



ACMS 51st annual meeting
May 4th
Baltimore Maryland

Update on Merkel cell carcinoma: Systemic therapy and clinical trials



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Cutaneous Surgery and Oncology
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Department of Dermatology
Michigan Medicine

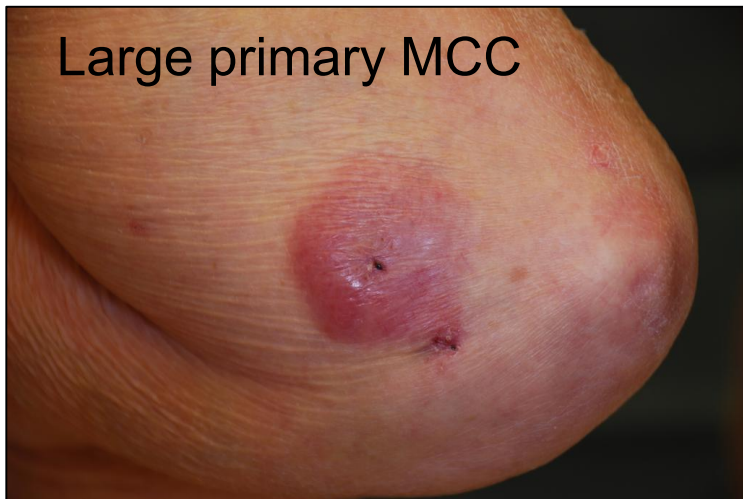
I have no conflicts of interest or
relationships with industry

Common presentations of MCC

Stage I and II

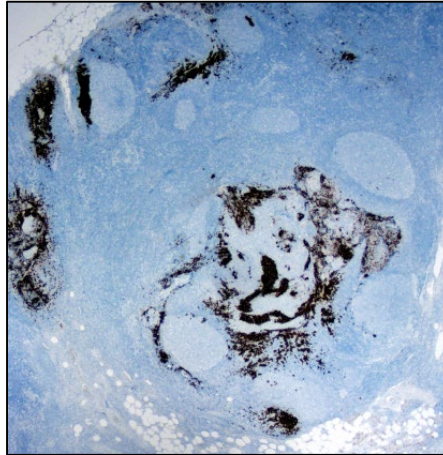


Small
primary
MCC

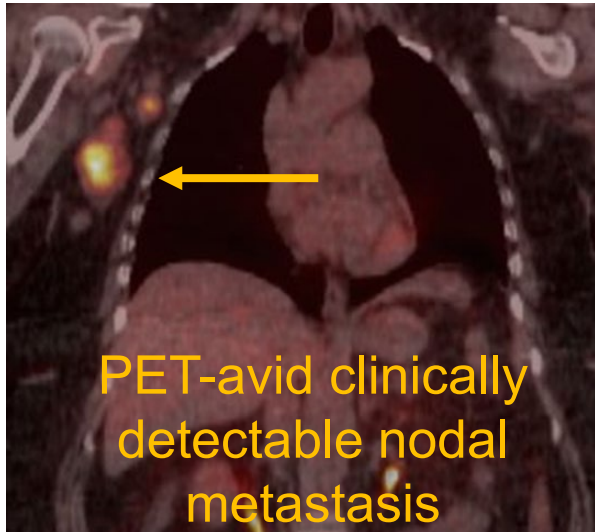


Large primary MCC

Stage III

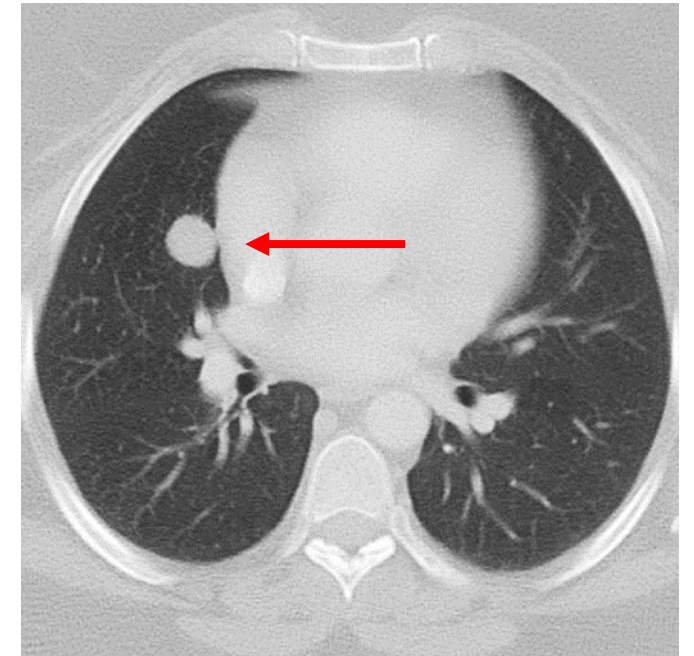


Microscopic
nodal
disease
+ SLNB
(CK20 stain)



PET-avid clinically
detectable nodal
metastasis

Stage IV



Lung metastasis

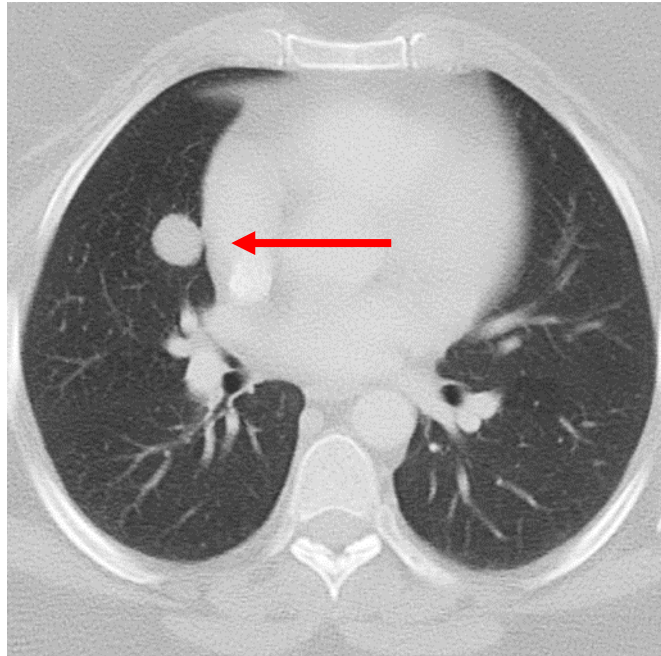
Overview

1. Describe the clinical presentation of Merkel cell carcinoma including locoregional clinical recurrence.
2. Review multidisciplinary management of Merkel cell carcinoma including management of the primary site and staging work-up.
3. Review role of systemic therapy and clinical trials for Merkel cell carcinoma.

Systemic therapy for stage IV MCC

Management of stage IV disease

Stage IV



Lung metastasis

Chemotherapy WAS the standard of care

Cancer Medicine

Open Access

ORIGINAL RESEARCH

Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma

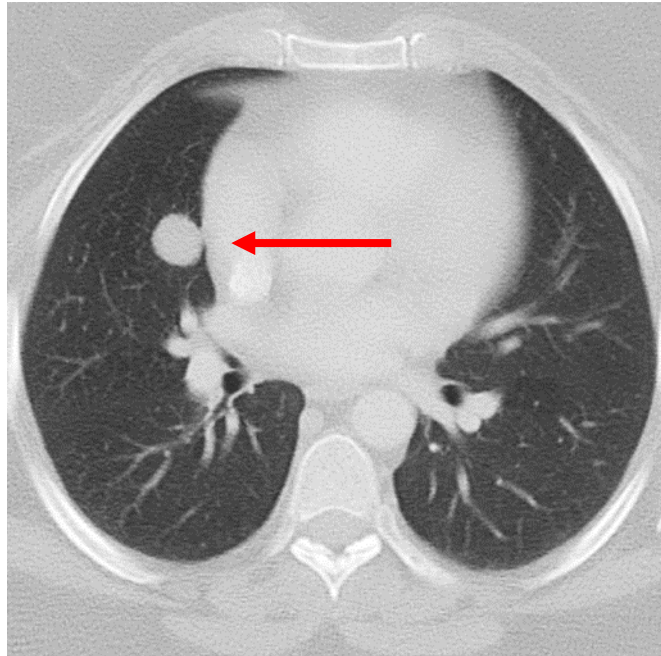
Jayasri G. Iyer¹, Astrid Blom¹, Ryan Doumani¹, Christopher Lewis¹, Erica S. Tarabadkar¹, Austin Anderson¹, Christine Ma¹, Amy Bestick¹, Upendra Parvathaneni², Shailender Bhatia³ & Paul Nghiem¹

- 62 patients with distant metastatic MCC, diagnosed between 2002-2014
- Retrospective study – patients received either 1st line or 2nd line chemotherapy
- Median survival after start of treatment: 9.5 months
- 1st line chemotherapy: median progression free survival 94 days

Iyer et al. 2016. Cancer Medicine.

Management of stage IV disease

Stage IV



Lung metastasis

Chemotherapy WAS the standard of care

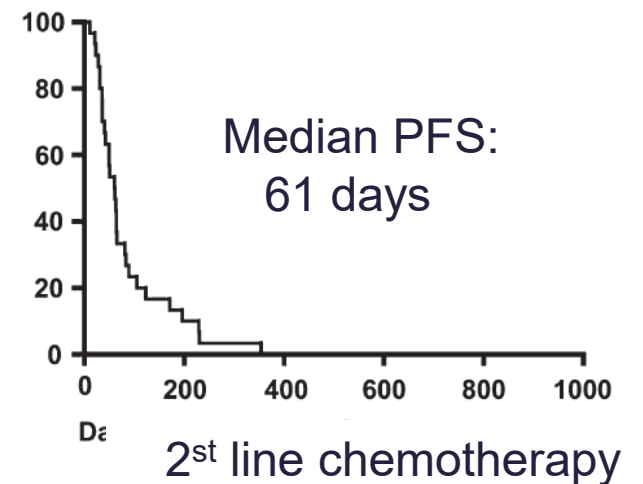
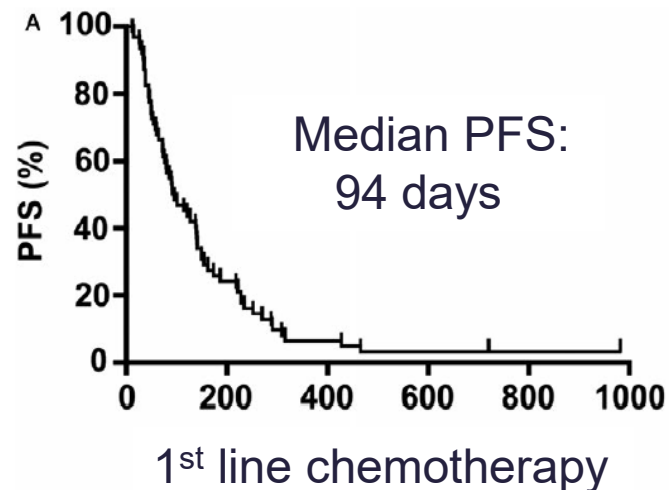
Cancer Medicine

Open Access

ORIGINAL RESEARCH

Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma

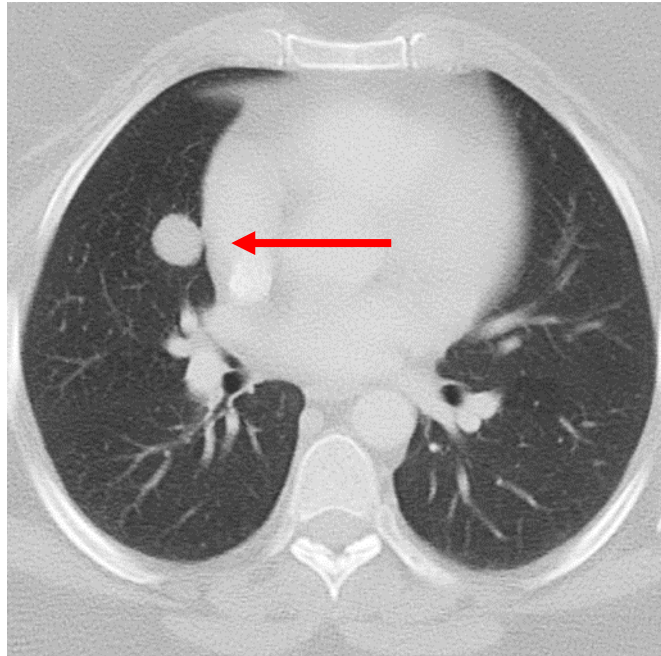
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Iyer et al. 2016. Cancer Medicine.

