Updates on systemic therapy for metastatic Merkel Cell Carcinoma and Squamous Cell Carcinoma

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Mayo Clinic Rochester
Systemic therapy for MCC and SCC

Disclosures

• None
Systemic therapy for MCC and SCC

Objectives

• Review the current data on the use of immune checkpoint inhibitors for metastatic MCC including ongoing clinical trials

• Discuss the mutational landscape and potential targeted therapies for MCC

• Review the data for EGFR for recurrent/metastatic SCC of the skin

• Discuss emerging data for the use of immune checkpoint inhibitors in recurrent/metastatic cutaneous SCC
Merkel Cell Carcinoma
Systemic therapy for MCC and SCC

Why the need for effective systemic therapy for MCC?

• High risk of recurrence disease
  • ≈ 50% of patients treated with curative intent

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>79%</td>
</tr>
<tr>
<td>IB</td>
<td>60%</td>
</tr>
<tr>
<td>IIA</td>
<td>58%</td>
</tr>
<tr>
<td>IIB</td>
<td>49%</td>
</tr>
<tr>
<td>IIC</td>
<td>47%</td>
</tr>
<tr>
<td>IIIA</td>
<td>42%</td>
</tr>
<tr>
<td>IIIB</td>
<td>26%</td>
</tr>
<tr>
<td>IV</td>
<td>18%</td>
</tr>
</tbody>
</table>

Banks et al. J Oncol Practice, 2016
Systemic therapy for MCC and SCC

Chemotherapy for MCC

Response to platinum/etoposide chemotherapy
Systemic therapy for MCC and SCC

Immune checkpoint inhibitors

Promotes tumor-specific effector T-cells
Systemic therapy for MCC and SCC
Rationale for immune checkpoint inhibitors for MCC

• Virus-positive MCC
  • Robust humoral and cellular immune response seen against MC polyomavirus
    • Viral oncoprotein-reactive CD4+ and CD8+ T cells found in tumor and patient blood
  • Tolerance over time $\rightarrow$ ↑ immune inhibitory receptors (PD-1, Tim-3)

• Virus-negative MCC
  • Subset with high expression of PDL-1
  • High mutation burden (UV light exposure)

Banks et al. J Oncol Practice, 2016
Systemic therapy for MCC and SCC

Immune checkpoint inhibitors for MCC: Pembrolizumab

- Phase 1 study of pembrolizumab (MK-3475; KEYNOTE 001)
- 32 patients enrolled; 30 treated at escalating doses
- 2 complete responses (1 MCC)
- 3 partial responses
- 15 stable disease

## KEYNOTE 001: Efficacy outcomes by investigator review per RECIST v1.1.

### Graph Depiction
- **Efficacy Outcomes**: The graph illustrates the efficacy outcomes of various cancers treated with different doses and schedules of a specific treatment.
- **Time (weeks)**: The x-axis represents the duration of treatment in weeks, ranging from 0 to 70.
- **Best Overall Response**:
  - Complete response
  - Partial response
  - Stable disease
  - Progressive disease
- **Treatment Status**:
  - Treatment ongoing
  - Last non-PD assessment
  - PD following non-PD

### Cancers Treated
- **Merkel cell carcinoma**
- **Melanoma**
- **Leiomyosarcoma**
- **Melanoma**
- **NSCLC**
- **Prostate**
- **Peripheral nerve sheath**
- **Carcinoid syndrome**
- **Melanoma (retinal)**
- **NSCLC**
- **NSCLC**
- **Pancreatic adenocarcinoma**
- **Pancreatic neuroendocrine**
- **Melanoma**
- **Prostate**
- **Kaposi sarcoma**
- **Colon adenocarcinoma**
- **NSCLC**
- **Rectal adenocarcinoma**
- **NSCLC**
- **Prostate**
- **Neuroendocrine of the skin**
- **NSCLC**
- **NSCLC**
- **Breast adenocarcinoma**

