Oncodermatopathology
The intersection of medical oncology and dermatopathology

Michael T. Tetzlaff MD, PhD
Associate Professor
Departments of Pathology,
Section of Dermatopathology
and Translational and Molecular Pathology

Executive Officer
Translational Research Program
The Alliance for Clinical Trials

Jonathan L. Curry MD
Associate Professor
Departments of Pathology,
Section of Dermatopathology
Translational and Molecular Pathology
Dermatology

The University of Texas MD Anderson Cancer Center
Outline

• Cutaneous toxicities to immune checkpoint blockade therapy
  • Hypersensitivity
  • Lichenoid
  • Immunobullous diseases
    • Bullous Pemphigoid pattern
    • Paraneoplastic pemphigus pattern
    • Pemphigus pattern
  • Granulomatous/sarcoid infiltrates
  • Psoriasiform Reaction pattern
  • Reactivation of autoimmune diseases (SLE and DM)
  • Alterations in melanocytic nevi and pigmentary alterations
Immune checkpoints are natural brakes on the immune system:

- CTLA4 binds B7
- PD-L1 binds PD-1

Dampen immune response to limit tissue damage

Engagement of PD-L1 with its ligand PD-1:
- Inhibitory signals
- Reduced T-cell proliferation
- Reduced T-cell activity

Immune checkpoint antibody blockade relieves inhibitory signals, allowing continued propagation of the immune system against tumor antigens.
Immune checkpoint blockade in cutaneous malignancy

- Ipilumab (α-CTLA-4)
  Approved by FDA in 2011

- Nivolumab and Pembrolizumab (α-PD-1)
  Approved by FDA in 2014

- Avelumab (α-PD-L1)

Ipilimumab
Nivolumab
Pembrolizumab
Avelumab
Nivolumab improves survival in patients with metastatic melanoma

n=418 patients with metastatic melanoma
  • Previously untreated
  • No BRAF mutation

Nivolumab
3 mg/kg/2 weeks

Dacarbazine
3 weeks
Pembrolizumab improves survival in patients with metastatic melanoma

Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial

(Lancet Oncol 2015; 16: 908–18)


n=540 patients with ipilimumab metastatic melanoma
If BRAFV600E mutation, also BRAF/MEKi refractory

Pembrolizumab 2 mg/kg/2 weeks
Pembrolizumab 10 mg/kg/2 weeks
Investigator choice chemotherapy
Significance of cutaneous toxicities to oncologic therapies

- Skin often exhibits toxicity early in the course of therapy and is accessible.
- Indicator of response to therapy
  - Response to EGFR inhibitor therapy correlates with development and severity of skin rash
  - Response to immune checkpoint blockade correlates with pigmentary alteration
- Mimicker of disease recurrence
  - Panniculitis can mimic disease recurrence
- May require alteration of therapy
  - Bullous pemphigoid in immune checkpoint blockade
Cutaneous toxicity to immune checkpoint blockade

- Skin toxicity of any type and any grade
  - ~ 50-70% in patients receiving anti-CTLA-4
  - ~ 20-30% in patients receiving anti-PD-1/PD-L1
- Specific types of skin toxicity are being recognized with these antibody therapies
  - Inflammatory, immunobullous, panniculitis and regressing nevi
- Important to recognize these occur as they can potentially mimic disease recurrence or cause interruption in therapy
Cutaneous toxicity in immune checkpoint blockade: eczema, lichenoid, vitiligo
Common cutaneous reaction to oncology therapy: *Hypersensitivity reaction*

‘Morbilliform rash’
Cutaneous toxicities to PD-1 blockade more commonly biopsied

- Lichenoid
- Immunobullous (bullous pemphigoid)
- Panniculitis
Lichenoid dermatitis with PD-1 blockade

Present as indurated erythematous scaly patches and plaques that coalesce to plaques and are variably pruritic