Management of stage IV disease

Stage IV



Lung metastasis

Chemotherapy WAS the standard of care

Cancer Medicine

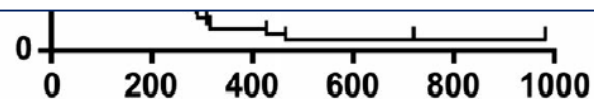
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ORIGINAL RESEARCH

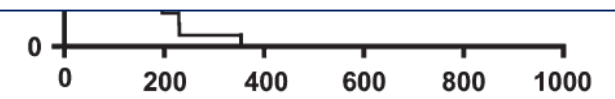
Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma

Jayasri G. Iyer¹, Astrid Blom¹, Ryan Doumani¹, Christopher Lewis¹, Erica S. Tarabaskar¹, Austin Anderson¹, Christine Ma¹, Amy Bestick¹, Upendra Parvathaneni², Shailender Rhatia³ & David Nohlem¹

We welcome immunotherapy for advanced and stage IV MCC



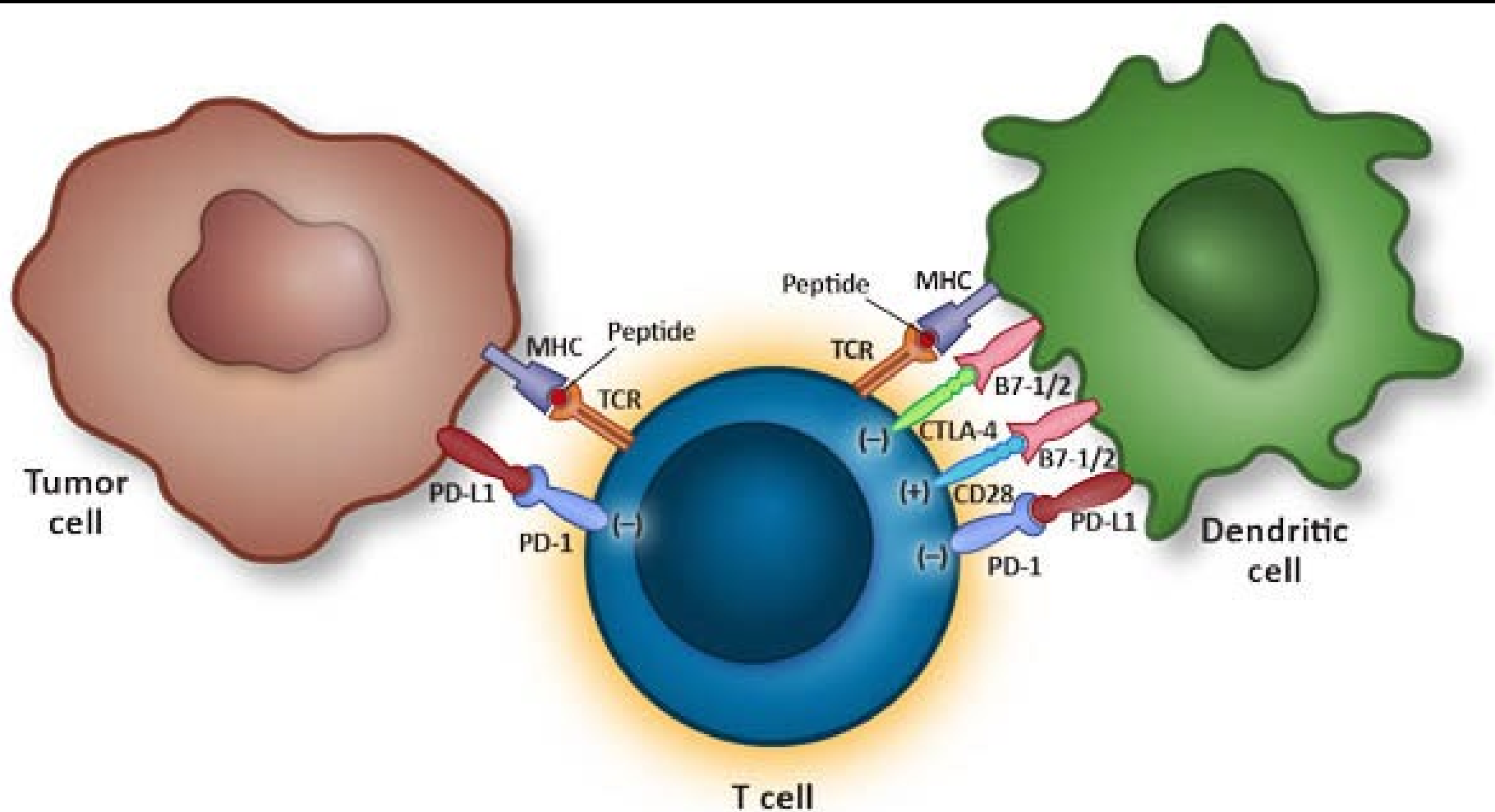
1st line chemotherapy



2nd line chemotherapy

Iyer et al. 2016. Cancer Medicine.

Immune checkpoint inhibition



anti-CTLA-4:

Ipilimumab

anti-PD-1:

Pembrolizumab

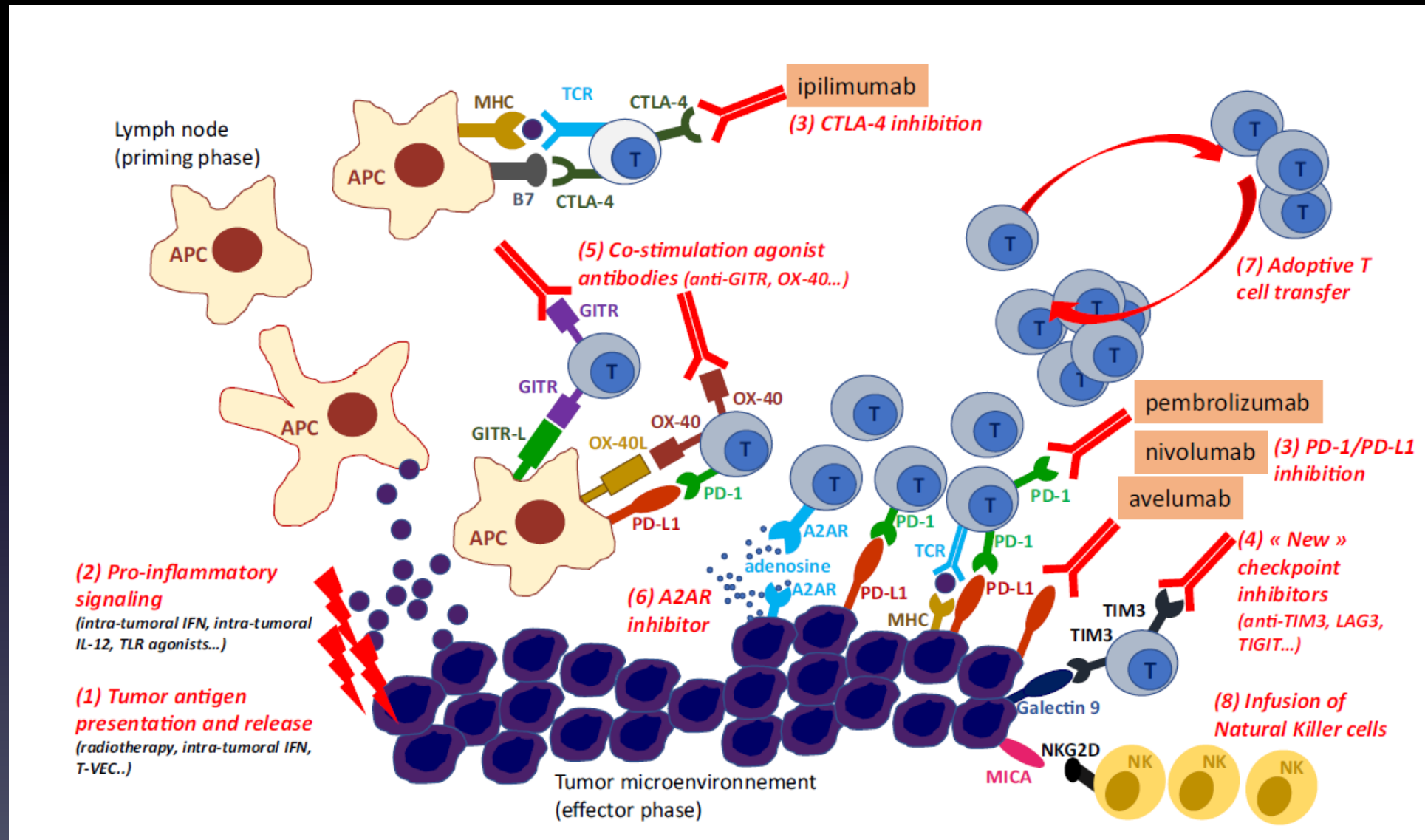
Nivolumab

anti-PD-L1:

Avelumab

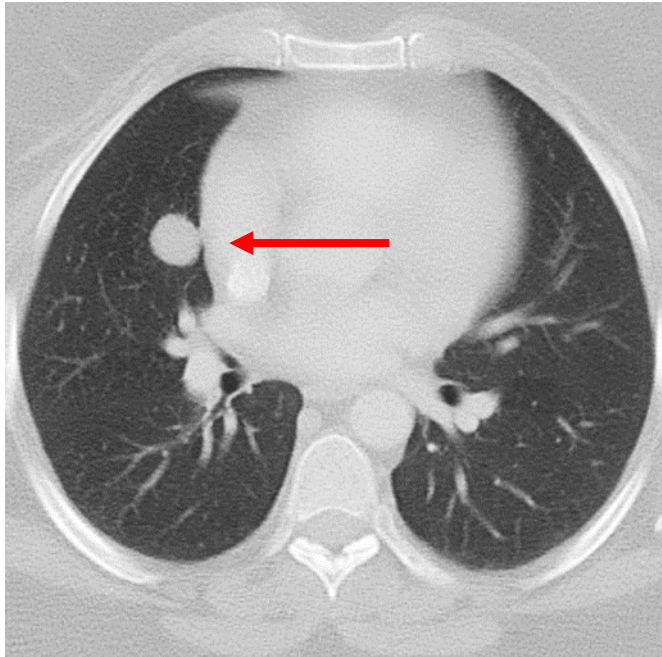
Atezolizumab

Immune checkpoint inhibition



Management of stage IV disease

Stage IV



Lung metastasis

- Avelumab approved on March 27, 2017
- Pembrolizumab approved on December 19, 2018

Avelumab (anti-PDL1) for advanced MCC

FDA U.S. FOOD & DRUG ADMINISTRATION

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Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

Avelumab (BAVENCIO)

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On March 23, 2017, the U.S. Food and Drug Administration (FDA) approved Avelumab (BAVENCIO, EMD Serono, Inc.) for the treatment of metastatic Merkel cell carcinoma (MCC). Avelumab is a programmed death-1 (PD-1) inhibitor antibody. This is the first FDA-approved PD-1 inhibitor for the treatment of MCC.

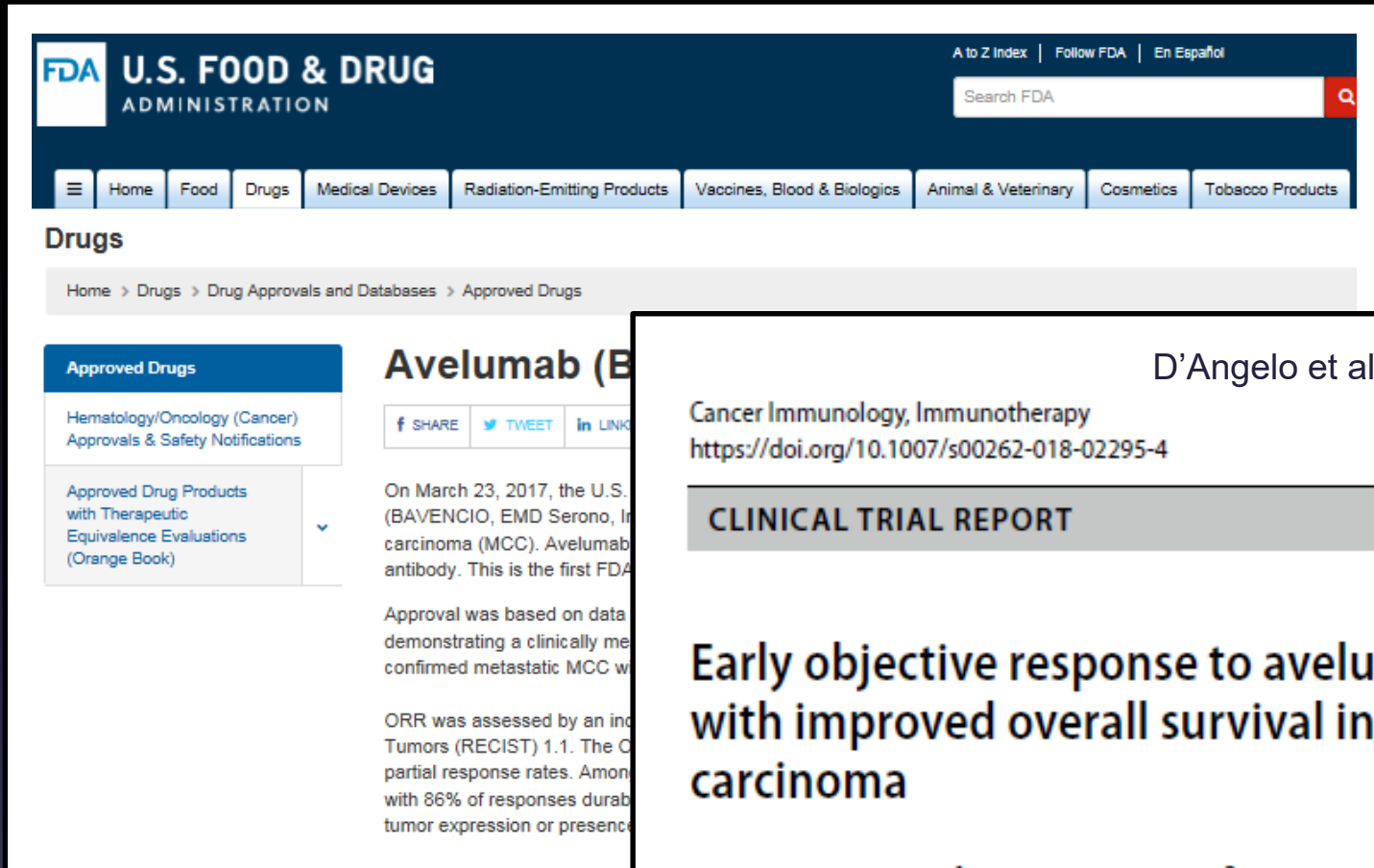
Approval was based on data from a phase 1b clinical trial demonstrating a clinically meaningful and durable response in patients with confirmed metastatic MCC with disease progression on prior therapy.

