Management of Dermatologic Adverse Reactions Associated With EGFR-Inhibitor Therapy
Skin Structure and Epidermal Changes With EGFR-Inhibitor Therapy
Structure of the Skin and Hair Follicle

- The skin is composed of 3 layers (epidermis, dermis, hypodermis)\(^1\)

- The epidermis is composed of keratinocytes (~90% of cells) that express EGFR at the highest concentration in the basal and suprabasal layers\(^1\)

- The outer root of the hair follicle is contiguous with the basal layer and shares biochemical properties and high EGFR expression\(^1\)

Reference

Epidermal Changes With EGFR-Inhibitor Therapy: Pretreatment

- Basal cells show EGFR expression and normal levels of downstream signal proteins (MAPK) and proliferation markers (K167)\(^1\)
- Suprabasal cells show expression of EGFR and proteins associated with the terminal differentiation of keratinocytes (KRT1, STAT3, p27)\(^1\)

Reference


Epidermal Changes With EGFR-Inhibitor Therapy: During Treatment

- Inhibition of phosphorylated EGFR and reduced MAPK expression\(^1\)
- Leads to growth arrest and premature differentiation\(^1\)
  - Exemplified by increased expression of differentiation proteins in the basal layer


Reference
Epidermal Changes With EGFR-Inhibitor Therapy: Abnormal Structure

- Epidermal thinning¹
  - A marked decrease in epidermal thickness is observed, resulting in a thin stratum corneum lacking the characteristic basket-weave structure

Reference
Model of EGFR-Inhibitor–Induced Reactions

EGFR Inhibition

- Growth, migration arrest, and apoptosis
- Inflammatory cell recruitment
- Chemokine expression
- Abnormal maturation and differentiation
- Cutaneous injury
  - Tenderness
  - Papulopustules
  - Periungual inflammation
  - Hair & nail plate disturbance
  - Xerosis & pruritus


Reference
Dermatologic Toxicities: Clinical Presentation and Potential Contributing Factors
Appearance of Papulopustular Rash

- Often described as acneiform based on its appearance\(^1\)
- The rash does **not** share the clinical or histologic features of acne vulgaris\(^1\)
  - Does not present with comedones (blackheads)
  - Lesions are typically itchy
  - Responds to anti-inflammatory drugs, **not** to anti-acne agents
  - May affect areas such as lower legs and dorsal arms

Reference

Other Key Rash-Related Terms

Crusts:
- When serum, blood, or pus dries on the skin surface, hardened deposits known as crusts are formed. They are yellow when derived from serum, or yellow-green-brown when derived from pus. Crusts may form when papulopustules dry out.¹

Papule:
- A small, solid, rounded lesion that arises from the skin and is usually less than 5 mm in diameter. This elevation is due to metabolic deposits or the accumulation of cells.¹

Pustule:
- A small amount of purulent exudate in the top layer of skin (epidermis) or just beneath it in the dermis. Pustules frequently form in sweat glands or hair follicles. Pus is composed of leukocytes and can either contain cellular debris or bacteria, or be sterile.¹

Reference
Potential Contributing Factors in Papulopustular Rash Formation: Skin Type

- Severity of rash may be associated with skin phototype
- There are 6 skin types as they pertain to sensitivity to UV radiation:

<table>
<thead>
<tr>
<th>Skin Phototype</th>
<th>Typical Features</th>
<th>Tanning Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pale white skin, blue/hazel eyes, blond/red hair</td>
<td>Always burns, does not tan</td>
</tr>
<tr>
<td>II</td>
<td>Fair skin, blue eyes</td>
<td>Burns easily, tans poorly</td>
</tr>
<tr>
<td>III</td>
<td>Darker white skin</td>
<td>Tans after initial burn</td>
</tr>
<tr>
<td>IV</td>
<td>Light brown skin</td>
<td>Burns minimally, tans easily</td>
</tr>
<tr>
<td>V</td>
<td>Brown skin</td>
<td>Rarely burns, tans darkly easily</td>
</tr>
<tr>
<td>VI</td>
<td>Dark brown or black skin</td>
<td>Never burns, always tans darkly</td>
</tr>
</tbody>
</table>

Adapted with permission from Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988;124:869-871.