Image courtesy of Susan Chon, MD.
Lichenoid dermatitis with PD-1 blockade

- Clinically distinct from benign lichenoid keratosis: single lesion (plaque)
- Clinically distinct from Lichen Planus: pruritic, polygonal, pruritic, purple papules

Image courtesy of Susan Chon, MD.
Lichenoid dermatitis with PD-1 blockade

5 patients had CPI withheld
2 patients treated with systemic steroids
Lichenoid Dermatitis

Histopathologically, these processes are indistinguishable from one another.
Clinically, these processes are generally distinguishable from one another.
55 yo woman with chemotherapy resistant ovarian serous carcinoma receiving Nivolumab.

After 3 cycles, she developed a widespread erythematous scaly and pruritic plaques on upper back, chest and neck.
Lichenoid dermatitis secondary to PD-1 inhibitor
66 yo man with BRAFV600E mutant anaplastic thyroid carcinoma, underwent surgical resection followed by vemurafenib, cobematinib and anti-PD-L1 (Atezolizumab). Patient tolerated regimen well with good response. After 11 cycles, he developed a 1.5 x 1.2 cm crusted erythematous scaly plaque on the abdomen.
Routine monthly dermatologic exam was then conducted, and the lesion on the abdomen progressively diminished in size. Approximately four months later, the patient developed a new 0.4 cm x 0.4 cm erythematous papule on the clavicle.
Lichenoid dermatitis with features of Mycosis Fungoides secondary to PD-1 inhibitor
Immunobullous disease with PD-1 blockade

- Bullous Pemphigoid is by far the commonest immunobullous toxicity from CPI
- Clinically and immunologically similar to bullous pemphigoid not associated with CPI
- Tense blisters on the extremities

Autoimmune dermatologic toxicities from immune checkpoint blockade with anti-PD-1 antibody therapy: a report on bullous skin eruptions

Immunobullous disease with PD-1 blockade
Direct Immunofluorescence (DIF) studies

Biopsy from patient’s peri-lesional skin

Add fluorescently labelled antibodies for α-complement (C3), α-IgG, α-IgA


Biopsy from patient’s peri-lesional skin

Add fluorescently labelled antibodies for α-complement (C3), α-IgG, α-IgA

Immunobullous disease with PD-1 blockade

α-ColIV
A total of 13 patients described:

- 9 Men: 4 Women
- Median age: 73 years (Range: 42-85y)
- Melanoma (n=8), Lung Adeno (n=2), SCC (n=2), Urothelial ca (n=1)
- Pembrolizumab (n=6), Nivolumab (n=6), Dirvalumab (n=1)
- Median time to diagnosis: 18 weeks (range: 6-84 weeks)
- Discontinuation of therapy: YES (n=5)
Case Example

75 yo man with recurrent metastatic SCC of the tongue. First treated with adjuvant chemoradiation. Seven years later, he developed recurrence and underwent surgical excision but with eventual disease progression including lymph node metastases.

Began pembrolizumab.
82 days after starting pembrolizumab, he developed erythematous plaques and tense blisters with erosions on the trunk, buttocks, and thighs. Of note, there was no oral or conjunctival ulceration.
• **DIF:**
  - Positive for IgG, IgA, C3 along basement membrane
  - Positive for IgG and C3 intercellular

• **Enzyme-linked immunosorbant assay (ELISA):**
  - anti-BP230 = 11.34 units (normal <9.0 units)
  - anti-BP180 = 5 units (normal <9.0 units)
Paraneoplastic pemphigus-like toxicity secondary to PD-1 inhibitor
Paraneoplastic Pemphigus