ORR was assessed by an independent review committee using RECIST 1.1. The ORR was 33% (95% CI: 22%, 45%). The partial response rates were 22% (95% CI: 13%, 32%) and the complete response rates were 11% (95% CI: 5%, 18%). Among the 29 patients with partial responses, 86% of responses were durable for 6 months or longer. Tumor expression or presence of Merck PD-1 was not a predictive factor for response.

JAVELIN Merkel 200 trial – chemotherapy refractory metastatic MCC

- Overall response rate: 33%
- Complete response: 11%
- Partial response: 22%

Avelumab (anti-PDL1) for advanced MCC



The screenshot shows the FDA's 'Approved Drugs' page for Avelumab (BAVENCIO). The header includes the FDA logo, 'U.S. FOOD & DRUG ADMINISTRATION', and navigation links. The 'Drugs' section is active, and the breadcrumb trail reads: Home > Drugs > Drug Approvals and Databases > Approved Drugs. On the left, a sidebar lists 'Approved Drugs' and 'Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)'. The main content area for Avelumab (BAVENCIO) states: 'On March 23, 2017, the U.S. Food and Drug Administration (FDA) approved Avelumab (BAVENCIO, EMD Serono, Inc.) for the treatment of advanced Merkel cell carcinoma (MCC). Avelumab is a monoclonal antibody. This is the first FDA approval of a monoclonal antibody for the treatment of advanced MCC. Approval was based on data demonstrating a clinically meaningful improvement in overall response rate (ORR) compared with placebo in a phase 3 clinical trial. The ORR was assessed by an independent review committee using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The ORR was 33% in the avelumab group compared with 11% in the placebo group. Among patients with partial responses, 86% of responses were durable (lasting for at least 24 weeks). Avelumab is indicated for the treatment of advanced MCC in patients with tumor expression or presence of programmed death-ligand 1 (PD-L1) on tumor cells.' Social media sharing links for Facebook, Twitter, and LinkedIn are also visible.

D'Angelo et al (2019) Cancer Immunology, Immunotherapy 68(4):609-618

Cancer Immunology, Immunotherapy
<https://doi.org/10.1007/s00262-018-02295-4>

CLINICAL TRIAL REPORT



Early objective response to avelumab treatment is associated with improved overall survival in patients with metastatic Merkel cell carcinoma

Sandra P. D'Angelo¹ · Matthias Hunger² · Andrew S. Brohl³ · Paul Nghiem⁴ · Shailender Bhatia⁵ · Omid Hamid⁶ · Janice M. Mehnert⁷ · Patrick Terheyden⁸ · Kent C. Shih⁹ · Isaac Brownell¹⁰ · Céleste Lebbé¹¹ · Karl D. Lewis¹² · Gerald P. Linette¹³ · Michele Milella¹⁴ · Michael Schlichting¹⁵ · Meliessa H. Hennessy¹⁶ · Murtuza Bharmal¹⁵

Avelumab (anti-PDL1) for advanced MCC

Cancer Immunology, Immunotherapy
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CLINICAL TRIAL REPORT



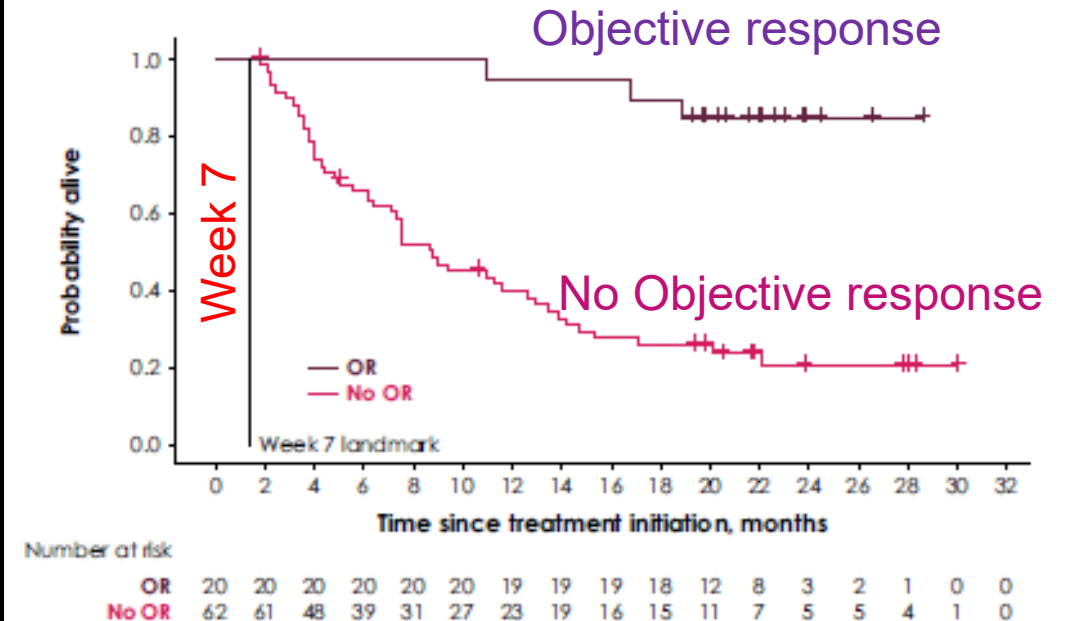
Early objective response to avelumab treatment is associated with improved overall survival in patients with metastatic Merkel cell carcinoma

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- Multicenter, phase 2, trial
- 2nd line avelumab (every 2 weeks)
- 88 patients enrolled
- Question: does objective response correlate with overall survival

Results

- Objective response at weeks 7 and 13 had significantly longer overall survival
- **Conclusion: early objective response is important**



Avelumab (anti-PDL1) for advanced MCC

The screenshot shows the FDA's 'Approved Drugs' page for Avelumab (BAVENCIO). The header includes the FDA logo and navigation links. The main content area is titled 'Avelumab (BAVENCIO)' and contains the following text:

On March 23, 2017, the U.S. Food and Drug Administration (FDA) approved Avelumab (BAVENCIO, EMD Serono, Inc.) for the treatment of advanced melanoma (MCC). Avelumab is a monoclonal antibody. This is the first FDA approval for Avelumab.

Approval was based on data from a phase III clinical trial demonstrating a clinically meaningful improvement in overall survival (OS) in patients with confirmed metastatic MCC who had received prior systemic therapy.

ORR was assessed by an independent review committee (IRC) using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The overall partial response rates (ORR) were 86% in the Avelumab group and 86% in the Placebo group. Among patients with 86% of responses durable (ORR), the median duration of response (DOR) was 10.1 months in the Avelumab group and 10.1 months in the Placebo group.

D'Angelo et al (2019) Cancer Immunology, Immunotherapy 68(4):609-618

Cancer Immunology, Immunotherapy
<https://doi.org/10.1007/s00262-018-02295-4>

CLINICAL TRIAL REPORT

Early objective response to avelumab treatment with improved overall survival in patients with advanced melanoma

Sandra P. D'Angelo¹ · Matthias Hunger² · Andrew S. Brohl³ · Paul Janice M. Mehnert⁷ · Patrick Terheyden⁸ · Kent C. Shih⁹ · Isaac Br Gerald P. Linette¹³ · Michele Milella¹⁴ · Michael Schlichting¹⁵ · M

What about 1st
line
Avelumab?


U.S. FOOD & DRUG
 ADMINISTRATION

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Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

Approved Drugs
 Hematology/Oncology (Cancer)
 Approvals & Safety Notifications

Approved Drug Products
 with Therapeutic
 Equivalence Evaluations
 (Orange Book)

Avelumab (BMS-936263)

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On March 23, 2017, the U.S. Food and Drug Administration (FDA) approved Avelumab (BAVENCIO, EMD Serono, Inc.) for the treatment of metastatic Merkel cell carcinoma (MCC). Avelumab is a human anti-PD-L1 monoclonal antibody. This is the first FDA approval of a PD-L1 inhibitor for the treatment of MCC.

Approval was based on data from a phase 1b clinical trial demonstrating a clinically meaningful and durable response in patients with confirmed metastatic MCC who had received prior systemic therapy.

Overall response rate (ORR) was assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The ORR was 33.3% (95% CI: 18.2-49.4). The partial response rates were 22.2% (95% CI: 10.4-37.5) and 11.1% (95% CI: 3.8-23.8) for patients with and without tumor expression or presence of PD-L1, respectively.

D'Angelo et al. | *Cancer Immunology, Immunotherapy* | <https://doi.org/10.1007/s00262-018-02295-4>

CLINICAL TRIAL REPORT

Early objective responses with improved overall survival in metastatic Merkel cell carcinoma

Research

JAMA Oncology | **Efficacy and safety of avelumab in patients with metastatic Merkel cell carcinoma: a phase 1b trial**

Cancer Immunology, Immunotherapy
<https://doi.org/10.1007/s00262-018-02295-4>

Early objective response
with improved overall
carcinoma

Research

JAMA Oncology | Brief Report

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

Avelumab (anti-PDL1) for advanced MCC

Research

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

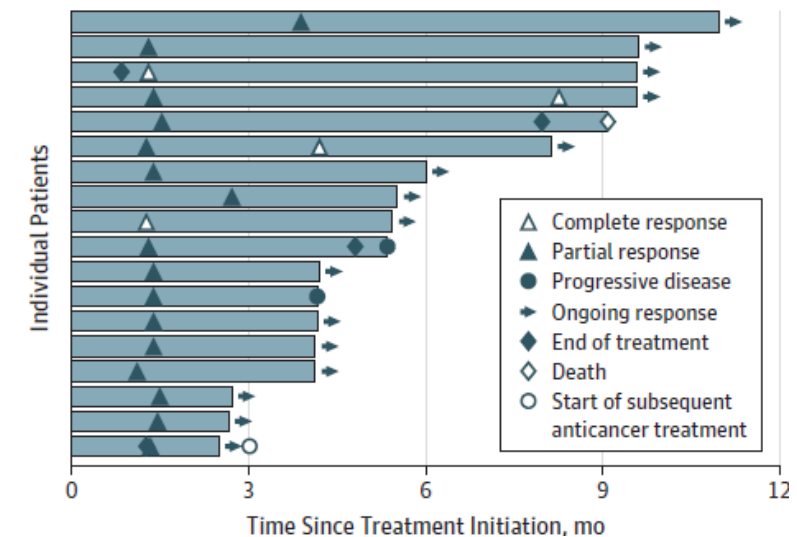
Sandra P. D'Angelo, MD; Jeffery Russell, MD, PhD; Céleste Lebbé, MD, PhD; Bartosz Chmielowski, MD, PhD; Thilo Gambichler, MD; Jean-Jacques Grob, MD; Felix Kiecker, MD; Guilherme Rabinowits, MD; Patrick Terheyden, MD; Isabella Zwiener, PhD; Marcis Bajars, MD; Meliessa Hennessy, MPH; Howard L. Kaufman,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

- JAVELIN Merkel part B
- 1st line Avelumab (every 2 weeks)
- 39 patients enrolled
- Endpoint: durable response of at least 6 months
- Median follow-up: 5.1 months

Results

- Objective response: 62.1%
- 18 patients with response and 3 months of follow-up
 - Ongoing response: 15/18 (arrow)
 - Complete response: 4/18 (white triangle)
 - Death (1), Progressive disease (2)

Duration of response and treatment



Pembrolizumab (anti-PD1) for advanced MCC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell

Paul T. Nghiem, M.D., Ph.D., Shailen
Evan J. Lipson, M.D., Ragini R. Kudchadkar, M.D.
Lakshmanan Annamalai, D.V.M., Ph.D., Sneha Berry
Adil Daud, M.B., B.S., Steven P. Fling, Ph.D., P
Harriet M. Kluger, M.D., Holbrook E. Kohrt, M.D.,
Kim Margolin, M.D., Alan Mitchell, M.Sc.,
Drew M. Pardoll, M.D., Ph.D., Sunil A. Reddy, M.D.
William H. Sharfman, M.D., Elad Sharon, M.D., M.P.H.
Michi M. Shinohara, M.D., Joel C. Sunshine, M.D.,
John A. Thompson, M.D., Steven M. Townson, Ph.D., J
Suzanne L. Topalian, M.D., and Martin

