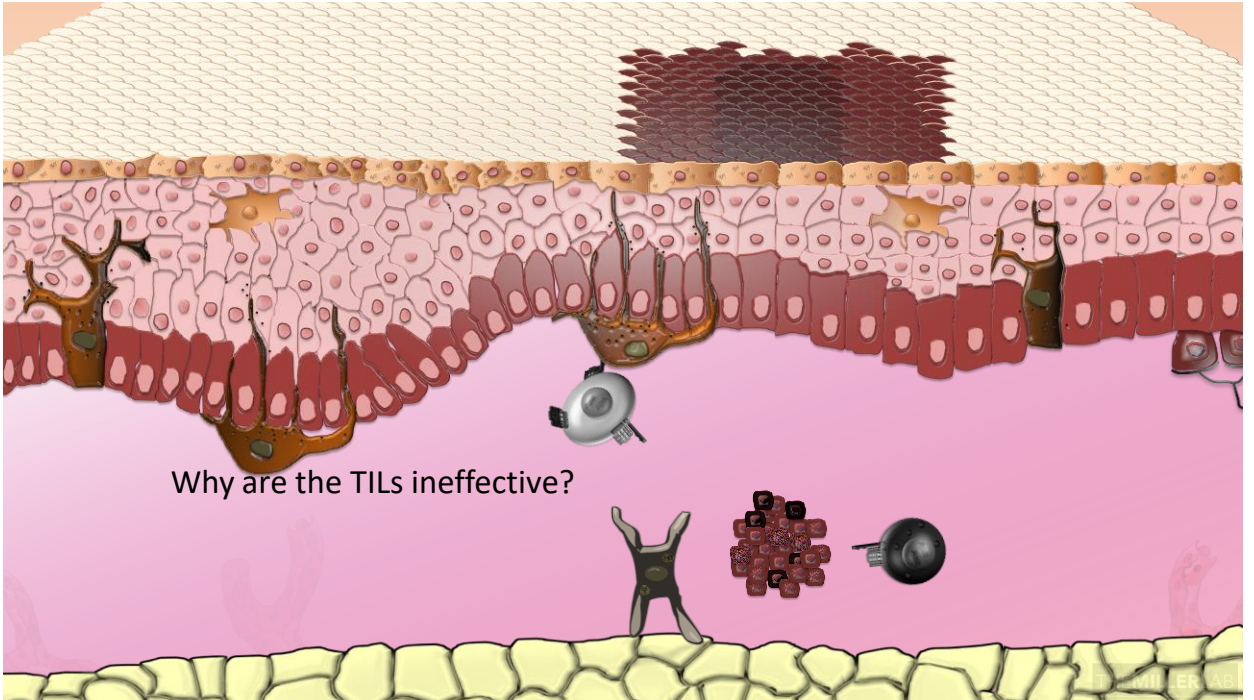
- Immune Checkpoint Inhibitor (ICI) Therapy