• The clinical manifestations of PNP are variable and subtypes
  – Pemphigus, BP, Erythema multiforme, Lichen planus-like
• Polymorphous blistering and non-blistering lesions seen clinically reflect the histopathology of PNP that includes either lichenoid/interface dermatitis with dyskeratosis and/or with a blister cavity
• Combined features of suprabasal acantholysis and dyskeratosis is suggestive of PNP
• The immunologic profile of PNP is complex with autoantibodies to: plakins, desmogleins, desmocollins, BP antigens, and alpha-2-macroglobulin-like protein
• DIF studies typically reveal multiple immunoglobulins (IgG, IgA, IgM, and C3) deposited (linear or granular) along the BMZ and/or intercellular space of epidermal keratinocytes
Granulomatous panniculitis with PD-1 blockade

- Granulomatous infiltrates common in the skin and lymph nodes of patients treated with CPI
- Clinically and radiographically mimic disease recurrence/progression
- Firm, indurated nodules
- Can be hypermetabolic
Granulomatous panniculitis with PD-1 blockade
Pembrolizumab-Induced Extensive Panniculitis and Nevus Regression: Two Novel Cutaneous Manifestations of the Post-immunotherapy Granulomatous Reactions Spectrum

JAMA Dermatology  July 2017  Volume 153, Number 7

Sara Burillo-Martínez, MD
Carlos Morales-Raya, MD
Marta Prieto-Barrios, MD
Jose-Luis Rodriguez-Peralto, MD, PhD
Pablo-Luis Ortiz-Romero, MD, PhD
39 year old Caucasian woman with history of stage III melanoma metastatic to the right axillary lymph node with a $\textit{BRAFV600E}$ mutation.

Enrolled in a clinical trial to receive ipilimumab and nivolumab in the neoadjuvant setting followed by surgical excision and single agent nivolumab.
Five months after surgery while on single agent nivolumab, she developed numerous painful subcutaneous nodules on her bilateral lower extremities, which progressively enlarged and were markedly $^{18}$F-FDG PET/CT avid.

Image courtesy of Omar Pacha, MD.
Five months after surgery while on single agent nivolumab, she developed numerous painful subcutaneous nodules on her bilateral lower extremities. These were $^{18}$F-FDG PET/CT avid.
Further work-up......

• Special stains (Gram/FITE/GMS) negative for bacterial (including acid-fast) and fungal organisms; cultures also negative.

• Immunohistochemical studies with an anti-melanocytic cocktail (HMB45, anti-MART1 and anti-tyrosinase) and antibodies for S100 and Sox-10 negative for metastatic melanoma

• No immunohistochemical evidence to support a subcutaneous T-cell or NK cell lymphoma.

• Further review of her chart:
  • No recent history of or clinical evidence to suggest recent/ongoing infection.
  • No history of (additional) recent changes in medication.
  • No evidence of pulmonary symptoms or hilar lymphadenopathy.
  • ACE levels within normal limits.
Pembrolizumab-Induced Extensive Panniculitis and Nevus Regression: Two Novel Cutaneous Manifestations of the Post-immunotherapy Granulomatous Reactions Spectrum

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Pembrolizumab-Induced Extensive Panniculitis and Nevus Regression: Two Novel Cutaneous Manifestations of the Post-immunotherapy Granulomatous Reactions Spectrum

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Granulomatous inflammatory infiltrate in skin/subcutis during immune checkpoint blockade: A rare but important mimicker of disease recurrence
• Median onset 24 weeks (3-85)
• Can impact lung, skin or both
• Can occur in setting of a variety of CPIs
• Mimic disease recurrence
• Marker of therapeutic response in ¾ of patients reviewed
Psoriasiform dermatitis with immune checkpoint blockade

Described 16 patients with non-lichenoid cutaneous irAE

- 5 psoriasiform, 3 Bullous Pemphigoid, 3 Grover’s like, 2 urticarial, 2 Granulomatous
- Median Age: 61.5 years (Range: 40-85), including 13 Men: 3 Women
- Three patients discontinued therapy, including 2 BP and 1 psoriasiform

5 patients with psoriasiform and spongiotic dermatitis.
Described 16 patients with non-lichenoid cutaneous irAE