### Dose and Schedule
- **1 mg/kg Q2W**
- **3 mg/kg Q2W**
- **10 mg/kg Q2W**
- **10 mg/kg Q3W**
- **2 mg/kg Q3W**

### References
Systemic therapy for MCC and SCC

Immune checkpoint inhibitors for MCC

ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma


## Patient Characteristics

**Table 1. Patient Characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 26)</th>
<th>Patients with Virus-Positive Tumors (N = 17)</th>
<th>Patients with Virus-Negative Tumors (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70.5±8.1</td>
<td>67.5±6.0</td>
<td>76.3±8.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>68 (57–91)</td>
<td>67 (57–83)</td>
<td>76 (64–91)</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (38)</td>
<td>4 (24)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (62)</td>
<td>13 (76)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Disease stage at study entry — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIIB</td>
<td>2 (8)</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>24 (92)</td>
<td>15 (88)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Previous duration of disease — wk†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>58.8±56.8</td>
<td>71.3±63.5</td>
<td>35.2±32.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>39 (3–227)</td>
<td>53 (3–227)</td>
<td>27 (5–104)</td>
</tr>
<tr>
<td>Baseline extent of disease — mm‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>81.7±53.9</td>
<td>88.7±63.1</td>
<td>68.6±28.7</td>
</tr>
<tr>
<td>Median (range)</td>
<td>69 (13–182)</td>
<td>62 (13–182)</td>
<td>75 (36–123)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
† Previous duration of disease was measured from the date of diagnosis to the date of the first dose of study treatment. An unknown day of diagnosis was imputed as mid-month for one patient.
‡ The extent of disease was measured before treatment initiation as the sum of the longest diameters of tumor target lesions.
Clinical Characteristics of Tumor Response to Pembrolizumab in Patients with Merkel-Cell Carcinoma

Kaplan–Meier Curve Showing Progression-free Survival among 26 Patients with Merkel-Cell Carcinoma Who Received Pembrolizumab

Historical 6 month PFS on chemotherapy 90%

Expression of PD-1 and PD-L1 in Pretreatment Tumor Specimens, Detected by Immunohistochemical Testing
Systemic therapy for MCC and SCC

Immune checkpoint inhibitors for MCC: Avelumab

• Phase 2 trial
• Metastatic MCC that had progressed on chemotherapy
• Avelumab single agent 10 mg/kg IV q 2 weeks
• 88 patients treated
• Led to designation as a breakthrough therapy by FDA

# Systemic therapy for MCC and SCC

## Immune checkpoint inhibitors for MCC: Avelumab

<table>
<thead>
<tr>
<th>N=88</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>72.5 years (33-88)</td>
</tr>
<tr>
<td>ECOG 0/1</td>
<td>56%/44%</td>
</tr>
<tr>
<td>Prior treatment lines (1/&gt;1)</td>
<td>66%/34%</td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>29.5%</td>
</tr>
<tr>
<td>Complete response</td>
<td>9.8% (6 pts)</td>
</tr>
<tr>
<td>Partial response</td>
<td>19.7% (12 pts)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11.5% (7 pts)</td>
</tr>
<tr>
<td>Duration of response</td>
<td>2.8-14.6+ months (median no reached)</td>
</tr>
<tr>
<td>6 months PFS</td>
<td>36%</td>
</tr>
</tbody>
</table>

Kaufman et al., ASCO 2016
Systemic therapy for MCC and SCC

Common side effects of immune checkpoint inhibitors

- Fatigue
- Anorexia
- Dyspnea
- Cough
- Fever
- Nausea/Vomiting
- Diarrhea
- Constipation
- Rash
- Pruritus
- Arthralgia
- Hypothyroidism
  - Up to 14% in H&N pts
- Elevated LFTs
- Hyperlipidemia
- Hypoglycemia
- Facial edema (H&N pts only)
Systemic therapy for MCC and SCC

Rare but serious side effects of immune checkpoint inhibitors

- Immune-mediated AEs
  - Pneumonitis (2-4%)
  - Colitis (2%)
  - Hepatitis (1%)
  - Hypophysitis (1%)
  - Hyperthyroidism (1-3%)
  - Arthritis (1-2%)
  - Diabetes mellitus (1%)
  - Nephritis (1%)