References
1. Luu M, et al. Poster presented at: ASCO; June 1-5, 2007; Chicago, IL.
Potential Contributing Factors in Papulopustular Rash Formation Based on a Limited Number of Case Reports: UV Exposure/Photosensitivity

- Rash may be more severe in areas of skin exposed to sunlight\(^1\)

Severe Sunburn on Hands After Minimal Sun Exposure\(^2\)

![Severe sunburn on hands](image1.png)

Photo used with permission from Mario Lacouture, MD.


Sunscreen Applied to Face & Neck\(^2\)

![Sunscreen applied to face and neck](image2.png)

References
ERBITUX® (cetuximab)
Injection for intravenous infusion

Related Rash
ERBITUX (cetuximab) Indications for Head and Neck Cancer

- ERBITUX® (cetuximab), in combination with radiation therapy, is indicated for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN)
- ERBITUX is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck
- ERBITUX, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Indications for Colorectal Cancer

ERBITUX is indicated for the treatment of KRAS mutation-negative (wild-type), epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use:

- in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan

Limitation of Use: ERBITUX is not indicated for treatment of KRAS mutation-positive colorectal cancer

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Important Safety Information: Boxed WARNING: Infusion Reactions

IMPORTANT SAFETY INFORMATION

Infusion Reactions

- Grade 3/4 infusion reactions occurred in approximately 3% of patients receiving ERBITUX® (cetuximab) in clinical trials, with fatal outcome reported in less than 1 in 1000
  - Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of ERBITUX, included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest
  - Immediately interrupt and permanently discontinue ERBITUX infusions for serious infusion reactions

- Approximately 90% of the severe infusion reactions were associated with the first infusion of ERBITUX despite premedication with antihistamines
  - Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions
  - Monitor patients for 1 hour following ERBITUX infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Longer observation periods may be required in patients who require treatment for infusion reactions

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients with squamous cell carcinoma of the head and neck treated with radiation therapy and ERBITUX, as compared to none of 212 patients treated with radiation therapy alone. In 3 patients with prior history of coronary artery disease, death occurred 27, 32, and 43 days after the last dose of ERBITUX. One patient with no prior history of coronary artery disease died one day after the last dose of ERBITUX. Fatal cardiac disorders and/or sudden death occurred in 7 (3%) of the 219 patients with squamous cell carcinoma of the head and neck treated with platinum-based therapy with 5-fluorouracil (5-FU) and Union (EU)-approved cetuximab as compared to 4 (2%) of the 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin.

- Carefully consider the use of ERBITUX in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks
- Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium during and after ERBITUX therapy

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Important Safety Information: Pulmonary Toxicity

Pulmonary Toxicity

- Interstitial lung disease (ILD), which was fatal in one case, occurred in 4 of 1570 (<0.5%) patients receiving ERBITUX in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Important Safety Information: Dermatologic Toxicities

Dermatologic Toxicities

In clinical studies of ERBITUX, dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (e.g., *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis, occurred in patients receiving ERBITUX therapy. Acneiform rash occurred in 76-88% of 1373 patients receiving ERBITUX in Studies 1, 3, 5, and 6. Severe acneiform rash occurred in 1-17% of patients.

- Acneiform rash usually developed within the first 2 weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days.
- Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae.
- Sun exposure may exacerbate these effects.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Important Safety Information: ERBITUX Plus Radiation Therapy and Cisplatin

ERBITUX (cetuximab) Plus Radiation Therapy and Cisplatin

- In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3-4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone.

- Adverse reactions with fatal outcome were reported in 20 patients (4.4%) in the ERBITUX combination arm and 14 patients (3.0%) in the control arm.

- Nine patients in the ERBITUX arm (2.0%) experienced myocardial ischemia compared to 4 patients (0.9%) in the control arm.

- The addition of ERBITUX to radiation and cisplatin did not improve progression-free survival (the primary endpoint).