- 5 psoriasiform, 3 Bullous Pemphigoid, 3 Grover’s like, 2 urticarial, 2 Granulomatous
- Median Age: 61.5 years (Range: 40-85), including 13 Men: 3 Women
- Three patients discontinued therapy, including 2 BP and 1 psoriasisform
Case Example

- An 80-year-old male with stage IIIIC cutaneous melanoma
- ~12 weeks after starting pembrolizumab therapy
- Presented with multiple pruritic, erythematous and well-demarcated plaques with adherent scales on his back, abdomen, scalp, and upper/lower extremities
Psoriasiform and Spongiotic Dermatitis Associated with Checkpoint Inhibitor Therapy

Cutaneous Eruptions in Patients Receiving Immune Checkpoint Blockade

Clinicopathologic Analysis of the Nonlichenoid Histologic Pattern

(Am J Surg Pathol 2017;41:1381–1389)

Genevieve J. Kaunitz, BA, MD,* Manisha Loss, MD,* Hira Rizvi, BA,† Sowmya Ravi, MD,* Jonathan D. Cuda, MD,* ‡ Karen B. Bleich, MD,§ Jessica Esandrio, BA,* Inbal Sander, MD,* Dung T. Le, MD,§ Luis A. Diaz, Jr, MD,§ Julie R. Brahmer, MD,§ Charles G. Drake, MD, PhD,§ Travis J. Hollmann, MD, PhD,§ Mario E. Lacouture, MD,§ Matthew D. Hellmann, MD,† Evan J. Lipson, MD,§ and Janis M. Taube, MD,* §§
Psoriasiform dermatitis with immune checkpoint blockade

*Treat with IL-17 inhibitors*

Key point: Uncouple the pathway driving the immune related adverse event from the efficacious pathways driving the anti-tumor response.

54 year old man with stage IV metastatic melanoma

- NO prior history of autoimmune disease
- Initiated on pembrolizumab
- Three months later, developed colitis and eventually cholecystitis
- Pembrolizumab withheld peri-operatively
- Nearly 2.5 months after last dose of pembrolizumab, he developed an erythematous non-pruritic eruption of edematous papules coalescing into plaques on back, chest, lateral arms, thighs and abdomen
Autoimmune disease after immune checkpoint blockade
Case Example

74 yo man with prior Adenocarcinoma of left lung S/P lobectomy now with new Squamous cell carcinoma of the lung receiving Pembrolizumab.

After 1\textsuperscript{st} infusion cycles, he noted a rash, facial redness and swelling.

Exam revealed
• Erythematous plaques and violaceous macules forming a violaceous rash on the abdomen, upper back, chest.
• Purple discoloration on the face and periorbital swelling with purple discoloration around the eyes.
• Coalescent erythematous papules and plaques on the bilateral thighs
• Coalescent violaceous papules and plaques on the dorsal hands.
Case Example
Reactivation of connective tissue disease (Dermatomyositis) secondary to PD-1 inhibitor
Pigmentary alterations in the context of immune checkpoint blockade
Mart-1/Ki-67
Pigmentary alterations in the context of immune checkpoint blockade

- 50 yo man with pT2a MM on R thigh.
- WLE and SLN-
- Disease progression @7 mos in inguinal LN→lung→CNS. Treated with MAGE-A3 + AS15→Dacarbazine→Ipi.
- During Ipi, nevi began to involute.
49 year old Caucasian woman with primary cutaneous melanoma in 1989. Presented in 2016, she presented with multifocal metastases to the head and neck, breast, chest, abdomen, pelvis, legs, left lung, adrenal glands, right femur, and brain. Received 5 doses pembrolizumab (mg/kg @ 3 weeks).