Nghiem et al. N

Journal of Clinical Oncology®

Volume 37, Issue 9 693

rapid communication

Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy

Paul Nghiem, MD, PhD¹; Shailender Bhatia, MD¹; Evan J. Lipson, MD²; William H. Sharfman, MD²; Ragini R. Kudchadkar, MD³; Andrew S. Brohl, MD⁴; Phillip A. Friedlander, MD⁵; Adil Daud, MD⁶; Harriet M. Kluger, MD⁷; Sunil A. Reddy, MD⁸; Brian C. Boulmay, MD⁹; Adam I. Riker, MD⁹; Melissa A. Burgess, MD¹⁰; Brent A. Hanks, MD, PhD¹¹; Thomas Olencki, DO¹²; Kim Margolin, MD¹³; Lisa M. Lundgren, MS¹⁴; Abha Soni, DO²; Nirasha Ramchurren, PhD¹⁴; Candice Church, PhD¹⁵; Song Y. Park, MD¹⁵; Michi M. Shinohara, MD¹⁵; Bob Salim, PhD¹⁶; Janis M. Taube, MD²; Steven R. Bird, MS¹⁷; Nageatte Ibrahim, MD¹⁷; Steven P. Fling, PhD¹⁴; Blanca Homet Moreno, MD, PhD¹⁷; Elad Sharon, MD, MPH¹⁸; Martin A. Cheever, MD¹⁴; and Suzanne L. Topalian, MD²

Nghiem et al. JCO 2019

Pembrolizumab (anti-PD1) for advanced MCC

Nghiem et al. JCO 2019

rapid communication

Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy

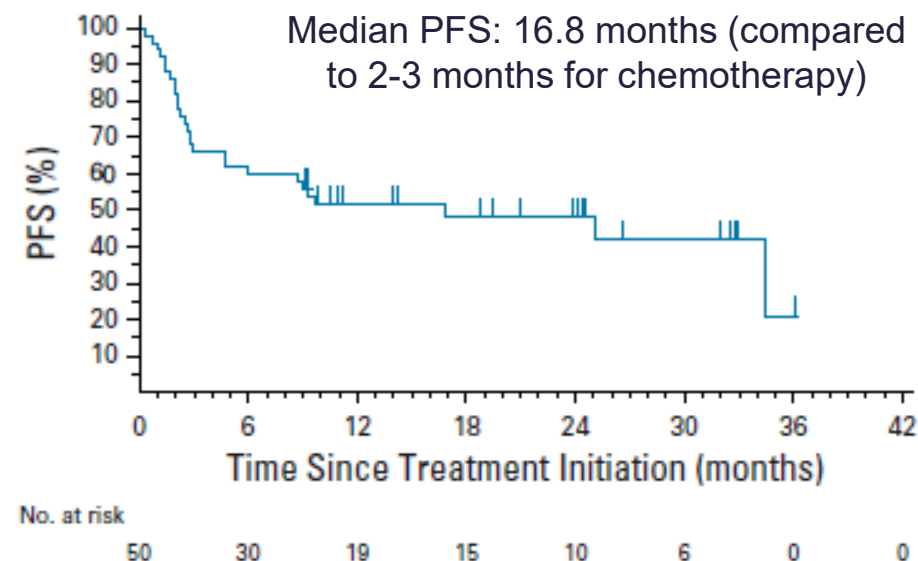
Paul Nghiem, MD, PhD¹; Shailender Bhatia, MD¹; Evan J. Lipson, MD²; William H. Sharfman, MD²; Ragini R. Kudchadkar, MD³; Andrew S. Brohl, MD⁴; Phillip A. Friedlander, MD⁵; Adil Daud, MD⁶; Harriet M. Kluger, MD⁷; Sunil A. Reddy, MD⁸; Brian C. Boulmay, MD⁹; Adam I. Riker, MD⁹; Melissa A. Burgess, MD¹⁰; Brent A. Hanks, MD, PhD¹¹; Thomas Olencki, DO¹²; Kim Margolin, MD¹³; Lisa M. Lundgren, MS¹⁴; Abha Soni, DO²; Nirasha Ramchurren, PhD¹⁴; Candice Church, PhD¹⁵; Song Y. Park, MD¹⁵; Michi M. Shinohara, MD¹⁵; Bob Salim, PhD¹⁶; Janis M. Taube, MD²; Steven R. Bird, MS¹⁷; Nageatte Ibrahim, MD¹⁷; Steven P. Fling, PhD¹⁴; Blanca Homet Moreno, MD, PhD¹⁷; Elad Sharon, MD, MPH¹⁸; Martin A. Cheever, MD¹⁴; and Suzanne L. Topalian, MD²

- Multicenter, phase 2, non-controlled study
- 1st line treatment with pembrolizumab, anti-PD-1 every 3 weeks
- 50 patients treated
- Median follow-up time: 14.9 months

Results

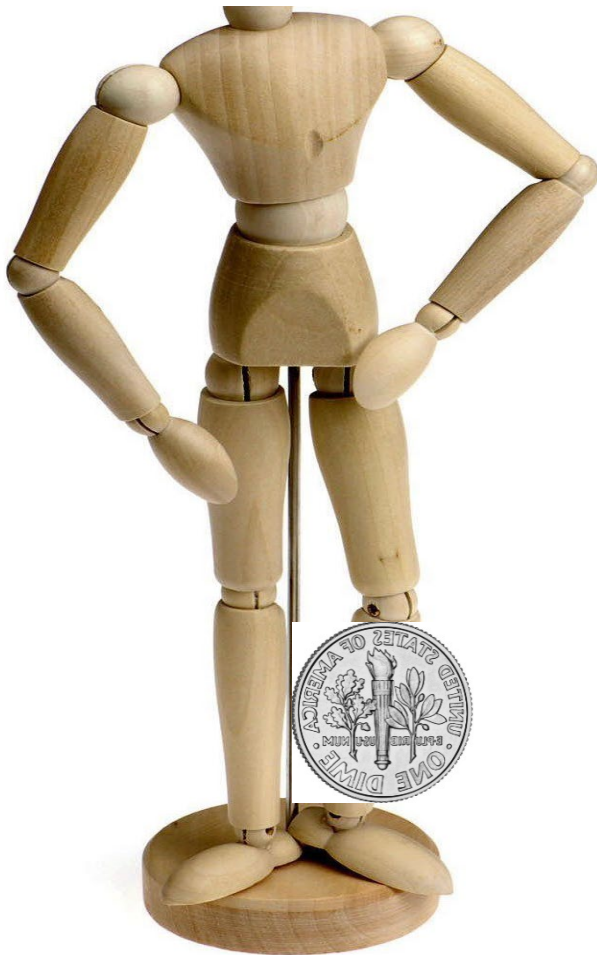
- Overall response rate: 56%
- Complete response: 26%
- Partial response: 32%
- Median progression free survival: 16.8 months

A



Case for stage IV MCC

Stage IV MCC

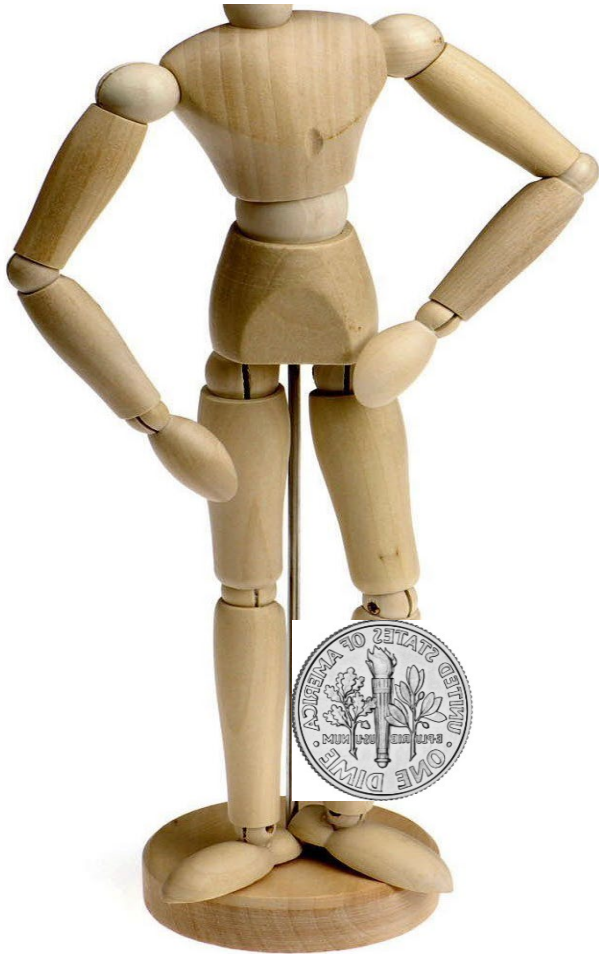


- Clinical: 60 YOM with “dime-sized” MCC on left shin
- Treatment:
 - WLE with 1.0 cm margins and SLNB
- Pathology:
 - Clear margins
 - SLNB revealed 4 negative left inguinal lymph nodes

What is the next step in management?

Case for stage IV MCC

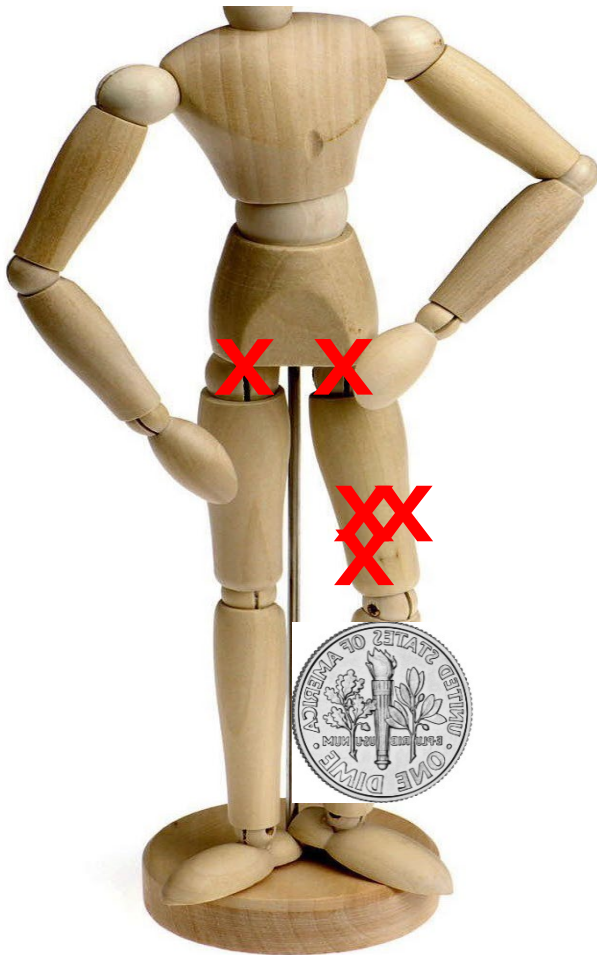
Stage IV MCC



- Plan:
 - No adjuvant XRT to primary site given small size
 - Clinical monitoring for recurrence

Case for stage IV MCC

Stage IV MCC

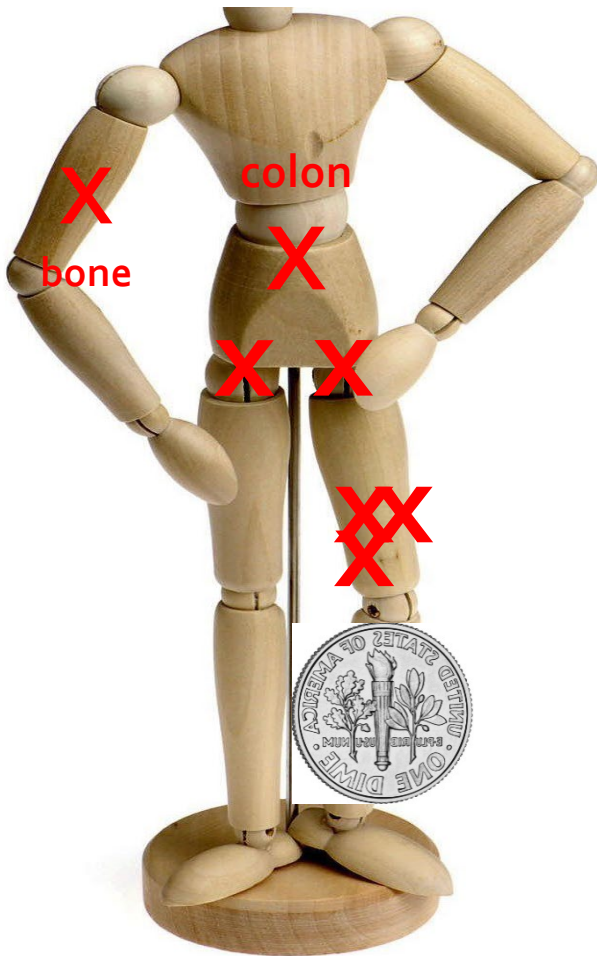


■ Follow up/Treatment:

- Developed multiple in-transit metastases, treated by excision and radiation
- Developed multiple lymph node metastases in inguinal and iliac lymph nodes, treated with radiation

Case for stage IV MCC

Stage IV MCC



- Developed bony metastasis to right humerus

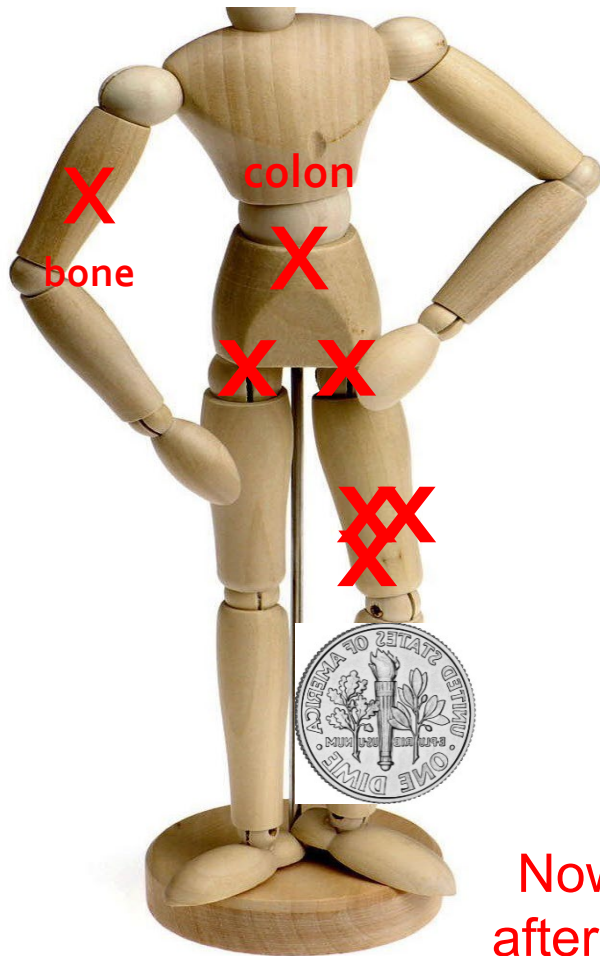
What is the next step in management?