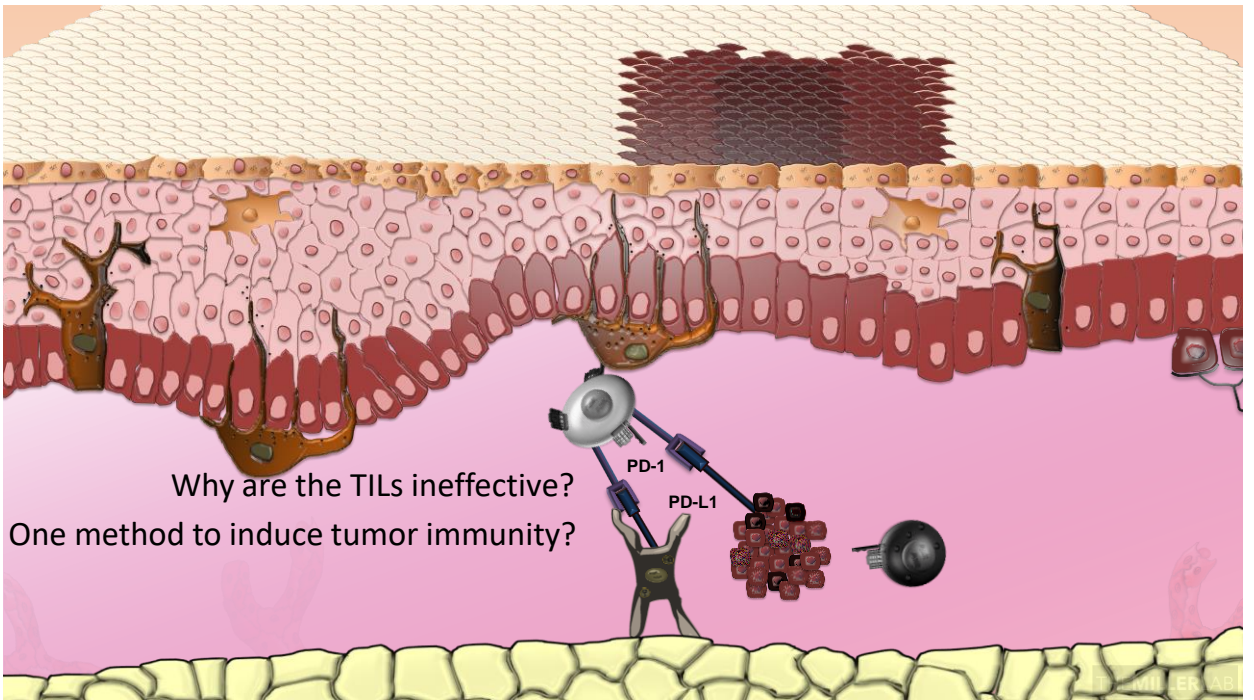
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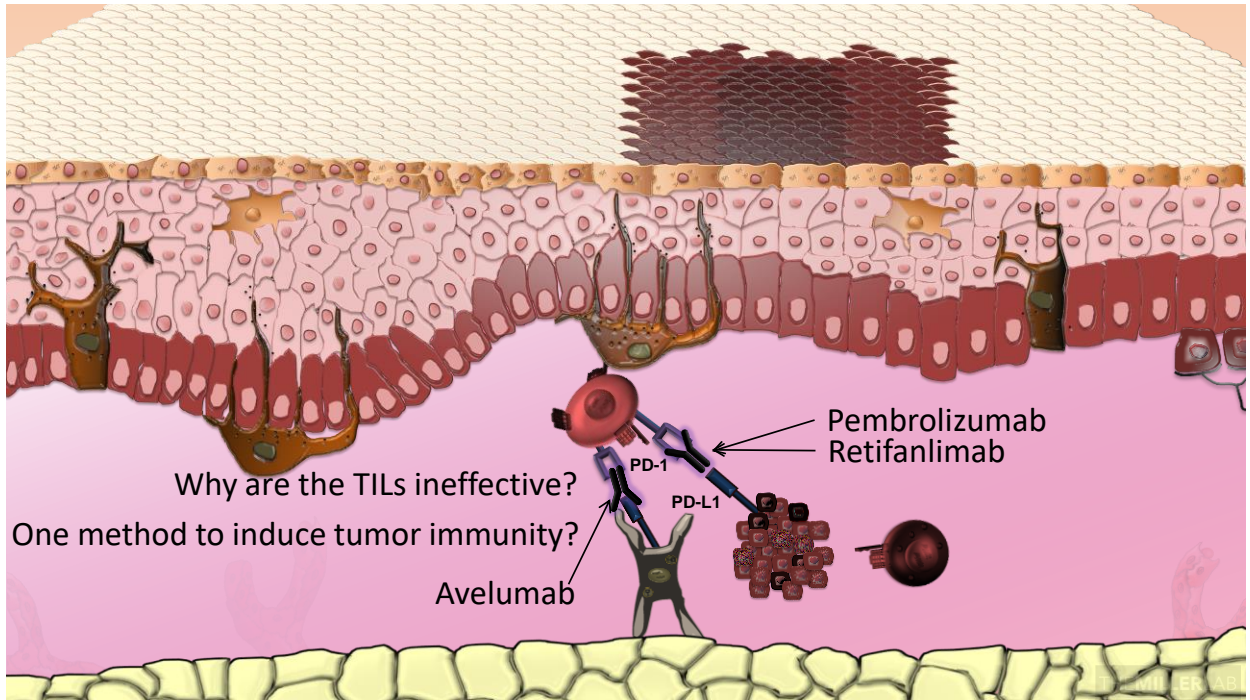
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Immunotherapy for Metastatic Disease

- Rationale
 - MCC is a highly immunogenic tumor¹⁻²
 - Two distinct molecular pathogenesis^{3,4}
 - Viral antigens from MCPyV
 - High tumor mutation burden from UVR

1. Paulson KG et al. JID 133:642 (2013)
2. Lyngaa R et al. Clin Cancer Research 20:1768 (2014)
3. Wong SQ et al. Cancer Res 75:5228 (2015)
4. Goh G et al. Oncotarget 7:3403 (2016)

86

Immunotherapy for Merkel Cell Carcinoma							
Therapy	Study	Target	Line of Therapy	N	Objective Response (%)	Median PFS (months)	Median OS (months)
Avelumab	Javelin ¹	PD-L1	1	39	62	Not Reached	Not Reached
Avelumab	Javelin ^{2,3}	PD-L1	≥2	88	33	3	13
Pembrolizumab	CITN-09 ⁴	PD-1	1	50	56	17	Not Reached
Nivolumab	CheckMate-358 ⁵	PD-1	1	15	73	24.8	Not Reached
Nivolumab	CheckMate-358 ⁵	PD-1	≥2	10	50	21.3	Not Reached
Nivolumab/Ipilimumab	CheckMate-358 ⁶	PD-1/CTLA4	1	33	64	15.4	35.58
Nivolumab/Ipilimumab	Moffitt IST ⁷	PD-1/CTLA4	1	13	100	Not Reached	Not Reached
Nivolumab/Ipilimumab	CheckMate-358 ⁶	PD-1/CTLA4	≥2	10	40	2.74	8.56
Nivolumab/Ipilimumab	Moffitt IST ⁷	PD-1/CTLA4	≥2	12	42	4.2	14.9
Nivolumab/Ipilimumab	MGB Retrospective ⁸	PD-1/CTLA4	≥2	13	0	1.3	4.7
Retifanlimab	POD1UM-201 ⁹	PD-1	1	65	52	NA	NA