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Electrolyte Depletion

Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in Study 5 and two other clinical trials in colorectal cancer and head and neck cancer, respectively, and was severe (NCI CTC grades 3 & 4) in 6-17%. In Study 2 the addition of EU-approved cetuximab to cisplatin and 5-FU resulted in an increased incidence of hypomagnesemia (14% vs 6%) and of grade 3–4 hypomagnesemia (7% vs 2%) compared to cisplatin and 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs 4%). No patient experienced grade 3–4 hypomagnesemia in either arm in the carboplatin subgroup. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of ERBITUX therapy.

- Monitor patients periodically for hypomagnesemia, hypocalcemia and hypokalemia, during, and for at least 8 weeks following the completion of, ERBITUX therapy
- Replete electrolytes as necessary
**ERBITUX (cetuximab) Important Safety Information: Late Radiation Toxicities**

Late Radiation Toxicities

- The overall incidence of late radiation toxicities (any grade) was higher with ERBITUX in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% vs 56%), larynx (52% vs 36%), subcutaneous tissue (49% vs 45%), mucous membranes (48% vs 39%), esophagus (44% vs 35%), and skin (42% vs 33%) in the ERBITUX and radiation versus radiation alone arms, respectively.
- The incidences of grade 3 or 4 late radiation toxicities were similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms.

Please see Full Prescribing Information including **Boxed WARNINGS** provided at this presentation.
ERBITUX (cetuximab) Important Safety Information:
Pregnancy and Nursing

Pregnancy and Nursing

- In women of childbearing potential, appropriate contraceptive measures must be used during treatment with ERBITUX and for 6 months following the last dose of ERBITUX. ERBITUX may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. ERBITUX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

- It is not known whether ERBITUX is secreted in human milk. IgG antibodies, such as ERBITUX, can be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ERBITUX, a decision should be made whether to discontinue nursing or to discontinue ERBITUX, taking into account the importance of ERBITUX to the mother. If nursing is interrupted, based on the mean half-life of cetuximab, nursing should not be resumed earlier than 60 days following the last dose of ERBITUX.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Important Safety Information: Adverse Reactions

Adverse Reactions

- The most **serious adverse reactions** associated with ERBITUX are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

- The most common adverse reactions associated with ERBITUX (incidence ≥25%) across all studies were cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

- The most frequent adverse reactions seen in patients with carcinomas of the head and neck receiving ERBITUX in combination with radiation therapy (n=208) versus radiation alone (n=212) (incidence ≥50%) were acneiform rash (87% vs 10%), radiation dermatitis (86% vs 90%), weight loss (84% vs 72%), and asthenia (56% vs 49%). The most common grade 3/4 adverse reactions for ERBITUX in combination with radiation therapy (≥10%) versus radiation alone included: radiation dermatitis (23% vs 18%), acneiform rash (17% vs 1%), and weight loss (11% vs 7%).

Please see Full Prescribing Information including **Boxed WARNINGS** provided at this presentation.
Adverse Reactions

The most frequent adverse reactions seen in patients with carcinomas of the head and neck receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU (CT) (n=219) versus CT alone (n=215) (incidence ≥40%) were acneiform rash (70% vs 2%), nausea (54% vs 47%), and infection (44% vs 27%). The most common grade 3/4 adverse reactions for cetuximab in combination with CT (≥10%) versus CT alone included: infection (11% vs 8%). Since U.S.-licensed ERBITUX provides approximately 22% higher exposure relative to the EU-approved cetuximab, the data provided above may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX.
ERBITUX (cetuximab) Important Safety Information: Adverse Reactions (cont’d)

Adverse Reactions

- The most frequent adverse reactions seen in patients with KRAS mutation-negative (wild-type), EGFR - expressing metastatic colorectal cancer treated with EU-approved cetuximab + FOLFIRI (n=317) versus FOLFIRI alone (n=350) (incidence ≥50%) were acne-like rash (86% vs 13%) and diarrhea (66% vs 60%). The most common grade 3/4 adverse reactions (≥10%) included: neutropenia (31% vs 24%), acne-like rash (18% vs <1%), and diarrhea (16% vs 10%). U.S.-licensed ERBITUX provides approximately 22% higher exposure to cetuximab relative to the EU-approved cetuximab. The data provided above are consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication. The tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Adverse Reactions