- Immune-mediated Aes (<1%)
  - Dermatitis/rash
  - Bullous pemphigoid
  - Uveitis
  - Myositis
  - Myasthenia gravis/GB
  - Vasculitis
  - Pancreatitis
  - Hemolytic anemia
  - Seizures
Systemic therapy for MCC and SCC

Pazopanib for MCC

- Phase 2 trial for unresectable MCC
- Pazopanib 800 mg or 600 mg
- Prior treatment allowed
- Primary endpoint: Response rate

Nathan et al, ASCO 2016
Systemic therapy for MCC and SCC
Pazopanib for MCC

<table>
<thead>
<tr>
<th>Results</th>
<th>16 evaluable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>73 years (56-90)</td>
</tr>
<tr>
<td>Median treatment duration</td>
<td>8 weeks (1-38)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (37%)</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Median OS</td>
<td>6.4 months</td>
</tr>
</tbody>
</table>

Nathan et al, ASCO 2016
Systemic therapy for MCC and SCC

Mutational landscape for MCC

• Distinct patterns of genomic alterations for virus-positive and virus-negative MCC
  • Higher mutation burden in virus-negative
  • UV damage signature in virus-negative
    • RB1, TP53, and a high frequency of mutations in NOTCH1 and FAT1
• Poorer survival for patients with mutations in RB1 or p53
  • 2 year OS 80% vs. 57%

1Wong SQ, Cancer Research, 2015
2Nathan et al, ASCO 2016
Systemic therapy for MCC and SCC

Mutational landscape for MCC

- Additional identified potentially targetable mutations for virus negative MCC
  - BRCA1
  - MSH2
  - ASXL, ARID1A/B
  - PIK3CA, AKT1, PIK3CG
  - HRAS, NF1
  - FGFR2
  - EGFR

Select ongoing clinical trials for metastatic Merkel Cell Carcinoma
NCT02196961: Prospective Randomized Trial of an Adjuvant Therapy of Completely Resected Merkel Cell Carcinoma (MCC) With 3 mg/kg BW Ipilimumab (Yervoy®) Every 3 Weeks for 12 Weeks Versus Observation

Dr. Schadendorf & colleagues, University Hospital Essen, Germany
NCT02514824: MLN0128 (mTOR inhibitor) in Recurrent/Metastatic MCC

*Standard 3x3 dose escalation phase 1

Dr. Rabinowits & colleagues, Dana Farber Cancer Center, Boston
NCT02465957: Phase II Study of aNK (Activated NK-92, Formerly Neukoplast) Infusions in Patients With Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Stage IIIB/IV Merkel Cell Carcinoma

aNK (activated natural killer cells)

UPMC and University of Washington
Metastatic Squamous Cell Carcinoma of the Skin
Systemic therapy for MCC and SCC
Metastatic squamous cell carcinoma of the skin

• Approximately 20% of non-melanoma skin cancer
• Risk factors:
  • UV light exposure (commonly induce p53 mutations)
  • Age
  • Caucasian/light-skinned
  • Ionizing radiation
  • Immunosuppression
  • Genetic risk factors (mutations in RAS, RAF, CDKN2A, KNSTRN gene)
  • Family history
  • Chronic inflammation
• Organ transplantation increases risk of SCC 65-250-fold
Systemic therapy for MCC and SCC

Cytotoxic chemotherapy for metastatic cutaneous SCC

- Platinum (cisplatin, carboplatin)
- Taxanes (paclitaxel, docetaxel)
- 5-Fluorouracil or capecitabine
- Bleomycin
- Doxorubicin
Systemic therapy for MCC and SCC
EGFR inhibitors for metastatic cutaneous SCC

• Cetuximab
• Panitumumab
Systemic therapy for MCC and SCC
Cetuximab for unresectable SCC of the skin

- Phase II study in first-line unresectable SCC
- Primary endpoint: Disease control rate at 6 weeks
- Secondary endpoints: RR, DCR, OS, PFS
- 36 patients enrolled; 31 evaluable for response