References: ¹ D'Angelo et al. (2018) ² Kaufman et al. (2018) ³ Kaufman et al. (2016) ⁴ Nghiem et al. (2016) ⁵ Topalian et al. (2017) ⁶ Bhatia et al. (2023) ⁷ Kim et al. (2022) ⁸ Shalhout et al. (2022) ⁹ Grignani et al. (2021)

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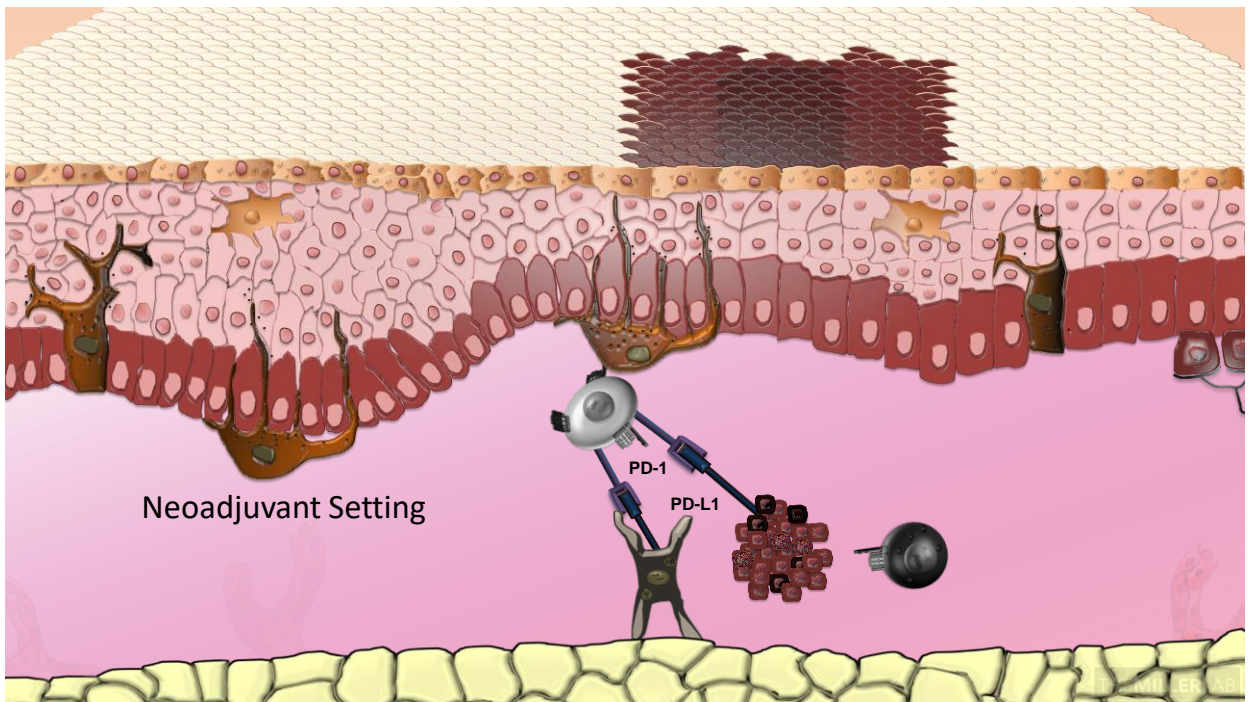
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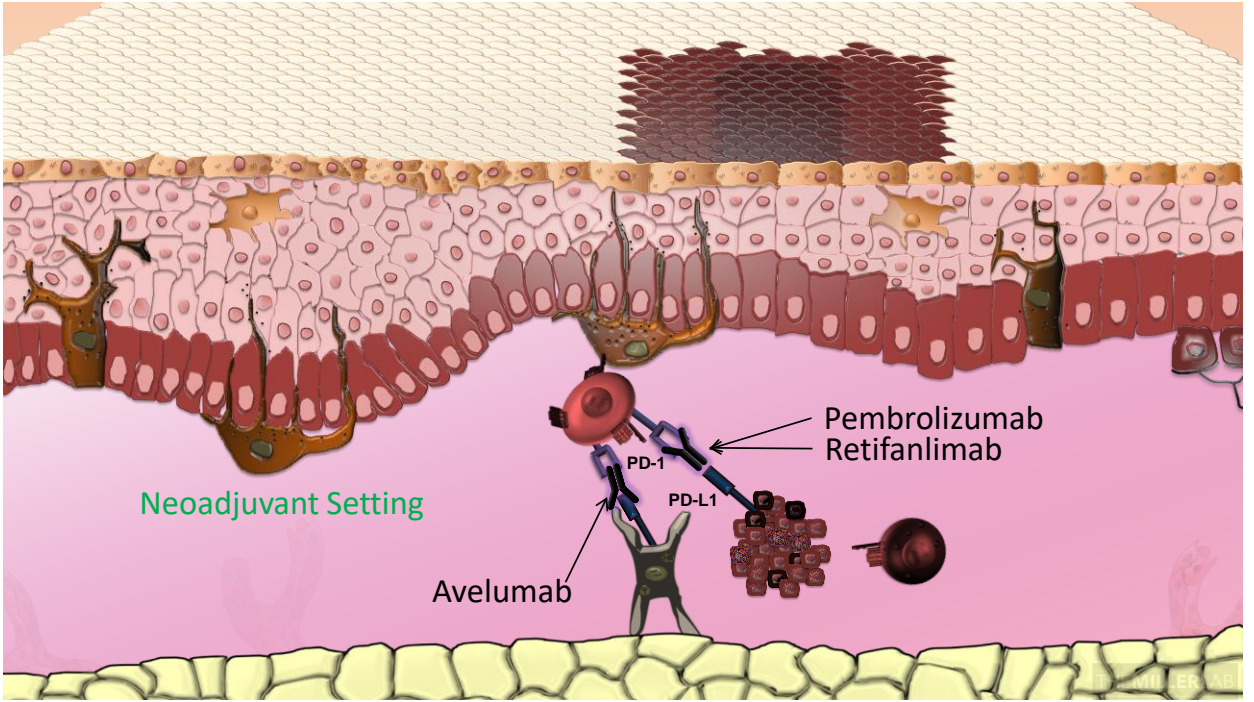
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Neoadjuvant and Adjuvant Therapy For MCC