She began protocol 2015-0696: ‘A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain treated with Nivolumab in Combination with Ipilimumab followed by Nivolumab Monotherapy’. After 2 years on therapy, patient notes depigmentation of scalp, eyebrow and pubic hair as well as pigmentary alteration on bilateral arms.
α-HMB-45/tyrosinase
Pigment alterations during immune checkpoint blockade: *Regression of nevi and vitiligo*

Regressed melanocytic nevi secondary to pembrolizumab therapy: an emerging melanocytic dermatologic effect from immune checkpoint antibody blockade

Shakuntala H. Mauzo, MD, Michael T. Tetzlaff, MD, PhD, Kelly Nelson, MD, Rodabe Amaria, MD, Sapna Patel, MD, Phyua P. Aung, MD, PhD, Priyadharshini Nagarajan, MD, PhD, Carlos A. Torres-Cabala, MD, Adi Diab, MD, Victor G. Prieto, MD, PhD, and Jonathan L. Curry, MD


<table>
<thead>
<tr>
<th>Melanocytic dermatologic effect</th>
<th>Anti-PD-1&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Anti-PD-L1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Anti-CTLA-4&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Primary tumor</th>
<th>References</th>
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<tr>
<td>Vitiligo</td>
<td>132&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5</td>
<td>18</td>
<td>Melanoma</td>
<td>1,11,13,20-24, 29</td>
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<td>New nevi</td>
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<td>NR</td>
<td>NR</td>
<td>Melanoma</td>
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<td>Regression of nevi/lesion</td>
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<td>NR</td>
<td>1</td>
<td>Melanoma</td>
<td>31, current report</td>
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<td>Pigmentary alteration</td>
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<td>NR</td>
<td>Melanoma</td>
<td>21,23</td>
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<td>Tumoral melanosis</td>
<td>NR</td>
<td>NR</td>
<td>9</td>
<td>Melanoma</td>
<td>10,25,26</td>
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<td>Melanoma, primary or metastasis</td>
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<td>NR</td>
<td>NR</td>
<td>Melanoma</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>5</td>
<td>28</td>
<td>Melanoma (96%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Other cancer types<sup>d</sup> (NSCLC and RCC)
Outline

• Cutaneous toxicities to oncology therapy
  • EGFR inhibitor therapy
  • BRAF inhibitor therapy
    • Cutaneous epithelial proliferations
    • Neutrophilic dermatoses/panniculitides
    • Changes in melanocytic nevi
  • Immune checkpoint blockade
    • Hypersensitivity
    • Lichenoid
    • Immunobullous diseases
      • Bullous Pemphigoid pattern
      • Paraneoplastic pemphigus pattern
      • Pemphigus pattern
    • Granulomatous/sarcoid infiltrates
    • Psoriasiform Reaction pattern
    • Reactivation of autoimmune diseases (SLE and DM)
    • Alterations in melanocytic nevi and pigmentary alterations

• Significance of cutaneous toxicity to immune checkpoint blockade
• Molecular studies to determine pathways driving cutaneous toxicities to immune checkpoint blockade
  • GOAL: Uncouple the toxicity from the tumor directed immune activation
Clinical significance of cutaneous immune related adverse events: Correlates with improved progression free survival

- 83 patients on a-PD-1 pembrolizumab
- 35 (42%) developed a cutaneous irAE (maculopapular eruption, pruritus and vitiligo)
Clinical significance of cutaneous immune related adverse events: Correlates with improved progression free survival

- 148 patients on two α-PD-1 nivolumab trials:
  - Nivo + peptide vaccine resectable IIIC/IV (n=33)
  - Nivo + peptide vaccine unresectable III/IV (n=115)
- 18 (55%) resectable and 46 (40%) unresectable patients developed a cutaneous maculopapular eruption

- Patients who developed an irAE showed improved OS compared to those who did not.
- NOT dose dependent
Clinical significance of cutaneous immune related adverse events: Correlates with improved progression free survival

- 148 patients on two α-PD-1 nivolumab trials:
  - Nivo + peptide vaccine resectable IIIC/IV (n=33)
  - Nivo + peptide vaccine unresectable III/IV (n=115)
- 18 (55%) resectable and 46 (40%) unresectable patients developed a cutaneous maculopapular eruption

- Patients who developed a rash or vitiligo showed improved OS compared to those who did not.
- NOT dose dependent
Clinical significance of cutaneous immune related adverse events: Correlates with improved progression free survival

- 137 studies identified
  - General immune stimulation (n=11)
  - Vaccines (n=84)
  - Antibody based (n=28)
  - Adoptive transfer (n=16)
Thank you!