- Chemotherapy with carboplatin. 4 cycles, complete response. But developed pancytopenia
- Developed recurrence in colon

What is the next step in management?

Case for stage IV MCC

Stage IV MCC

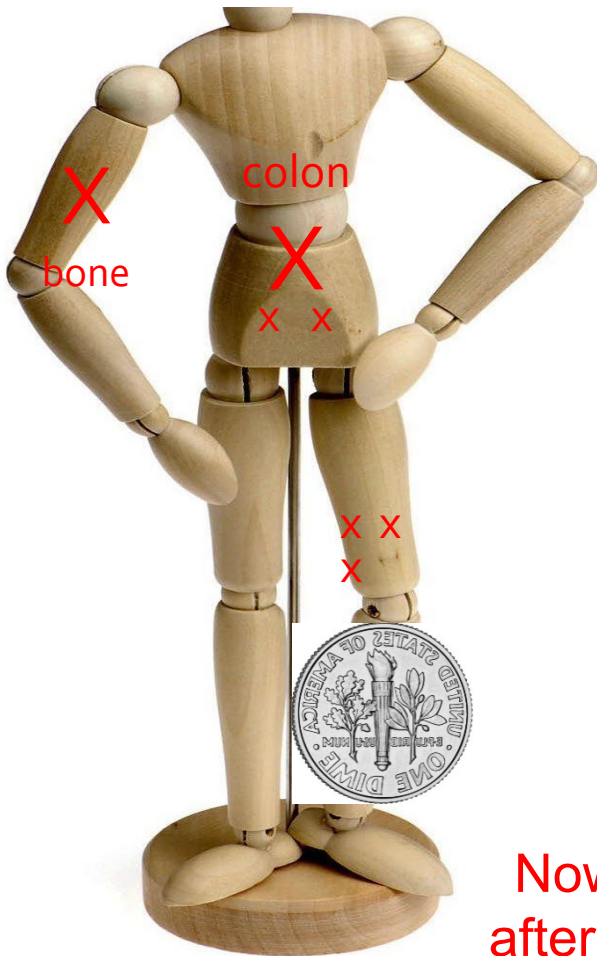


Now 7 years
after diagnosis

- Colon metastasis was treated with resection
- Started on second-line pembrolizumab for 1 year
- Pembrolizumab stopped due to immune-mediated nephritis.
- Had ongoing response after discontinuation of pembrolizumab, now with complete response.

Case for stage IV MCC

Stage IV MCC



Now 7 years
after diagnosis

- Significant progress in MCC therapies, especially with FDA approval of Avelumab and pembrolizumab for stage IV disease
- What is next?

Next steps?

We have:

- Management options for the primary site, nodal basin, and distant disease

We need:

- Additional treatments for stage IV disease (some cannot receive immunotherapy, such as transplant patients)
- Treatment for immunotherapy-resistant stage IV MCC
- Adjuvant and neo-adjuvant systemic therapies

Clinical trials for MCC

Clinical trials for MCC at clinicaltrials.gov

4/29/19 – 31 studies recruiting



Showing: 1-10 of 31 studies studies per page

Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Pembrolizumab (MK-3475) as First-line Therapy for Advanced Merkel Cell Carcinoma (MK-3475-913)	• Merkel Cell Carcinoma	• Drug: Pembrolizumab (MK-3475)	• Calvary Mater Newcastle (Site 0402) Waratah, New South Wales, Australia • Princess Margaret Cancer Centre (Site 0051) Toronto, Ontario, Canada • CHU de Bordeaux- Hopital Saint Andre (Site 0203) Bordeaux, France • (and 14 more...)
2	☐	Recruiting	A Study of INCMGA00012 in Metastatic Merkel Cell Carcinoma	• Metastatic Merkel Cell Carcinoma	• Drug: INCMGA00012	• Georgetown University - Lombardi Comprehensive Cancer Center Washington, District of Columbia, United States • Rutgers Cancer Institute of New Jersey New Brunswick, New Jersey, United States • Roswell Park Cancer Institute Buffalo, New York, United States • (and 11 more...)
3	☐	Recruiting	Adjuvant Therapy of Completely Resected Merkel Cell Carcinoma With Immune Checkpoint Blocking Antibodies Versus Observation	• Merkel Cell Carcinoma	• Drug: Ipilimumab • Drug: Nivolumab	• University Hospital Essen, Dermatology Essen, NRW, Germany • Charité Universitätsmedizin Berlin Berlin, Germany • Elbeklinikum Buxtehude Buxtehude, Germany • (and 8 more...)
4	☐	Recruiting	This Study Evaluates KRT-232, a Novel Oral Small Molecule Inhibitor of MDM2, for the Treatment of Patients With (p53WT) Merkel Cell Carcinoma Who Have Failed Anti-PD-1/ PD-L1 Immunotherapy	• Merkel Cell Carcinoma	• Drug: KRT-232	• Massachusetts General Hospital Boston, Massachusetts, United States • Dana-Farber Cancer Institute Boston, Massachusetts, United States • Washington University School of Medicine in St. Louis • (and 1 more...)

MCC Clinical Trials

anti-PD-L1:

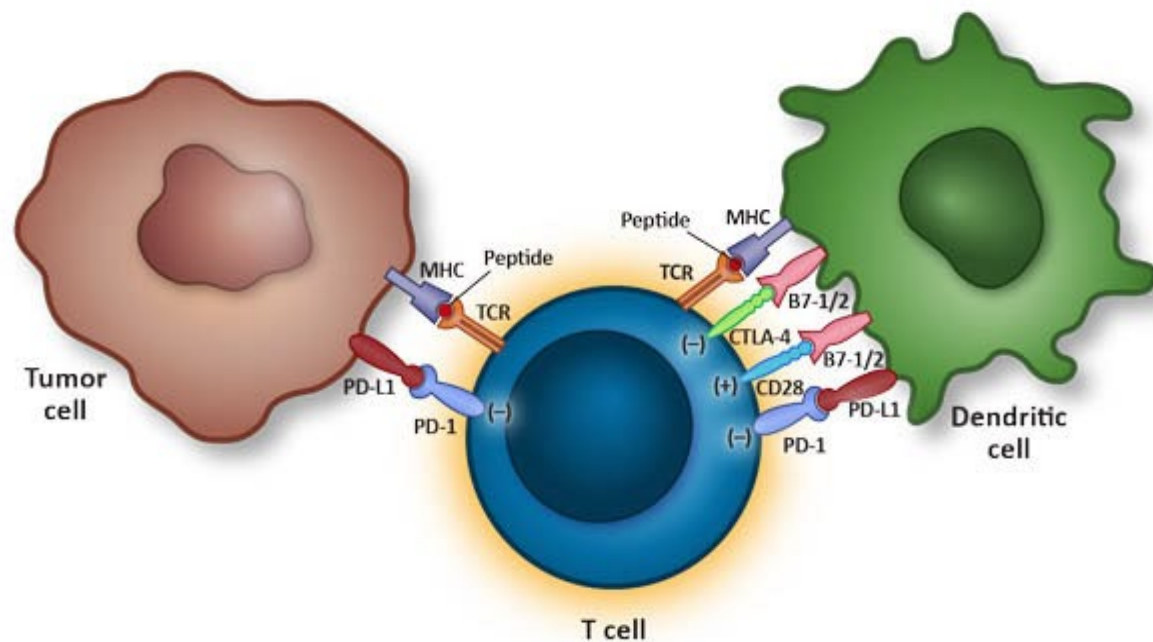
Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}

- Checkpoint inhibition in metastatic setting:
 - PD1/PDL-1 inhibitors monotherapy for metastatic MCC
 - PD1/PDL-1 alone or in combination with CTLA-4 inhibitor and/or radiation for metastatic MCC
 - PD-1/PDL-1 inhibitor combined with other therapies
 - Notch inhibitor or anti-CD38 antibody

MCC Clinical Trials

anti-PD-L1:

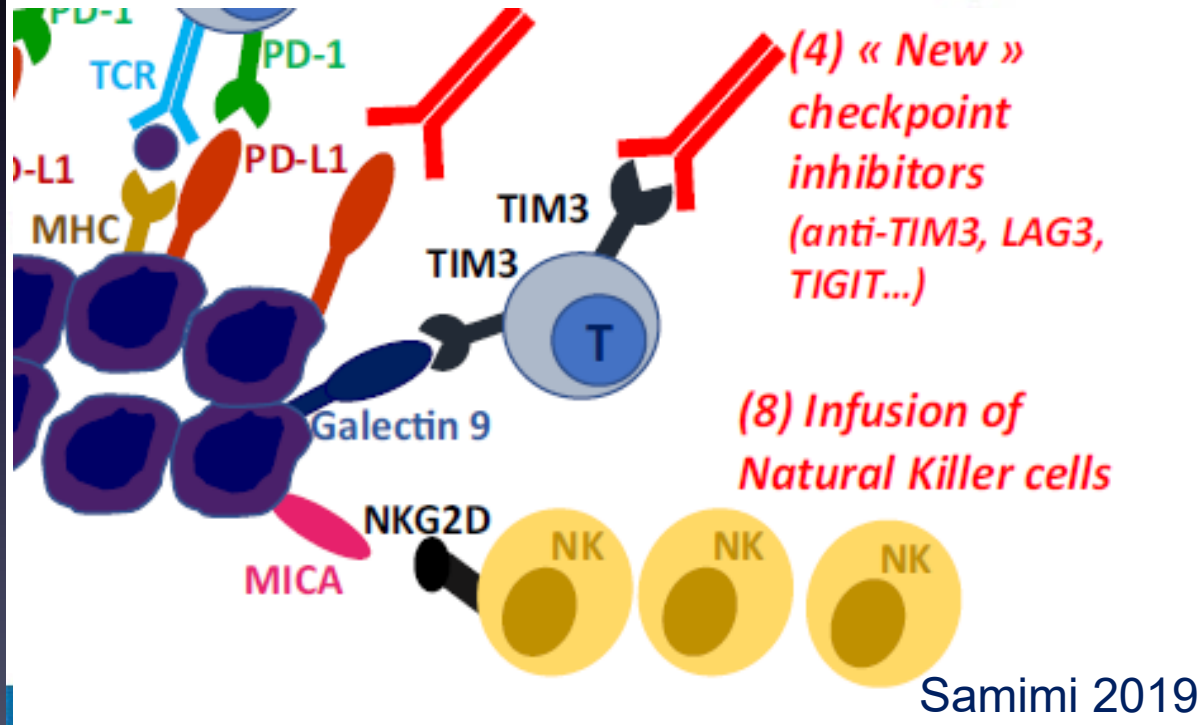
Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab



American Journal of Clinical Dermatology
<https://doi.org/10.1007/s40257-019-00427-9>

REVIEW ARTICLE



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}

- Next-generation checkpoint inhibitors, alone or combined with PD-1/PDL1 inhibitors:
- INCAGN02390 (anti-TIM3) for advanced disease*
- INCAGN02385 (anti-LAG3) for metastatic MCC
- AB154 (anti-TIGIT) +/- AB122 (anti-PD1) for advanced disease*
- Relatlimab (anti-LAG3) + Nivo (CheckMate358)
* recruiting

MCC Clinical Trials

anti-PD-L1:

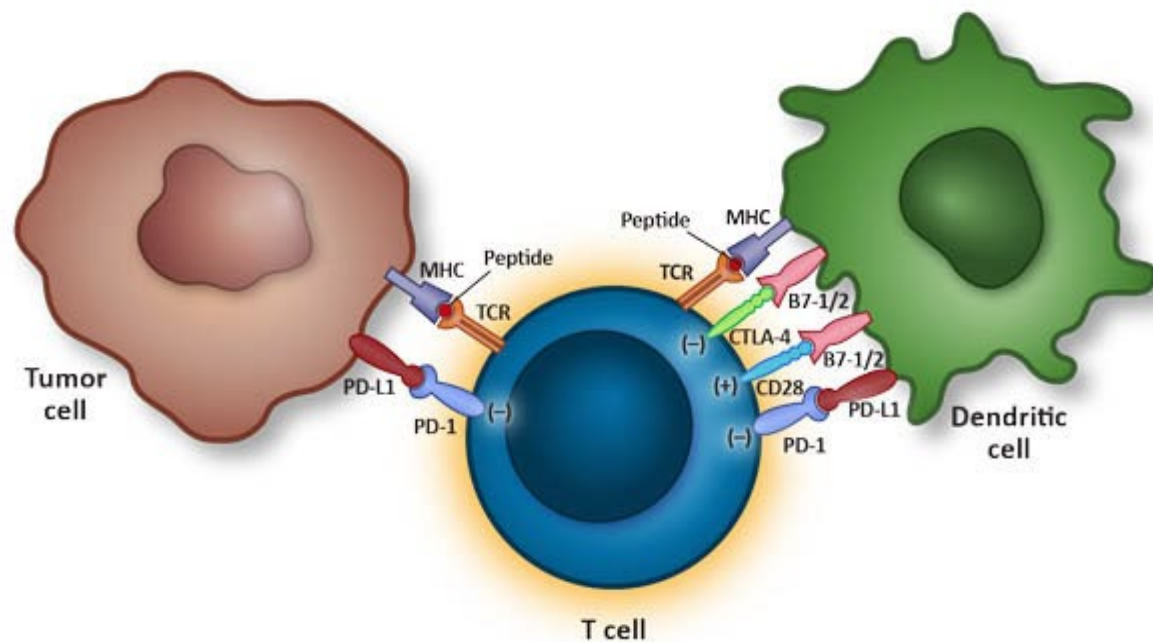
Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

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Ipilimumab



Medscape

American Journal of Clinical Dermatology
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REVIEW ARTICLE



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}

- Checkpoint inhibition in adjuvant setting:
 - PD-1/PDL-1 inhibitors alone or in combination with CTLA-4 inhibitors and/or radiation
 - Pembro vs. observation in all resected MCC
 - Avelumab vs placebo in resected stage IIIB
 - Nivo or ipi vs observation in resected stage III
 - Nivo /XRT vs. Nivo/IPI in resected stage III

MCC Clinical Trials

anti-PD-L1:

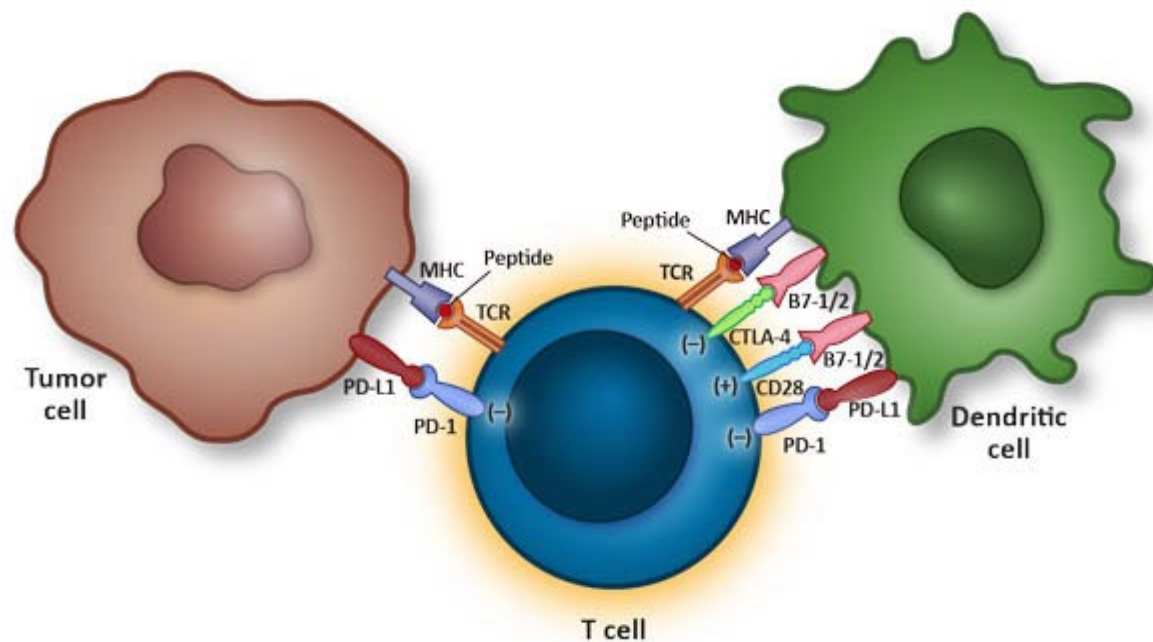
Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}

- Checkpoint inhibition in neoadjuvant setting:
 - Nivolumab (CheckMate 358) for resectable stage IIA-IV

MCC Clinical Trials

anti-PD-L1:

Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab

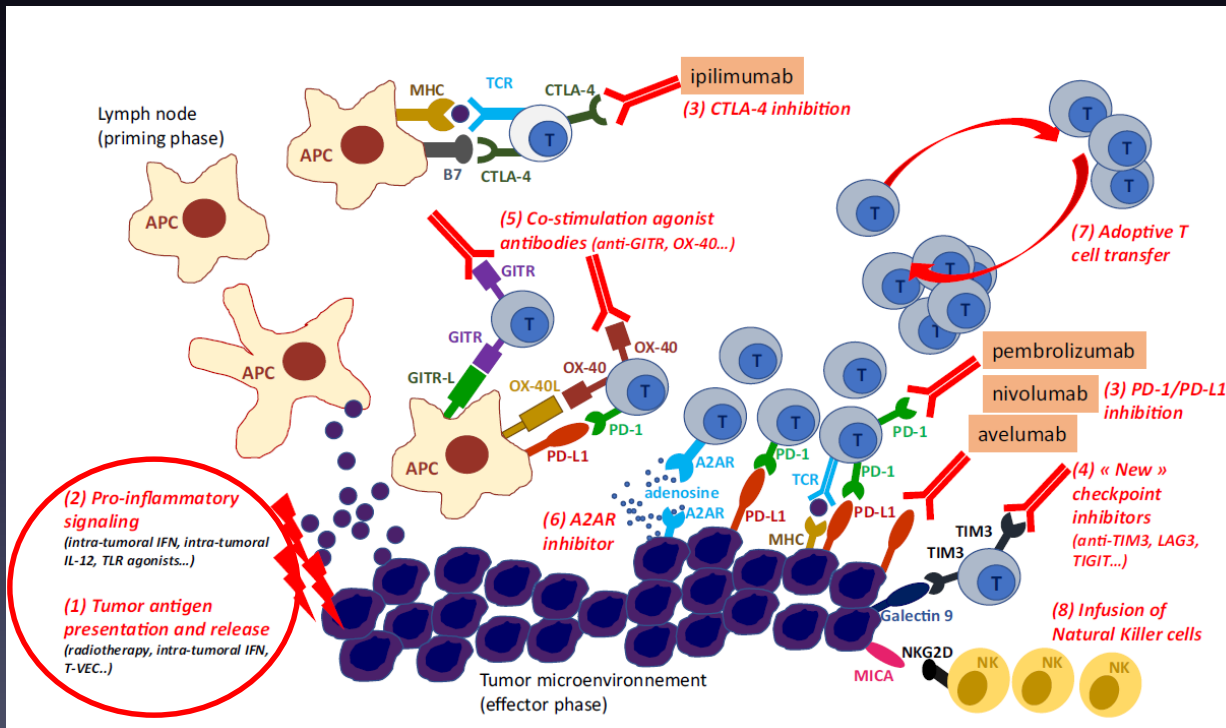
American Journal of Clinical Dermatology
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REVIEW ARTICLE



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}



Other immune based-strategies for metastatic disease

- TLR agonists, alone or in combination with other immunotherapies
- T-VEK, T-VEK+/- XRT, T-VEK + nivo

* recruiting

MCC Clinical Trials

anti-PD-L1:

Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab

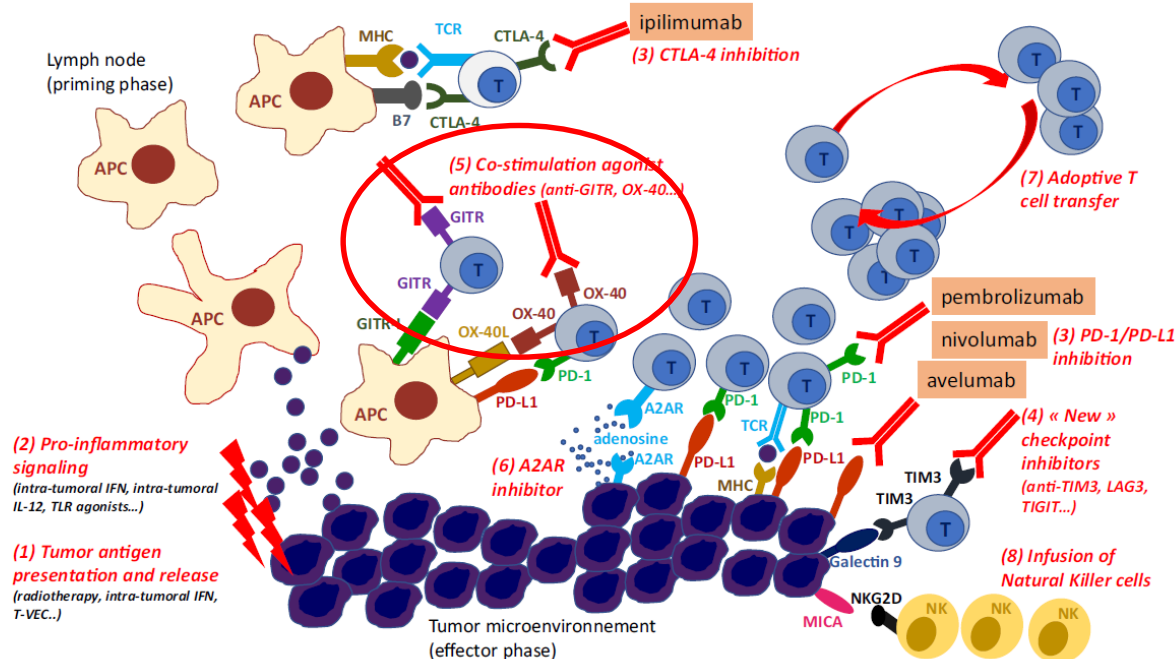
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REVIEW ARTICLE



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}



Other immune based-strategies for metastatic disease

- Co-stimulatory checkpoint agonists, alone or combined with immunotherapy
 - anti-Ox40 agonistic antibody
 - Anti-GITR agonistic antibody

MCC Clinical Trials

anti-PD-L1:

Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab

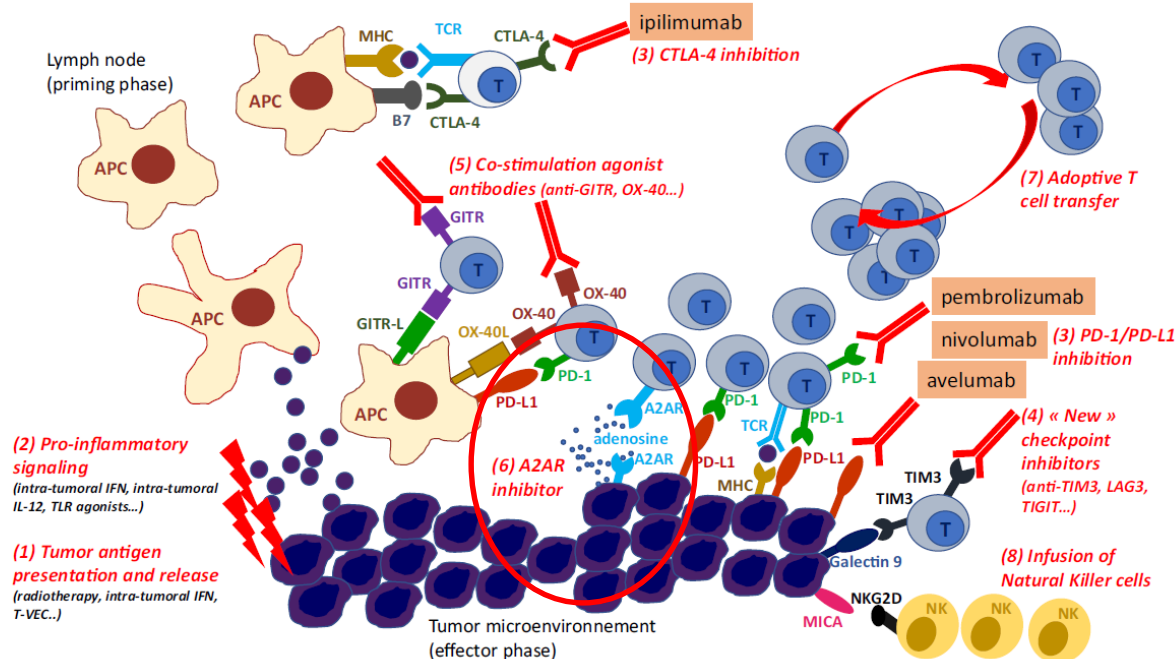
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REVIEW ARTICLE