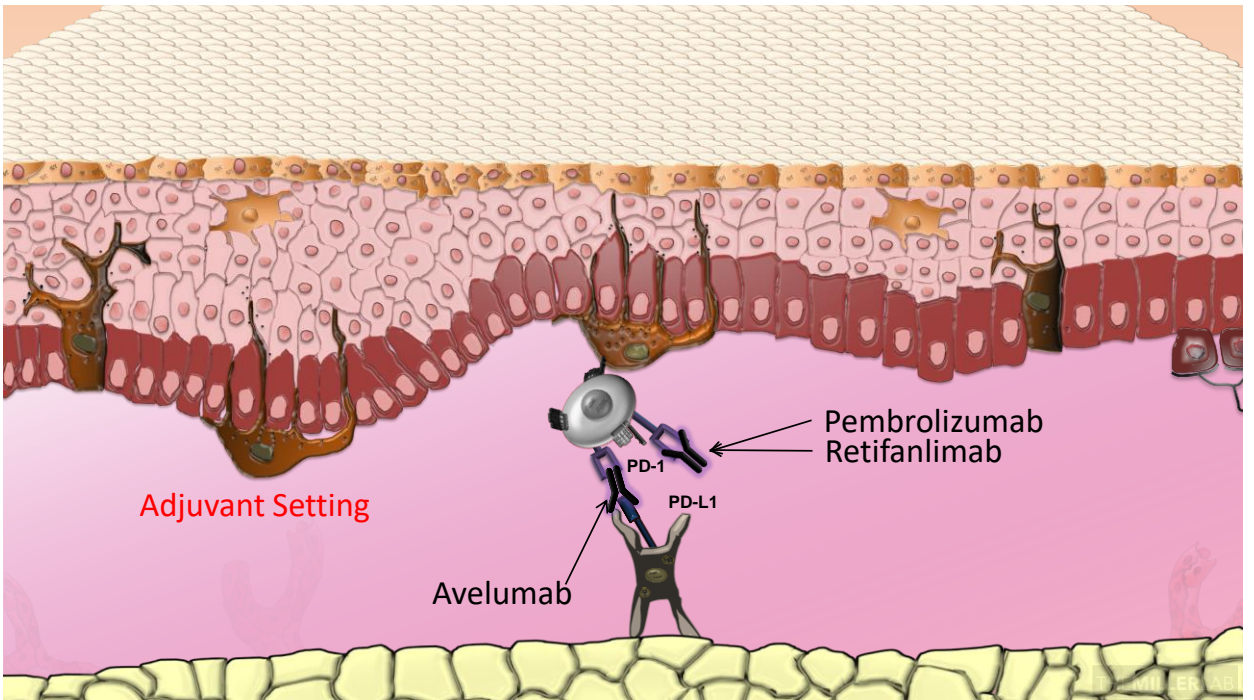
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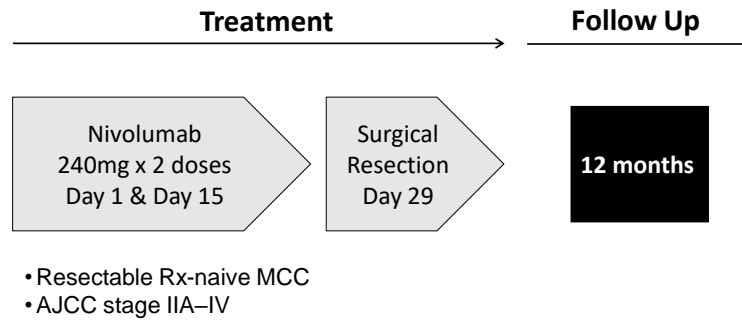