Eve Maubec et al. JCO 2011;29:3419-3426
### Systemic therapy for MCC and SCC

**Cetuximab for unresectable SCC of the skin**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>21/15</td>
<td>58%/42%</td>
</tr>
<tr>
<td>Median age 79 years (64% greater than 70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 0/1/2</td>
<td>11/17/8</td>
<td>31%/47%/22%</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>5</td>
<td>14%</td>
</tr>
<tr>
<td>Extremities</td>
<td>14</td>
<td>39%</td>
</tr>
<tr>
<td>Trunk</td>
<td>17</td>
<td>47%</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>17</td>
<td>47%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>16</td>
<td>44%</td>
</tr>
<tr>
<td>Distant mets</td>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15</td>
<td>42%</td>
</tr>
<tr>
<td>Surgery</td>
<td>12</td>
<td>33%</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>7</td>
<td>19%</td>
</tr>
<tr>
<td>RT</td>
<td>2</td>
<td>8%</td>
</tr>
</tbody>
</table>

**EGFR expression by IHC**

- 28% moderate
- 72% strong

Eve Maubec et al. JCO 2011;29:3419-3426
### Systemic therapy for MCC and SCC

**Cetuximab for unresectable SCC of the skin**

<table>
<thead>
<tr>
<th>Results</th>
<th>Cetuximab</th>
<th>Panitumumab (16 pts)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease control rate @ 6 weeks</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Response rate @ 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 pt (3%)</td>
<td>3 pts (8%)</td>
<td></td>
</tr>
<tr>
<td>21 (58%)</td>
<td>6 (17%)</td>
<td></td>
</tr>
<tr>
<td>Best overall response rate</td>
<td>28%</td>
<td>31%</td>
</tr>
<tr>
<td>*Complete</td>
<td>2 patients (6%)</td>
<td>2 patients (12%)</td>
</tr>
<tr>
<td>**Partial</td>
<td>8 pts (22%)</td>
<td>3 patients (19%)</td>
</tr>
<tr>
<td>*Sustained complete responses &gt;2.5 years after stopping therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Delayed responses seen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


* Sustained complete responses >2.5 years after stopping therapy
** Delayed responses seen
Representative examples of patients showing response to cetuximab.

Eve Maubec et al. JCO 2011;29:3419-3426
Kaplan-Meier plot of (A) overall survival and (B) progression-free survival in the intention-to-treat population and per-protocol population

Eve Maubec et al. JCO 2011;29:3419-3426
Systemic therapy for MCC and SCC
Chemotherapy for recurrent/metastatic SCC

Response to carboplatin/paclitaxel/cetuximab in 73 year old man with recurrent squamous cell carcinoma of the skin
Systemic therapy for MCC and SCC
Comprehensive genomic profiling for cutaneous mSCC

<table>
<thead>
<tr>
<th>N=122</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Median age</td>
<td>65 years</td>
</tr>
<tr>
<td>Gender</td>
<td>83% male</td>
</tr>
<tr>
<td>Genomic alteration (GA)/sample</td>
<td>9.2</td>
</tr>
<tr>
<td>Clinically relevant GA/sample</td>
<td>2.5</td>
</tr>
<tr>
<td>TP53</td>
<td>85%</td>
</tr>
<tr>
<td>CDKN2A (cell cycle dysregulation)</td>
<td>62%</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>43%</td>
</tr>
</tbody>
</table>

Note
similarities to
sun-associated
virus-negative
MCC

Ross et al, ASCO 2016
Systemic therapy for MCC and SCC
Role for immune checkpoint inhibitors for cutaneous SCC?

Cytotoxic chemotherapy

Immunotherapy
Systemic therapy for MCC and SCC
Rationale for immune checkpoint inhibitors in cutaneous SCC

• PD1 expression 80% and PDL1 26% in 70 specimens of advanced cutaneous SCC¹

• Most cutaneous SCC associated with UV exposure and have a high mutational burden
  • Predicts response to immune checkpoint inhibitors in other tumor types

• Case reports of response to nivolumab or pembrolizumab in immunocompetent and immunocompromised patients

