S008- Systemic Therapies for Medical Oncology

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Outline and Objectives

• Background: Systemic treatment of NMSC

• Special considerations in cancer patients

• Immune checkpoint inhibitors: safety and monitoring
When to consider systemic therapy?

- Basal cell carcinoma
- Squamous cell carcinoma

- Location/size
- Locally advanced
- Perineural
- Recurrent
- Metastatic
- Poorly differentiated
Background: Systemic therapy for BCC

PTCH inhibitors

- Vismodegib 150 mg daily (30-43% response)
- Sonidegib 200 mg daily (15-47% response)
- Sonidegib versus vismodegib
  - Longer PFS for sonidegib

Background: Systemic therapy for BCC

**PTCH inhibitors**

- AEs: fatigue, muscle cramps, GI, alopecia
  - Resolves in 1-3 months
- Many dose limiting toxicities
- Screening labs: pregnancy test
  - Sonidegib: CK, creatinine, LFTs

Background: Systemic therapy for cSCC

Cytotoxic chemotherapy

• Methotrexate
• Platinum-based therapies
• 5-fluorouracil
• Bleomycin
• Interferon

EGFR inhibitors

- Monoclonal antibodies (30-50% response)
  - Cetuximab
  - Panitumumab
- Small molecule inhibitors (10-20% response rate)
  - Erlotinib
  - Gefitinib

Background: Immune checkpoint inhibitors
Background: Immune checkpoint inhibitors
Immune Checkpoint Inhibitors

Melanoma
• BRAF inhibitors (vemurafenib, dabrafenib)
• MEK inhibitors (trametinib, cobimetinib, binimetinib)
• Immune checkpoint inhibitors (anti CTLA-4, anti PD-1, anti PD-L1)

Merkel cell carcinoma (rare tumor trials)
• PD-1/PD-L1 inhibitors
Immune checkpoint inhibitors

**CTLA4 inhibitors**
- Ipilimumab- Mar 2011, metastatic melanoma
- Tremelimumab- failed Phase III trials for melanoma, Phase I-III trials for various solid organ malignancies

**PD-1 inhibitors**
- Nivolumab- Dec 2014, metastatic melanoma
- Pembrolizumab- Sep 2014, metastatic melanoma
- Cemiplimab- Sep 2018, cutaneous squamous cell carcinoma

**PD-L1 inhibitors**
- Atezolizumab- May 2016, urothelial carcinoma
- Avelumab- March 2017, Merkel cell carcinoma
- Durvalumab- May 2017, urothelial carcinoma

**Combination therapy**
- Clinical trials, metastatic melanoma
PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

Immune Checkpoint Inhibitors for NMSC

**Cemiplimab**

350 mg IV Q3 weeks

- Phase I
  - 50% overall response rate
  - 65% durable response (> 105 days)

- Phase II
  - 47% overall response rate
  - 57% durable response (> 6 months)

Safety First!

- Cutaneous history
- Genetic history
- Oncology history
- Autoimmune history
- Current medications
Safety First!

- *Cutaneous history*
- Genetic history
- Oncology history
- Autoimmune history
- Current medications
- Inflammatory skin disease
- NMSC
- Melanoma
Safety First!

- Cutaneous history
- **Genetic history**
- Oncology history
- Autoimmune history
- Current medications
- P53
- BRCA2
- Muir-Torre/Lynch syndrome
Safety First!

- Cutaneous history
- Genetic history
- **Oncology history**
- Autoimmune history
- Current medications

- Primary malignancy
  - Myelodysplastic syndrome
  - CLL/SLL
  - Stem cell transplant

- Metastases
  - Hepatic
  - Renal

- Recent therapies
  - Bone marrow suppression
  - Risk of hemolysis
Safety First!

- Cutaneous history
- Genetic history
- Oncology history
- *Autoimmune history*
- Current medications
- Inflammatory bowel disease
- Connective tissue disease
- Inflammatory arthritis
- Interstitial lung disease
- Sarcoidosis
Safety First!

- Cutaneous history
- Genetic history
- Oncology history
- *Current medications*
  - Antimicrobials
    - Voriconazole
  - Immunosuppressants
  - Cancer therapy
    - EGFR inhibitors
    - BRAF inhibitors

*Everyone is immunosuppressed!!*
### Cemiplimab for cSCC Phase I and II trials

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<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO</th>
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<tr>
<td></td>
<td>N=163</td>
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<tr>
<td></td>
<td>All Grades %</td>
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<tr>
<td>Skin and Subcutaneous Tissue</td>
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</tr>
<tr>
<td>Rash*</td>
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</tr>
<tr>
<td>Pruritus†</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Fatigue‡</td>
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<tr>
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<td>Musculoskeletal pain*</td>
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<td>Metabolism and Nutrition</td>
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<td>Decreased appetite</td>
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https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761097s000lbl.pdf
Cemiplimab for cSCC Phase I and II trials

- Serious AEs (28%) of patients
  - Cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection
- Most common Grade 3-4 AEs (≥ 2%)
  - Cellulitis, sepsis, pneumonia, urinary tract infection
  - Hypertension, musculoskeletal pain, skin infection, and fatigue
- Permanently discontinued due to AE (5%)
  - Pneumonitis
  - Autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761097s000lbl.pdf
Adverse Events in Cemiplimab

• Phase I and II trials for cSCC
  – Deaths: none due to treatment-related adverse events
  – Serious AEs leading to discontinuation
    • Phase I: 2/26 (7.7%)
    • Phase II: 4/59 (6.8%)
• 534 patients on trial with cemiplimab for ALL indications

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<th>imARs</th>
<th>Incidence, %</th>
<th>Discontinuation rate, %</th>
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<tr>
<td>Pneumonitis</td>
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<td>Colitis</td>
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<td>Hepatitis</td>
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<td>Adrenal insufficiency</td>
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<td>Not reported (NR)</td>
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<td>Hypophysitis</td>
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<td>Hypothyroidism</td>
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<td>Dermatologic ARs</td>
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<td>Other imARs</td>
<td>&lt;1% for each</td>
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Safety Monitoring in ICPI

- CBC, CMP, TSH with infusions
- Team of specialists
  - Cardiology
  - GI
  - Pulmonology
  - Endocrinology
  - Rheumatology

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Future Directions for Inoperable NMSC

- Intralesional therapy
- Combination therapy
  - ICPI and radiation
  - Combination ICPI
- Neoadjuvant
- Adjuvant

- Human papilloma virus
  - Potentiates effects of UV
  - Increased in cutaneous SCC
- MicroRNAs
  - Suppress or upregulate expression of target genes
- Cyclin-dependent kinase 16 (CDK16)
  - Upregulated in cSCC
Ongoing Trials for Inoperable NMSC

- Cemiplimab (systemic and intralesional)
- Pembrolizumab (anti PD-1)
- CK-301 (anti PD-L1)
- Avelumab (anti PD-L1)
- Atezolizumab (anti PD-L1)

- SCC and BCC
Summary

• Systemic therapies for skin cancers are expanding
  – Toxicity profiles are decreasing

• Safety first!
  – Detailed history, lab review
  – Communication with oncology and support team