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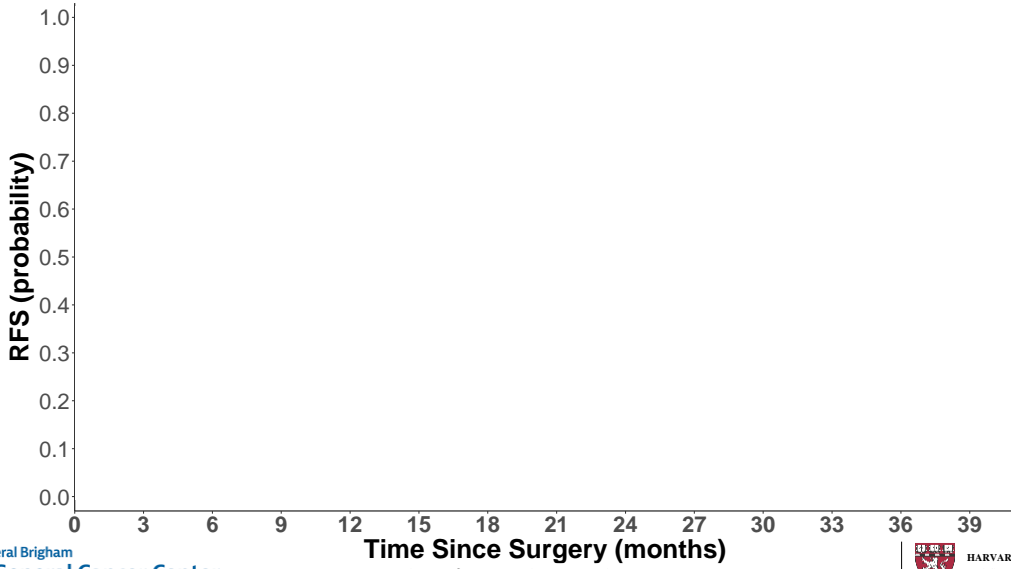
CheckMate 358 Neoadjuvant Nivolumab



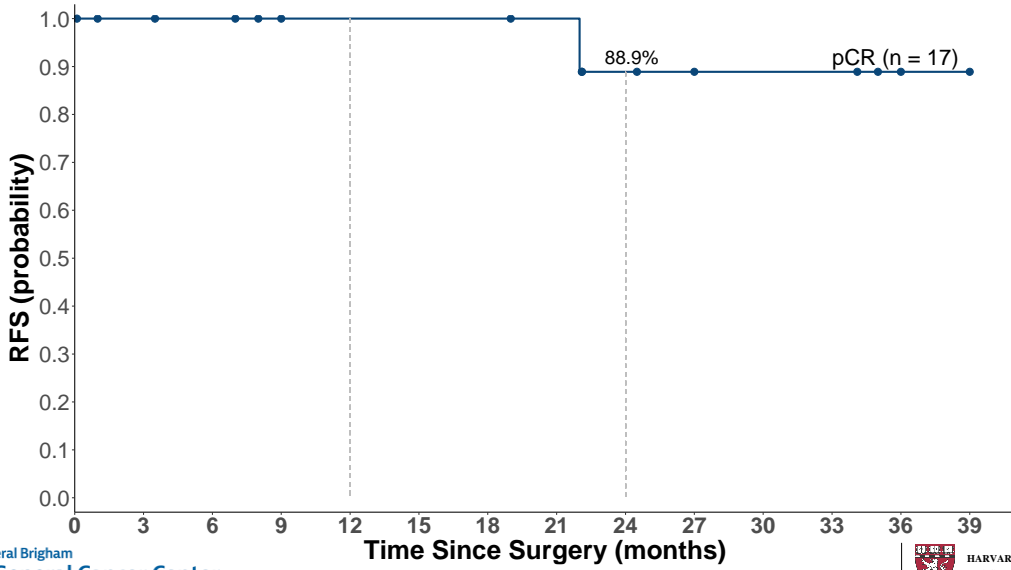
Neoadjuvant Nivolumab Pathologic Response

- 61.5% pCR + mPR (16/26)
 - MPR = $\leq 10\%$ viable tumor seen on microscopic inspection