¹Varki et al, ASCO 2016
| Case 1 | 79 years, male  
Risk factors: Radiation for acne and thyroid disease  
Tumor sites: Multifocal CSSC with ulcerations on right scalp and vertex, left fronto-temporal scalp, Cervical LN  
Brain metastases with axial skeleton involvement | Treatment history: Surgeries  
Capazolamide  
Erlotinib  
Radiation  
Carboplatin  
Paclitaxel  
Stretocenic radiosurgery*  
(brain)  
Pembrolizumab (Keytruda®)  
2 mg/kg, every 3 weeks  
Administration ongoing | Anti-PD1: Pembrolizumab (Keytruda®)  
2 mg/kg, every 3 weeks  
Administration ongoing | Response: PFS, OS | Side effects: Transient fatigue  
Transient brain edema  
ECOG status 1 | Remarks: |

| Case 2 | 69 years, male  
Chronic sun exposure  
Smoking  
Tumor sites: Multifocal CSSC with ulcerations of right hemifacel, left fronto-temporal region  
Invasion of axial skeleton  
Cervical LN | Treatment history: Surgeries  
Capazolamide  
Erlotinib  
Radiation  
Carboplatin  
Paclitaxel  
Capazolamide  
Radiation | Anti-PD1: Nirbulumab (Opdivo®)  
3 mg/kg, every 2 weeks  
Administration ongoing | Response: PR of skin ulcerations  
PR of brain mass  
PR of cervical LN  
PFS ≥ 7 months  
OS: NE | Side effects: ECOG status 1 | Remarks: |

| Case 3 | 61 years, female  
Liver transplanted Polychemotherapy  
Tumor sites: Basaloid-squamous carcinoma of left shoulder and axilla with infiltration of chest muscles and bones  
Lung metastases  
Cervical LN | Treatment history: Surgeries  
Radiation  
Vemuragib  
Paclitaxel  
Amputation of the arm  
Nab-paclitaxel  
Docetaxel | Anti-PD1: Nirbulumab (Opdivo®)  
3 mg/kg, every 2 weeks  
Total of 4 cycles in 10 weeks | Response: SD of lung metastatic nodules  
PFS: 8.5 months  
OS: 5.5 months | Side effects: Fatigue  
ECOG status 1  
Grade II hepatitis  
Deceased 5.5 months after initiation (bacterial pneumonia, ileus) | Remarks: |

| Case 4 | 69 years, male  
Chronic sun exposure  
Tumor sites: Multifocal CSSC on right shoulder  
LN involvement  
Axial and appendicular skeleton metastases  
Lung metastases | Treatment history: Surgeries  
Radiation  
Vemuragib  
Paclitaxel  
Docetaxel  
Capazolamide  
Paclitaxel  
Capazolamide  
Docetaxel | Anti-PD1: Nirbulumab (Opdivo®)  
3 mg/kg, every 2 weeks  
Total of 5 cycles in 8 weeks | Response: SD of multiple metastatic lung nodules  
PFS: 6 months  
OS: 6 months | Side effects: Weight loss  
Nausea, fatigue  
ECOG status 2  
Hypotension  
grade 1  
Discontinued 6 months after therapy start (anxietyemia) | Remarks: |

| Case 5 | 69 years, male  
HIV infection  
Tumor sites: CSSC with invasion of the left cheek and neck  
LN involvement | Treatment history: Surgeries  
Radiation  
Carboplatin  
Carboplatin  
Paclitaxel  
Carboplatin  
Carboplatin  
Paclitaxel  
Capazolamide  
Carboplatin  
Paclitaxel  
Radiation  
Pembrolizumab (Keytruda®)  
2 mg/kg, every 3 weeks  
Administration ongoing | Anti-PD1: Pembrolizumab (Keytruda®)  
2 mg/kg, every 3 weeks  
Administration ongoing | Response: SD of metastatic lung nodules  
PFS: 4.4 months  
OS: NE | Side effects: ECOG status 1  
HIV viral load undetectable | Remarks: |

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Borradori et al., *British J Derm*, 2016

Lipson et al., *NEJM*, 2016
Systemic therapy for MCC and SCC

Conclusions

• Immune checkpoint inhibitors showing promise in MCC
• Progress has been made in understanding the biology and mutational landscape of virus-positive and –negative MCC
• EGFR inhibitors a good and well-tolerated alternative to cytotoxic therapy for patients with R/M cutaneous SCC
• Role of immunotherapy for cutaneous SCC evolving