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}



Other immune based-strategies for metastatic disease

- Reversal of other immune evasion mechanisms alone or in combination with immunotherapy
 - antagonist of adenosine receptor A2ar and A2bR + anti-PD1 antibody

MCC Clinical Trials

anti-PD-L1:

Avelumab
Atezolizumab

anti-PD-L1:

Avelumab
Atezolizumab

anti-CTLA-4:

Ipilimumab

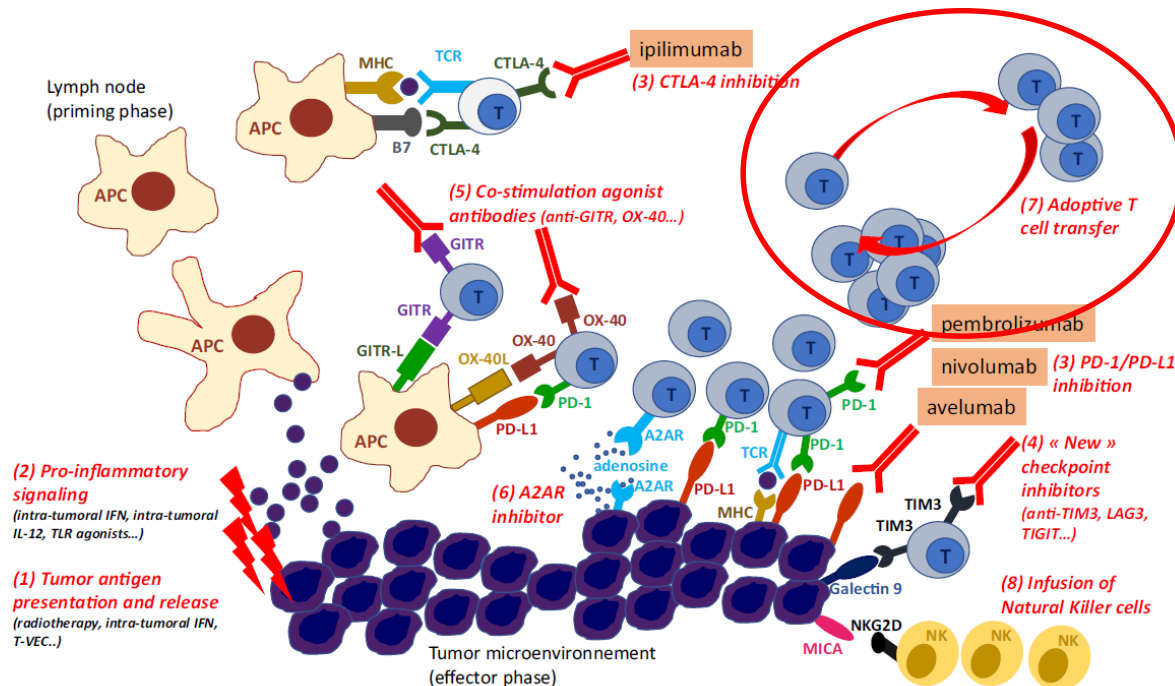
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REVIEW ARTICLE



Immune Checkpoint Inhibitors and Beyond: An Overview of Immune-Based Therapies In Merkel Cell Carcinoma

Mahtab Samimi^{1,2}



Other immune based-strategies for metastatic disease

- Adoptive T cell transfer combined with immunotherapy
- Innate immune cell therapy
 - neukoplast infusions

Clinical Trials at Michigan

- Neoadjuvant immunotherapy
 - Checkmate 358 (NCT02488759)– neoadjuvant nivolumab in virus-associated cancers
- Adjuvant immunotherapy
 - ADAM NCT03271372 (Adjuvant Avelumab in Merkel)

Clinical trial using neo-adjuvant immunotherapy



- **HPI**: 63 YO healthy male with a 6 month history of a skin colored growing mass on the left upper thigh.
- **Work-up**: Referred to surgery for excision of lipoma. Lesion became red, and I&D was recommended. During I&D, mass was identified and a biopsy was performed.
- **Pathology**: MCC (March 2018)

Clinical trial using neo-adjuvant immunotherapy



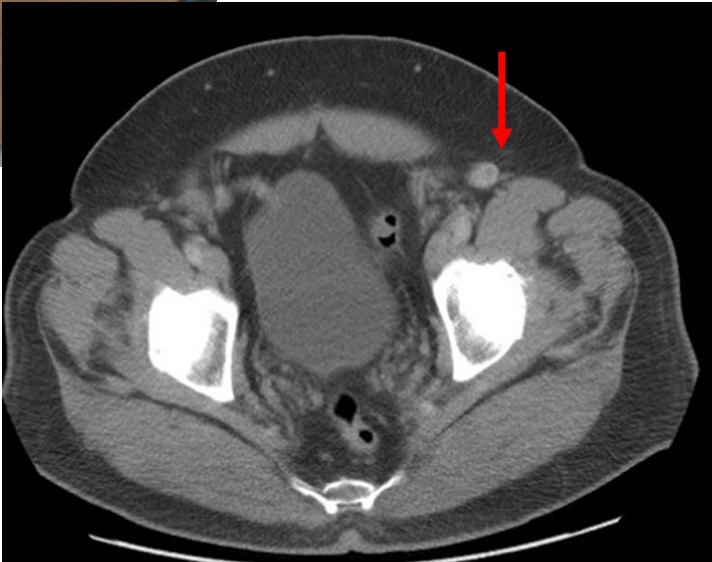
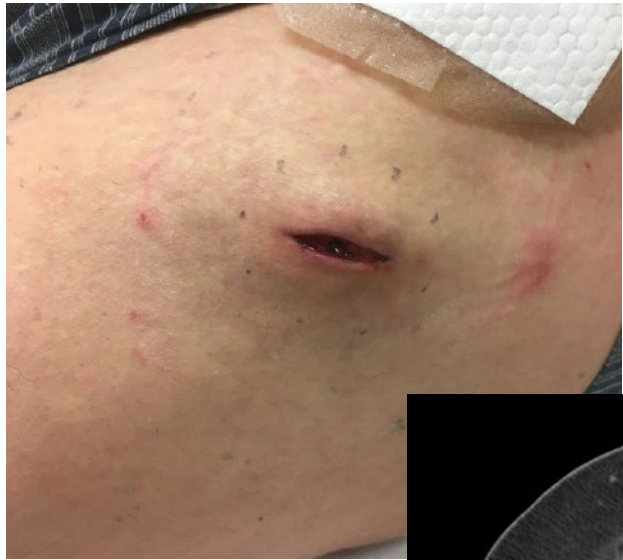
- Physical exam: 2 cm mass in left groin
- Fine needle biopsy: metastatic MCC
- Staging imaging: revealed 2.5 cm enlarged lymph node in left groin, no distant disease

Clinical trial using neo-adjuvant immunotherapy



- Physical exam: 2 cm mass in left groin
- Fine needle biopsy: metastatic MCC
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Clinical trial using neo-adjuvant immunotherapy



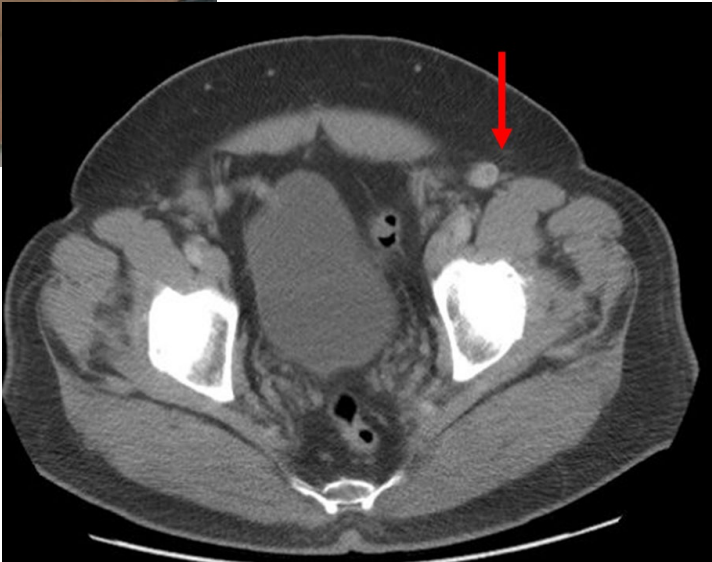
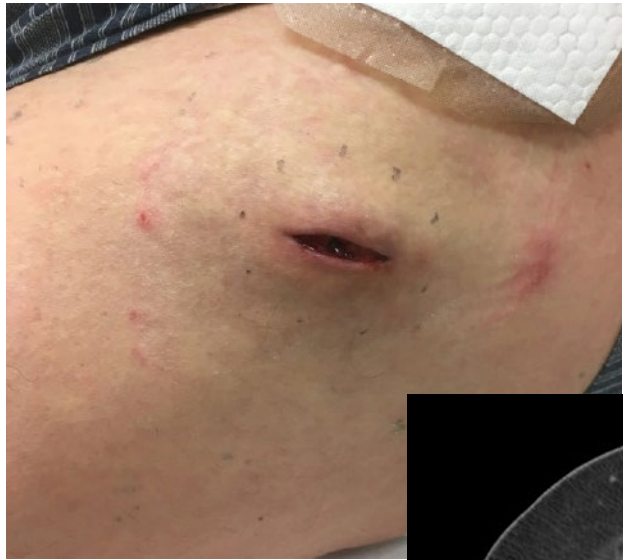
■ Tumor board consultation:

- LND and XRT
- neo-adjuvant clinical trial

■ Clinical Trial:

- neoadjuvant nivolumab (CheckMate 358, NCT02488759)
- 2 doses every 2 weeks followed by standard of care
- tumor response ($2.8 \times 1.9 \rightarrow 2.3 \times 1.4$ cm)

Clinical trial using neo-adjuvant immunotherapy

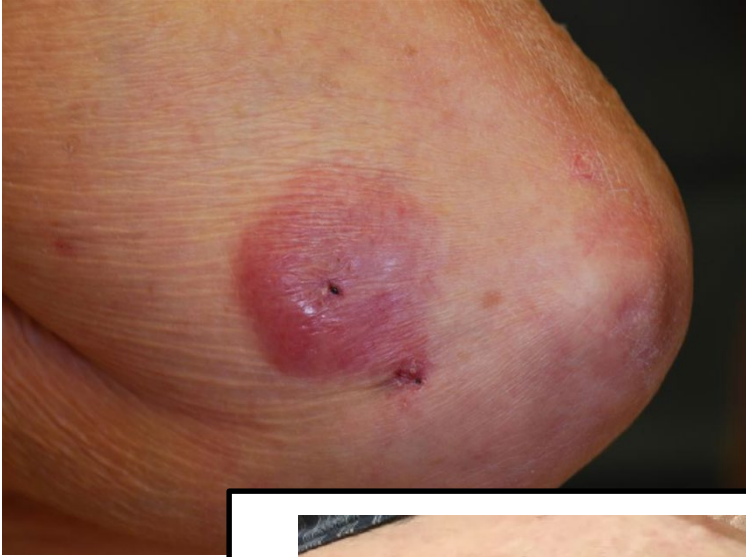


- WLE with 1.0 cm margins in left ILND
 - Primary site pathology: residual MCC to within 0.5mm of the inferior peripheral margin
 - CLND: 1/11 positive nodes, no extranodal extension
- Adjuvant XRT to primary site
- Close monitoring for recurrence on trial

Clinical trial using adjuvant Avelumab (vs. placebo) for resected stage IIIB MCC

- Multi-center, randomized, double-blinded, placebo-controlled, phase 3 trial for adjuvant Avelumab versus placebo in stage IIIB MCC
- Inclusion criteria: stage IIIB disease, treated with surgery +/- radiation
- Dosing: induction and maintenance phase for 2 years
- Primary outcome: relapse free survival
- Secondary outcome: MCC-specific survival, distant metastasis-free survival, adverse events, overall survival