The most frequent adverse reactions seen in patients with KRAS mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer treated with ERBITUX + best supportive care (BSC) (n=118) versus BSC alone (n=124) (incidence ≥50%) were rash/desquamation (95% vs 21%), fatigue (91% vs 79%), nausea (64% vs 50%), dry skin (57% vs 15%), pain-other (59% vs 37%), and constipation (53% vs 38%). The most common grade 3/4 adverse reactions (≥10%) included: fatigue (31% vs 29%), pain-other (18% vs 10%), rash/desquamation (16% vs 1%), dyspnea (16% vs 13%), other-gastrointestinal (12% vs 5%), and infection without neutropenia (11% vs 5%)

The most frequent adverse reactions seen in patients with EGFR-expressing metastatic colorectal cancer (n=354) treated with ERBITUX plus irinotecan in clinical trials (incidence ≥50%) were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3/4 adverse reactions (≥10%) included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%)

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
## Dosing and Administration for Head and Neck Cancer

### Locally or Regionally Advanced Head and Neck Cancer*†1,2

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERBITUX (cetuximab) 400 mg/m² loading dose</td>
<td>ERBITUX 250 mg/m² (week 1-7)</td>
<td>RT: 6-7 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ERBITUX**

**400 mg/m² loading dose**

**ERBITUX 250 mg/m² (week 1-7)**

### Recurrent/Metastatic Head and Neck Cancer1

<table>
<thead>
<tr>
<th>ERBITUX 400 mg/m² loading dose</th>
<th>ERBITUX 250 mg/m² weekly Until Disease Progression or Unacceptable Toxicity</th>
</tr>
</thead>
</table>

RT=radiation therapy.

*The radiation regimen to be used with ERBITUX is at the discretion of the treating physician.

†Complete ERBITUX administration 1 hour prior to RT.

### References

1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including **Boxed WARNINGS** provided at this presentation.
In colorectal cancer, the dosing schema is the same for ERBITUX (cetuximab), whether used in combination with irinotecan or as a single agent

Maximum infusion rate for ERBITUX is 10 mg/min

Reference
1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Recommended Premedication and Dosing Modifications for Infusion Reactions

- **Recommended Premedication:**
  - Premedicate with an H₁ antagonist (eg, 50 mg of diphenhydramine) IV 30-60 minutes prior to the first dose¹
    - Premedication should be administered for subsequent doses based upon clinical judgment and presence/severity of prior infusion reactions¹

- **Dosing Modifications for Infusion Reactions:**
  - Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3 infusion reactions¹
  - Immediately and permanently discontinue ERBITUX for serious infusion reactions, requiring medical intervention and/or hospitalization¹

**Reference**
1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including **Boxed WARNINGS** provided at this presentation.
ERBITUX (cetuximab): Incidence of Dermatologic Toxicities in ≥10% of H&N Patients

<table>
<thead>
<tr>
<th>Patients With Locoregionally Advanced SCCHN ≥10% of Patients (%)¹,²</th>
<th>ERBITUX Plus Radiation (n = 208)</th>
<th>Radiation Therapy Alone (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Acneiform Rash*</td>
<td>87</td>
<td>17</td>
</tr>
<tr>
<td>Radiation Dermatitis</td>
<td>86</td>
<td>23</td>
</tr>
<tr>
<td>Application Site Reaction</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

*Acneiform rash was defined as “acne,” “rash,” “maculopapular rash,” “pustular rash,” “dry skin,” or “exfoliative dermatitis.”

References
1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
ERBITUX (cetuximab) Plus Radiation Therapy and Cisplatin

In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3-4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone.

Adverse reactions with fatal outcome were reported in 20 patients (4.4%) in the ERBITUX combination arm and 14 patients (3.0%) in the control arm.