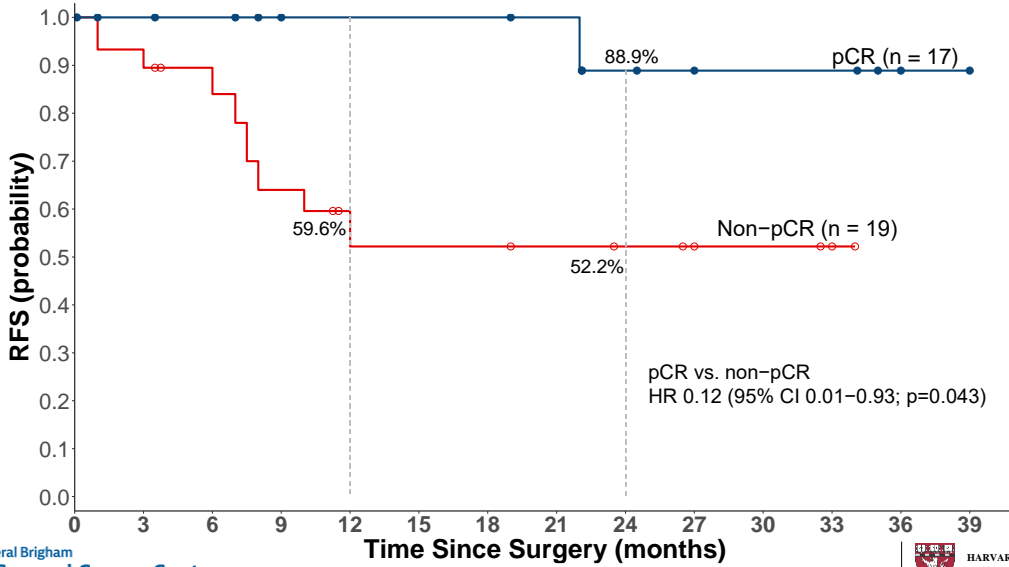
CheckMate-358



CheckMate-358



CheckMate-358



Adjuvant Treatment for MCC

Adjuvant PD-1/PD-L1 mAb

- Adjuvant **Pembrolizumab** (EA6174; NCT03304639)
 - Phase III, randomized vs. observation
- Adjuvant **Avelumab** (ADAM; NCT03271372)
 - Phase III, randomized placebo-controlled
- Adjuvant **Nivolumab** (ADMEC-O; NCT0216961)
 - Phase II, randomized vs. observation

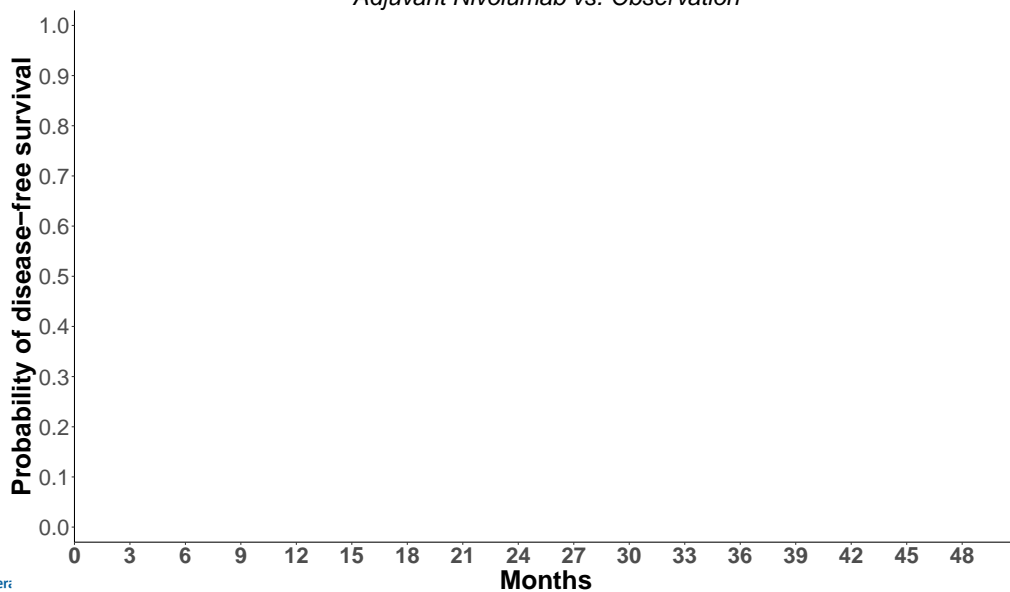
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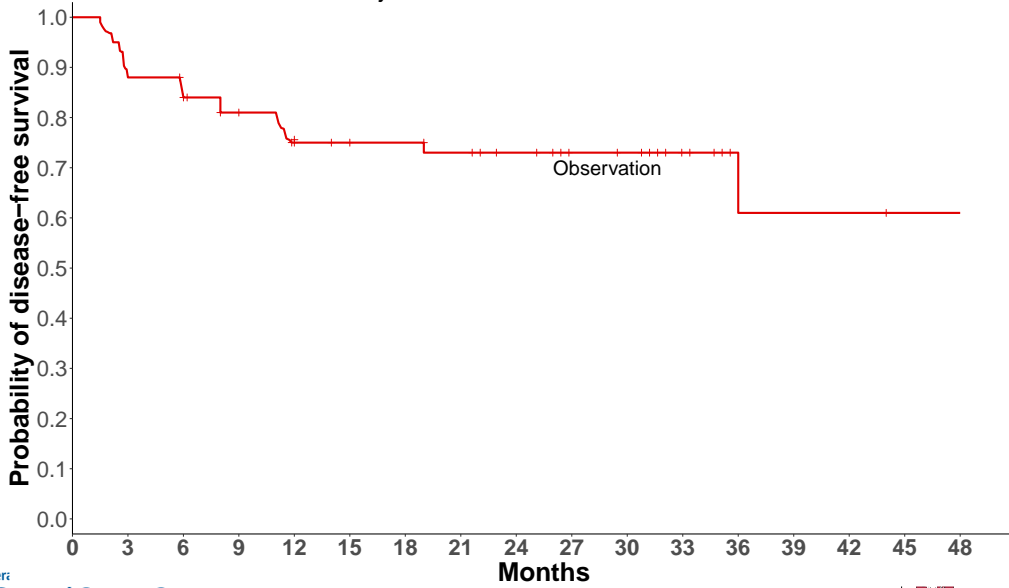
ADMEC-O Adjuvant Nivolumab vs. Observation