Department of Pathology, Section of Dermatopathology, MDACC
- Victor G. Prieto MD, PhD
- Carlos A. Torres-Cabala MD
- Doina Ivan MD
- Priyadharsini Nagarajan MD, PhD

Department of Melanoma Medical Oncology
- Michael A Davies MD, PhD
- Roda Amaria MD
- Hussein Tawbi MD

Department of Surgical Oncology
- Jennifer A. Wargo MD
What are unique immune drivers of cutaneous irAEs? 
Transcriptional and immune profiling identifies markers of innate immunity.
• Nanostring RNA expression profiling 770 genes
• Significant log$_2$ fold difference in 167 genes

• 74 mRNA transcripts up-regulated
• 93 mRNA transcripts down-regulated

Increased expression of CD14 in LD irAE compared to BLK

- LD irAE exhibits a unique mRNA and protein expression profile from BLK despite a similar histology.
- Dysregulation of normal skin homeostasis and immune functions
  - Recruitment of unique CD14+ → potent antigen presenting cell
  - Possible role for innate immunity
  - Toll-like receptors and complement also increased in LD irAE compared to BLK
Differential diagnosis: Sub-epidermal bullous disease

- Porphyria Cutanea Tarda
- Acute graft versus host disease
- Burn related bulla
- Suction blister
- Erythema multiforme
- Lichen sclerosus
- Bullous drug eruption
- Bullous insect bite eruption

- Bullous Pemphigoid (BP)
- Cicatricial Pemphigoid
- Epidermolysis Bullosa Acquisita (EBA)
- Bullous Lupus Erythematosus
- Anti p200 pemphigoid
- Dermatitis Herpetiformis (DH)
- Linear IgA disease
Differential diagnosis: Sub-epidermal bullous disease

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Differential diagnosis: Sub-epidermal bullous disease

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- Cicatricial Pemphigoid
- Epidermolysis Bullosa Acquisita (EBA)
- Bullous Lupus Erythematosus
- Anti p200 pemphigoid
- Dermatitis Herpetiformis (DH)
Indirect Immunofluorescence studies: “SALT SPLIT” skin

1.0 M NaCl
Add patient serum
Add fluorescent α-IgG

Salt split image courtesy of Dr. Ryan Hick, MD, Propath Labs.
Indirect Immunofluorescence studies: “SALT SPLIT” skin

1.0 M NaCl
Add patient serum
Add fluorescent α-IgG

Salt split image courtesy of Dr. Ryan Hick, MD, Propath Labs.
<table>
<thead>
<tr>
<th>Dermatologic Toxicity</th>
<th>No. Cases</th>
<th>M:F</th>
<th>Age (range)</th>
<th>Immune Checkpoint Antibody</th>
<th>Primary Disease</th>
<th>Onset of DT in Months (range)</th>
<th>Treatment</th>
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<tr>
<td>Lichenoid dermatitis</td>
<td>34</td>
<td>9:8</td>
<td>67 (18-83)</td>
<td>Nivo=8 Pembro= 7 anti-PD-1 =16 anti-PD-L1=3</td>
<td>Melanoma=24 NSCLC=4 Urothelial CA=3 Other=3</td>
<td>3 (&lt;1 to 9)</td>
<td>Topical steroids ±systemic</td>
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<tr>
<td>Bullous pemphigoid</td>
<td>12</td>
<td>7:3</td>
<td>73 (63:85)</td>
<td>Nivo=6 Pembro=3 anti-PD-L1=1 NS=2</td>
<td>Melanoma=5 NSCLC=2 Urothelial CA=2 Other=3</td>
<td>6 (&lt;1 to 21)</td>
<td>Systemic steroids ± topical</td>
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<tr>
<td>Regressed nevi</td>
<td>3</td>
<td>3:0</td>
<td>70 (50-82)</td>
<td>Pembro=2 Ipi=1</td>
<td>Melanoma=3</td>
<td>7 (4-12)</td>
<td>Biopsy or excision</td>
</tr>
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</table>
Cutaneous toxicity to EGFR-inhibitor