Nine patients in the ERBITUX arm (2.0%) experienced myocardial ischemia compared to 4 patients (0.9%) in the control arm.

The addition of ERBITUX to radiation and cisplatin did not improve progression-free survival (the primary endpoint).

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Late Radiation Toxicities

The overall incidence of late radiation toxicities (any grade) was higher with ERBITUX in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% vs 56%), larynx (52% vs 36%), subcutaneous tissue (49% vs 45%), mucous membranes (48% vs 39%), esophagus (44% vs 35%), and skin (42% vs 33%) in the ERBITUX and radiation versus radiation alone arms, respectively.

- The incidence of grade 3 or 4 late radiation toxicities were similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
# ERBITUX (cetuximab): Incidence of Dermatologic Toxicities in Advanced CRC

## Patients With Advanced CRC ≥10% of Patients (%)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>ERBITUX + BSC (n = 288)</th>
<th>BSC Alone (n = 274)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Rash/ Desquamation</td>
<td>89</td>
<td>12</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>Other-Dermatology</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Nail Changes</td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

**Reference**
1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including **Boxed WARNINGS** provided at this presentation.
Dermatologic toxicity is one of the most serious adverse reactions associated with ERBITUX.

Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae.

Instruct patients to limit sun exposure during ERBITUX therapy.
Duration of Severe Rash

- Severe acneiform rash occurred in 1-17% of 1373 patients
- Acneiform rash may occur a few days after the start of therapy, but most commonly developed within the first 2 weeks of therapy and resolved in a majority of patients after cessation of therapy. However, in nearly half, the event continued beyond 28 days

References
2. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including **Boxed WARNINGS** provided at this presentation.
Acneiform Rash Is Generally Reversible Over Time

- Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of cases, the event continued beyond 28 days¹
  - Dermatologic toxicity is one of the most serious adverse reactions associated with ERBITUX.

Reference
1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Assessment, Grading, and Management Strategies for Dermatologic Toxicities
## Grading Dermatologic Adverse Reactions Associated With EGFR-Inhibitor Therapy

### NCI-CTCAE Version 4.0: Relevant Dermatologic Toxicities

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dry Skin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covering &lt;10% BSA and no associated erythema or pruritus</td>
<td>Covering 10-30% BSA and associated erythema or pruritus, limiting instrumental ADL*</td>
<td>Covering &gt;30% BSA and associated with pruritus; limiting self-care ADL†</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

| **Paronychia** | | | | |
| Nail fold edema or erythema; disruption of the cuticle | Localized intervention indicated; oral intervention indicated (eg, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL | Surgical intervention or IV antibiotics indicated; limiting self-care ADL | — | — |

| **Pruritus** | | | | |
| Mild or localized; topical intervention indicated | Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts), oral intervention indicated; limiting instrumental ADL | Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated | — | — |

NCI-CTCAE=National Cancer Institute-Common Toxicity Criteria for Adverse Events; BSA=body surface area.

*Instrumental activities of daily living (ADLs) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

**Reference**

## Grading Dermatologic Adverse Reactions Associated With EGFR-Inhibitor Therapy (cont’d)

### NCI-CTCAE Version 4.0: Relevant Dermatologic Toxicities

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rash acneiform</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papules and/or pustules covering &lt;10% BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL</td>
<td>Papules and/or pustules covering &gt;30% BSA, which may or may not be associated with symptoms of pruritus and/or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus and/or tenderness and associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences</td>
<td>Death</td>
</tr>
<tr>
<td><strong>Dermatitis radiation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema</td>
<td>Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
<td>Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

### Reference

Alternative Grading Recommendations

- A recent forum of medical professionals put together an alternate grading system for EGFR-inhibitor–associated rash.
- The recommendations shown here should not be interpreted as evidence-based guidelines, as there are currently no existing consensus guidelines in managing rash caused by EGFR inhibitors.
- These severity criteria are not derived from the NCI-CTC and are based solely on the authors’ clinical experience.
- This information is not meant to substitute your own medical assessment.
- The ERBITUX (cetuximab) Prescribing Information recommends monitoring patients for dermatologic toxicities and infectious sequelae, instructing patients to limit sun exposure, and modifying the dose of ERBITUX for severe acneiform rash, as shown on the next slides.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Proposed Management of Mild Skin Reactions Based on Anecdotal Evidence