- Phase II study of 177 patients
 - 118 patients randomized to 480 mg nivolumab x 12 months
 - 61 patients randomized to observation
- Primary endpoint was disease-free survival
- Interim results published August 2023

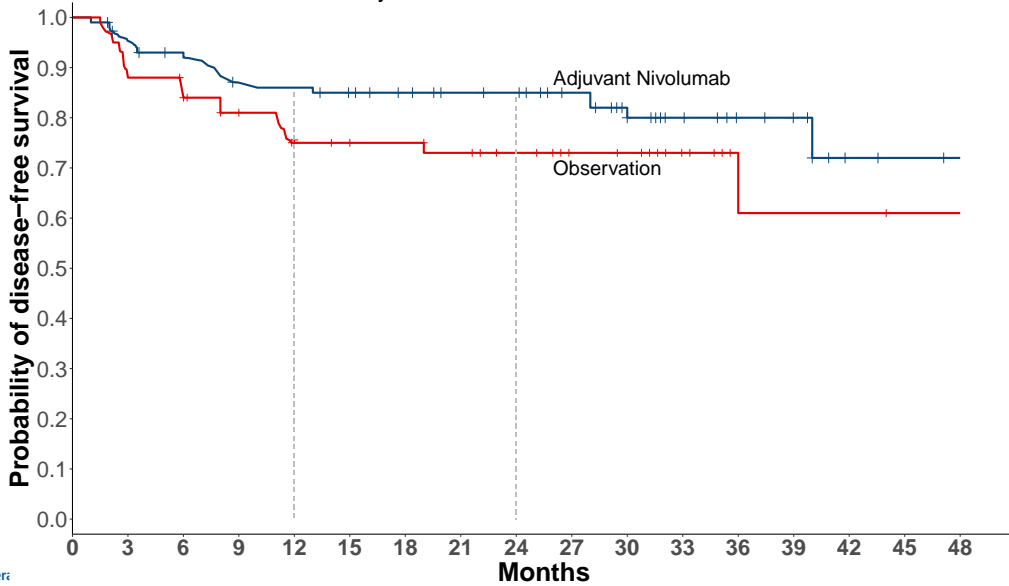
ADMEC-O Interim Results *Adjuvant Nivolumab vs. Observation*



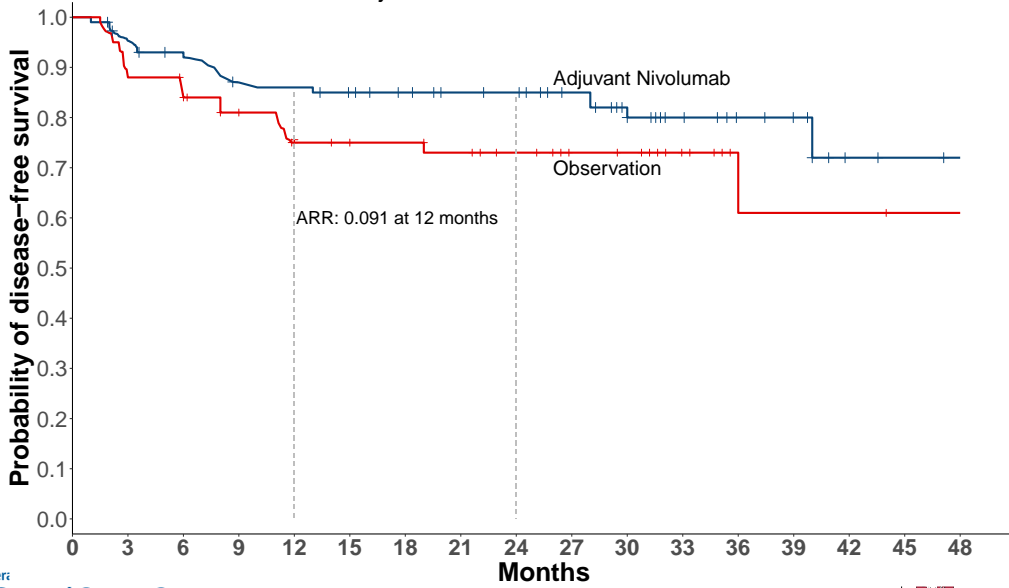
ADMEC-O Interim Results Adjuvant Nivolumab vs. Observation