- EGFR is a transmembrane protein that transmits mitogenic signals via intracellular tyrosine kinase domain

- Anti-EGFR inhibitors
  - Monoclonal antibodies to EGFR: centuximab, panitumumab
  - Small molecular inhibitor: erlotinib, gefitinib
  - Dual kinase inhibitors: lapatinib, neratinib, afatinib

- EGFR expressed in skin and skin adnexal structures

- Most common reactions to EGFR inhibitors
  - Papulopustular eruption
  - Xerosis
  - Changes in hair and nails
  - Mucositis
Papulopustular eruption to EGFR-inhibitor

- Reported in up to 90% of patients on EGFRi
  - Most develop within 1-2 weeks of initiating therapy
  - Dose dependent
  - More severe with monoclonal antibodies than small molecular inhibitors
  - Severity of rash correlated with response to therapy
    - Marker of therapeutic efficacy

- Follicular papules/pustules on T-zone of face or seborrheic areas, scalp, and upper trunk
Papulopustular eruption to EGFR inhibitors
Other changes due to EGFR-inhibitor

- **Paronychia**
  - 20% of treated patients
  - Involvement of thumbs and big toes, predominant
  - Develops after 4-8 weeks of treatment

- **Alopecia**
  - Seen in 5% of treated patients
  - Late toxicity, occurs months after EGFRi therapy
  - Non-scarring or scarring alopecia

- **Hand and foot skin reaction (HFSR)**
  - Common with class II EGFRi therapy and with multi-kinase inhibitors (e.g. sorafenib)
  - Skin fissures

- **Trichomegaly**
- **Xerosis**

Cutaneous reaction to EGFR-inhibitor therapy  
A marker of therapeutic efficacy

Determinants of Tumor Response and Survival With Erlotinib in Patients With Non–Small-Cell Lung Cancer

Table 6. Univariate and Multivariate Analyses to Predict Survival Including Rash

Factors | Univariate P | Multivariate P | HR | 95% CI
--- | --- | --- | --- | ---
Factors in the final model
Rash, grade 2/3, grade 2/3 v no rash | < .0001 | < .0001 | 0.05 | 0.02 to 0.15
Rash, grade I, grade I v no rash | < .0001 | < .0001 | 0.13 | 0.06 to 0.30
Age, ≥ 70 v < 70 years | .12 | .017 | 2.30 | 1.16 to 4.58
Time from last chemotherapy, < 6 v ≥ 6 months | .007 | .038 | 0.44 | 0.20 to 0.96
Stage of disease, IIIB v IV | .52 | .057 | 0.45 | 0.20 to 1.02
Factors not in the final model
ECOG performance status, 0, 1, 2 | .019 | .40
Histology, adenocarcinoma v other | .69 | .48
HER1/EGFR staining intensity, weak, weak/strong, strong | .91 | .50
Sex, male v female | .48 | .52
No. of prior chemotherapy regimens, 1 v ≥ 2 | .91 | .74
Time since initial diagnosis, < 12 months v ≥ 12 months | .0001 | .81

Grade of Rash | No. of Pts | Median (95% CI) Months
--- | --- | ---
0 | 14 | 1.5 (1-2.2)
1 | 26 | 8.5 (4.8-14.8)
2/3 | 17 | 19.6 (10.8+)
P (0 v 1) < .0001
P (0 v 2/3) < .0001
P (0 v 2/3) = .018