Rash Severity
- Mild
  - Generally localized
  - Minimally symptomatic
  - No impact on ADL
  - No sign of superinfection

Proposed Intervention
- Continue EGFR inhibitor at current dose and monitor for change in severity
- No treatment OR use of topical steroids* or topical antibiotics
- Reassess after 2 weeks; if reactions worsen or do not improve, manage as moderate rash (see next slide)

The intervention recommendations shown here should not be interpreted as evidence-based guidelines. They are adapted from the article by Lynch et al (Oncologist. 2007;12:610-621) and are based solely on the authors’ clinical experience.

ADL = activities of daily living.
*The use of topical steroids should be employed in a pulse manner based on your institution’s guidelines.

Reference

Proposed Management of Moderate Skin Reactions Based on Anecdotal Evidence

Rash Severity

- **Moderate**
  - Generalized
  - Mild symptoms (e.g., pruritus, tenderness)
  - Minimal impact on ADL
  - No sign of superinfection

Proposed Intervention

- Continue EGFR inhibitor at current dose and monitor for change in severity; continue treatment of skin reaction with the following:
  - Topical steroids,* topical antibiotics, or topical immunomodulators PLUS oral antibiotics
- Reassess after 2 weeks; if reactions worsen or do not improve, manage as severe rash (see next slide)

The intervention recommendations shown here should not be interpreted as evidence-based guidelines. They are adapted from the article by Lynch et al (*Oncologist*. 2007;12:610-621) and are based solely on the authors’ clinical experience.

ADL = activities of daily living.

*The use of topical steroids should be employed in a pulse manner based on your institution’s guidelines.

Reference


Proposed Management of Severe Skin Reactions Based on Anecdotal Evidence

Rash Severity

- Generalized
- Severe symptoms (eg, pruritus, tenderness)
- Significant impact on ADL
- Potential for superinfection

Proposed Intervention

- Reduce or discontinue EGFR inhibitor dose as per label and monitor for change in severity; continue treatment of skin reaction with the following:
  - Topical steroids,* topical antibiotics, or topical immunomodulators PLUS oral antibiotics PLUS oral steroids
- Reassess after 2 weeks; if reactions worsen, dose interruption or discontinuation may be necessary

The intervention recommendations shown here should not be interpreted as evidence-based guidelines. They are adapted from the article by Lynch et al (Oncologist. 2007;12:610-621) and are based solely on the authors’ clinical experience.

ADL = activities of daily living.

*The use of topical steroids should be employed in a pulse manner based on your institution’s guidelines.

Reference

Dose Modifications of ERBITUX (cetuximab) for Severe Acneiform Rash

1st Occurrence

2nd Occurrence

3rd Occurrence

4th Occurrence

Response

Delay Infusion 1-2 Weeks

Outcome

Improvement

No Improvement

ERBITUX Dose Modification

Continue at 250 mg/m²

Discontinue ERBITUX

Reduce dose to 200 mg/m²

Discontinue ERBITUX

Reduce dose to 150 mg/m²

Discontinue ERBITUX

Reference

1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
General Skin Care Suggestions: A Proactive Approach Is Key

Advise patients to:

- Use a thick, alcohol-free emollient cream
- Limit sun exposure
  - Wear protective clothing, such as a broad-brimmed hat
  - Use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium oxide
- Take short showers using lukewarm water and unscented soaps, and moisturize soon after bathing
- Avoid laundry detergents with strong perfumes
- Remain hydrated
- Keep fingernails and toenails clean and trimmed, avoid tight-fitting shoes
- Wear gloves to wash dishes and while using cleaning agents
- Call a healthcare professional as soon as any skin toxicity symptoms develop