Clinical pearls: primary tumor

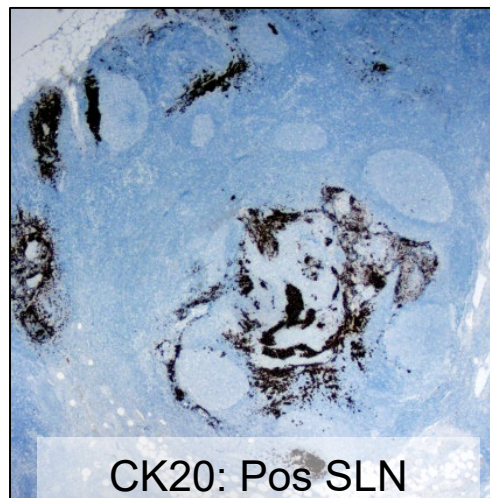
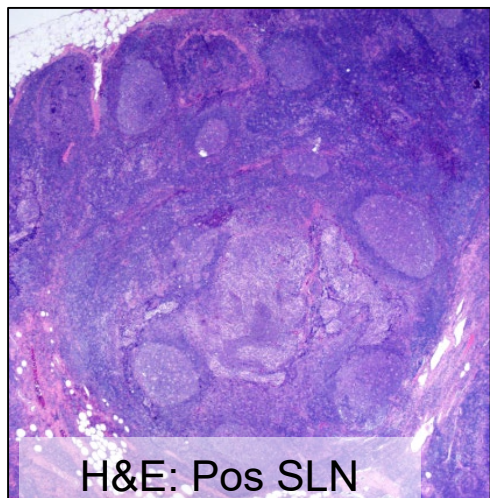


- Clinically start small and grow quickly over 3 months
- Often delay in presentation as lesion is non-descript and asymptomatic
- Often initially treated as an inflamed cyst with I&D and antibiotics before diagnosis is made



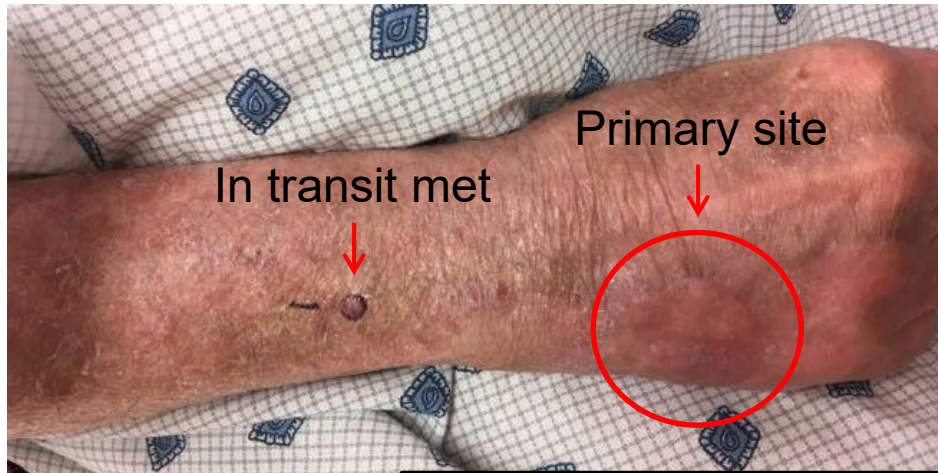
MCC with cyst-like presentation

Clinical pearls: positive SLNB



- Even smallest MCC tumors have a risk of at least 15-20% nodal metastasis
- Recommend SLNB in all patients with clinically node-negative disease

Clinical pearls: monitor for recurrence



- In transit metastases can initially be subtle; have a low threshold for biopsy for early detection



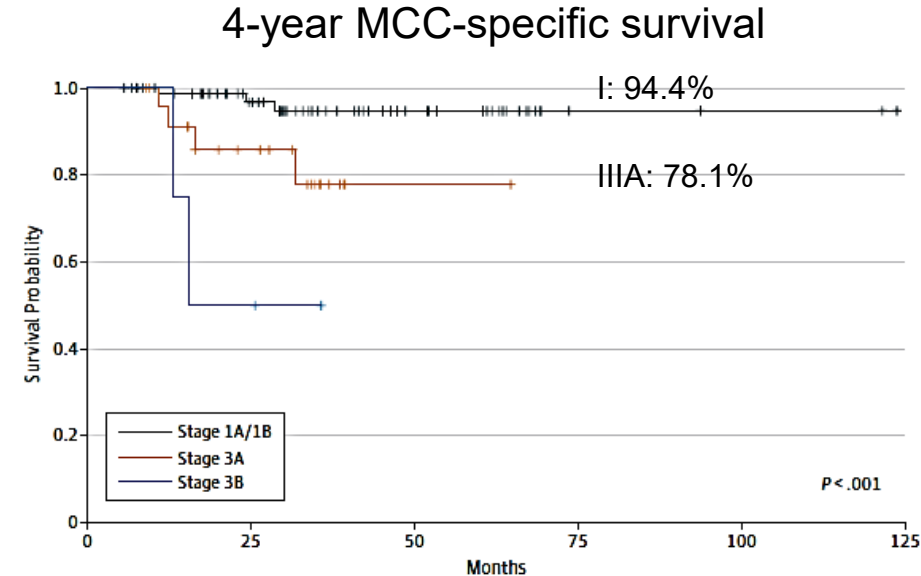
- Patients may develop few or multiple in-transit metastases; in-transit disease may be distal to primary tumor

Clinical pearls: MCC specific survival

JAMA Dermatology | Original Investigation

Recurrence and Survival in Patients With Merkel Cell Carcinoma Undergoing Surgery Without Adjuvant Radiation Therapy to the Primary Site

Marcus L. Frohm, MD; Kent A. Griffith, MPH, MS; Kelly L. Harms, MD, PhD; James A. Hayman, MD; Douglas R. Fullen, MD; Christine C. Nelson, MD; Sandra L. Wong, MD; Jennifer L. Schwartz, MD; Christopher K. Bichakjian, MD



Frohm et al. (2016) JAMA Derm Sept;152(9)1001-1007

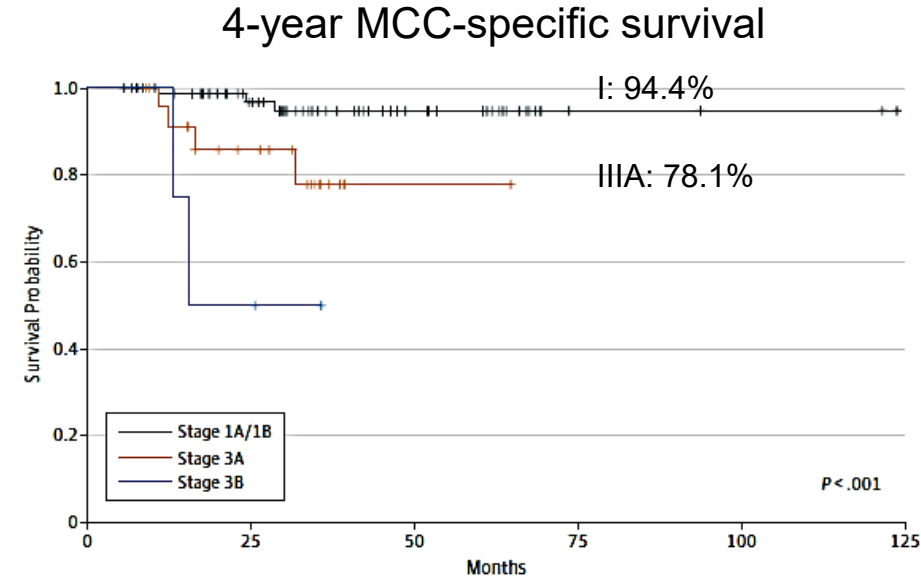
- At centers for multidisciplinary management of Merkel cell carcinoma, MCC-specific survival is much improved compared to overall survival using national cancer databases

Clinical pearls: MCC specific survival

JAMA Dermatology | Original Investigation

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Ann Surg Oncol
DOI 10.1245/s10434-016-5266-4

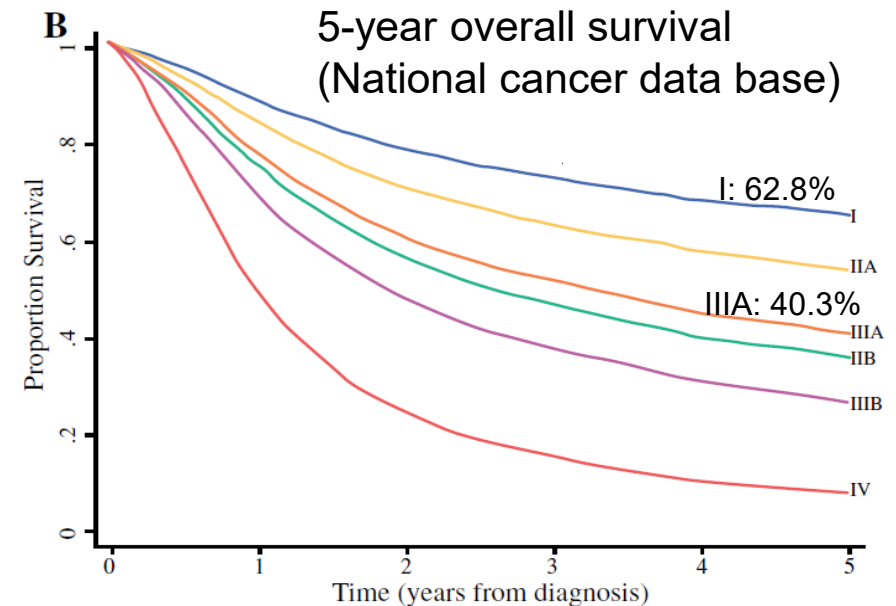
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY



ORIGINAL ARTICLE – MEDICAL ONCOLOGY

Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System

Kelly L. Harms, MD, PhD¹, Mark A. Healy, MD^{2,3}, Paul Nghiem, MD, PhD^{4,5,6}, Arthur J. Sober, MD⁷, Timothy M. Johnson, MD^{1,2,8}, Christopher K. Bichakjian, MD¹, and Sandra L. Wong, MD, MS^{2,3,9}



Harms, K et al. (2016) Ann Surg Oncol Oct;23(11)3564-3571

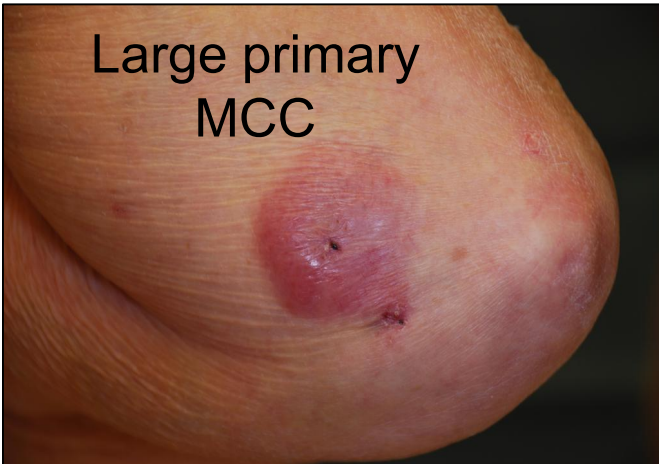
There are many presentations of Merkel cell carcinoma.

Multidisciplinary management is critical.

Stage I and II

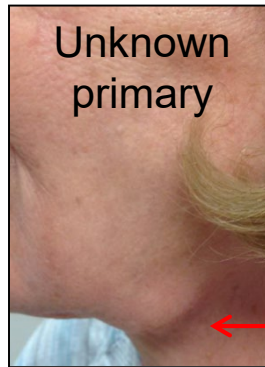


Small
primary
MCC

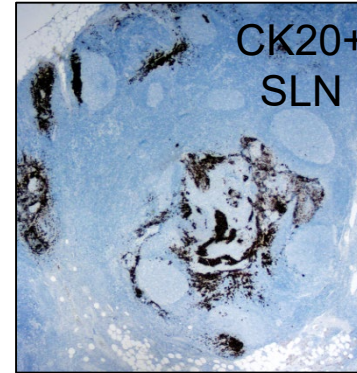


Large primary
MCC

Stage IIIA

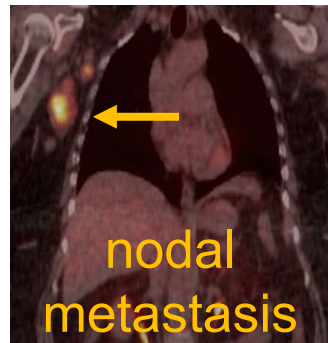


Unknown
primary



CK20+
SLN

Stage IIIB

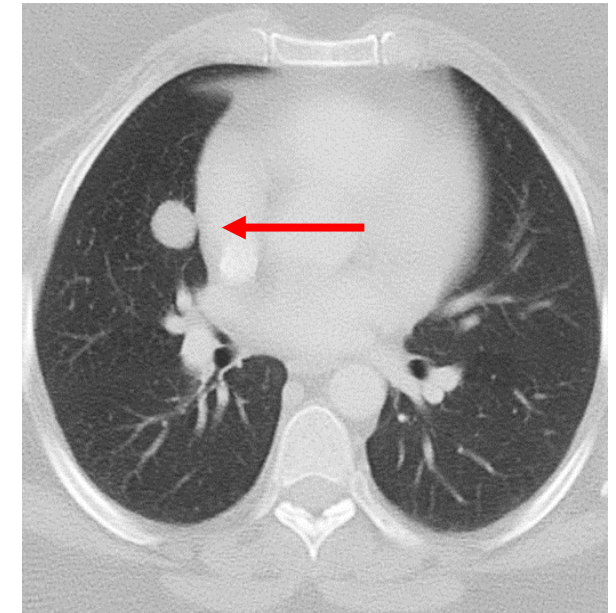


nodal
metastasis



In transit
disease

Stage IV



Lung metastasis

Questions