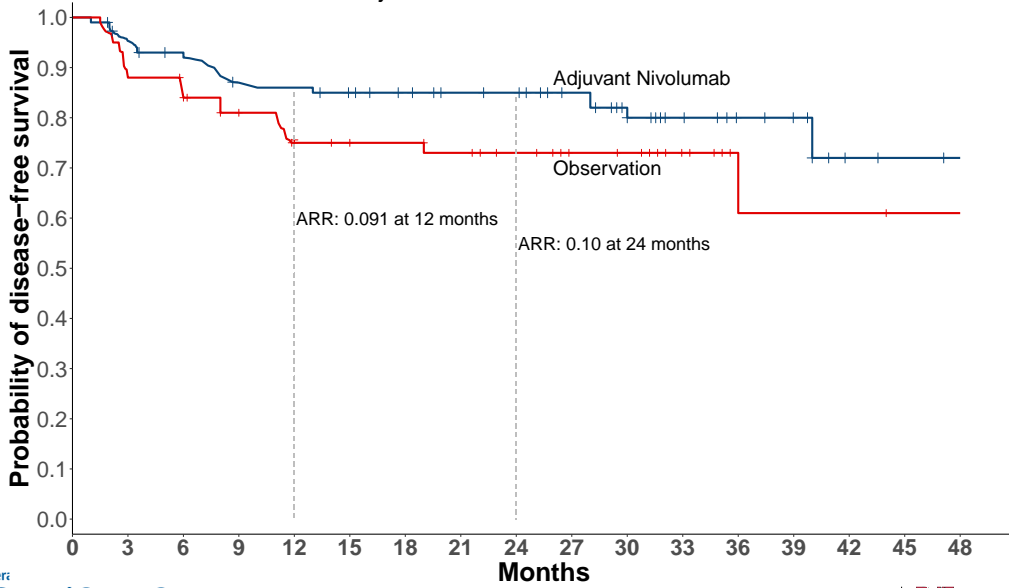
ADMEC-O Interim Results Adjuvant Nivolumab vs. Observation

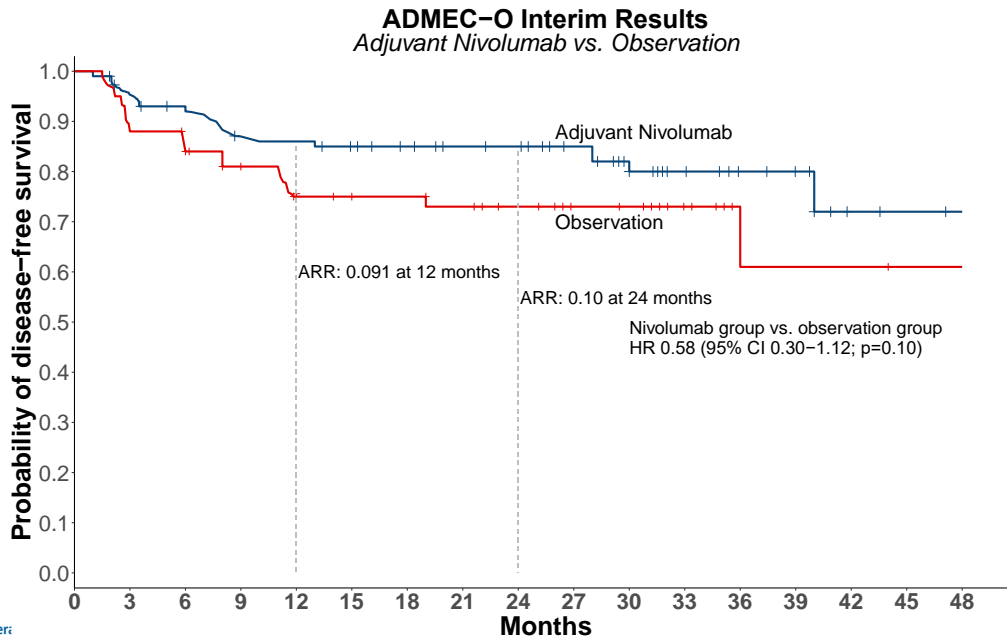


ADMEC-O Interim Results Adjuvant Nivolumab vs. Observation



ADMEC-O Interim Results Adjuvant Nivolumab vs. Observation





Refractory Disease Setting

- Clinical Investigations
- Immunotherapeutic Approaches
 - Combination Immune Checkpoints
 - Cytokine-directed therapy
 - Oncolytic Virus
 - TLR agonists
- Target Therapies
 - MDM2 inhibitor

Summary

- New insights into the pathophysiology of MCC has led to **novel diagnostic tests** and **therapeutic interventions**
- Encourage cross-sectional imaging with **PET-CT** at initial diagnosis
- The **MCPyV serum antibody test** can be used at the time of diagnosis for prognostic information as well as a potential **marker of disease recurrence**
- **ctDNA** may assist in identifying rapid progressor phenotype and tx response
- Therapies that target **immune checkpoints** have ushered in a new era of effective agents in metastatic MCC
 - Use of ICIs in the **neoadjuvant** and **adjuvant setting** are being investigated to improve outcomes in patients with high-risk MCC

Acknowledgements

- Pennsylvania Academy of Dermatology and Dermatologic Surgery
- MGH Center for Merkel Cell Carcinoma
- Project Data Sphere
- ECOG-ACRIN
- American Skin Association