References
Dermatologic Management Strategies
Based on Anecdotal Evidence

Monitoring:

- Patients experiencing dermatologic toxicities should be monitored for inflammation or infectious sequelae. Appropriate treatment should be initiated. Dose modifications should be instituted in cases of severe acneiform rash.

| Antibiotics | Topical and/or oral antibiotics may be considered for inflammatory or infectious sequelae. 
| Emollients | Alcohol-free moisturizers can prevent and alleviate skin dryness.
| Antipruritus | Cool compresses and antihistamines may lessen itching, as well as products such as Aveeno® Colloidal Oatmeal Lotion.
| Sun protection | ERBITUX (cetuximab) patients should wear sunscreen containing zinc oxide or titanium oxide, wear hats, and limit sun exposure.
| Makeup | Concealers should not worsen rash-related symptoms; dermatologist-approved brands are preferable.
  - Makeup should be removed with a mild cleanser.
| Over-the-counter medications | Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised; this rash is not like acne vulgaris, and these treatments could make it worse.

Aveeno is a registered trademark of Johnson & Johnson Consumer Companies, Inc.

References

1. ERBITUX Package Insert, December 2012.

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Patient support programs that teach side-effect recognition and self-care techniques can reinforce the education and care you provide. The ERBITUX (cetuximab) Patient Support Program includes:

- **A patient education booklet** explaining treatment with ERBITUX
- **A self-care kit**, which includes:
  - The *Helping You Care for Your Skin, Nails, and Hair* brochure, which provides clear, concise information about dermatologic changes and helpful tips for patients
  - Lotions, sunscreen products, gentle bathing products, and a nail-care kit
  - Tools to reinforce the importance of HCP communication with patients
- **A support hotline** to reinforce your team’s efforts and provide support

Please see Full Prescribing Information including Boxed WARNINGS provided at this presentation.
Other Selected Dermatologic Adverse Reactions: Paronychia, Xerosis, Pruritus
Overview of Paronychia

- Develops in 12-16% of patients\(^1\)
- Can affect fingernails or toenails\(^2\)
- Usually occurs after 4-8 weeks of EGFR-inhibitor therapy\(^1\)
- May present as dryness and shedding of fingertips and toes, acute paronychia, pyogenic granuloma-like infection, or ingrown nails\(^2\)

Reproduced with permission from Lacouture M, Lai SE. The PRIDE (Papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to epidermal growth factor receptor inhibitors) syndrome. *Br J Dermatol.* 2006;155:852-854.

References
Overview of Xerosis

- Dry skin can be attributed to abnormal keratinocyte differentiation leading to disturbed stratum corneum and interference of sebaceous gland function.\(^1\)
  - Translates to loss of water-retaining function of the epidermis.\(^1\)
  - Reported in 4-35% of patients.\(^2\)
- It normally takes 14 days for differentiated, postmitotic epidermal cells to reach the stratum corneum resulting in delayed appearance of dry skin during EGFR-inhibitor therapy.\(^1\)
  - In one small study, xerosis was observed in 10 patients with a mean onset of 20 days.\(^3\)

References


Overview of Pruritus

- Pruritus (itchy skin) may be associated with papulopustular rash

Reference

Summary

- Take a proactive approach to skin care¹
- Counsel patients about taking appropriate precautions to help minimize rash, such as limiting sun exposure²
- Treatment with ERBITUX (cetuximab) should continue without dose modification in patients with mild and moderate skin toxicity²
- If a patient experiences severe acneiform rash (papulopustular rash), ERBITUX dosage adjustments should be made²
- In clinical studies of ERBITUX, dermatologic toxicities, including acneiform rash (papulopustular rash), skin drying and fissuring, paronychial inflammation, infectious sequelae (e.g., S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis, occurred in patients receiving ERBITUX therapy²
- Acneiform rash occurred in 76-88% of 1373 patients receiving ERBITUX in clinical trials²
- Severe acneiform rash occurred in 1-17% of patients²
  - Acneiform rash (papulopustular rash) usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days
  - Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae
  - Sun exposure may exacerbate these effects

References