The recent development of novel anti-cancer therapies targeted to specific molecular pathways has led to increased survival and decreased systemic toxicity compared to traditional cytotoxic agents. Cetuximab and panitumumab belong to a class of monoclonal antibodies specific to the epidermal growth factor receptor (EGFR) that are FDA-approved for the treatment of advanced squamous cell carcinoma of the head and neck (SCCHN) and metastatic colorectal cancer (mCRC) as monotherapy or in combination with chemotherapy and/or radiation treatment. These monoclonal antibodies are indicated for the treatment of EGFR-expressing, KRAS mutation-negative mCRC. Erlotinib is a small molecule tyrosine kinase inhibitor (TKI) that also targets the EGFR and is approved in the U.S. for the treatment of pancreatic cancer and non-small cell lung cancer. EGFR represents a therapeutic target due to its role in molecular pathways mediating cellular proliferation, differentiation, and survival. If EGFR is overexpressed or constitutively active, its effects at the cellular level may explain its role in tumorigenesis. Therefore, EGFR inhibitors act to mitigate cancer-promoting EGFR signaling pathways in cell division, apoptosis, and angiogenesis, thereby impeding tumor growth.

CUTANEOUS TOXICITY
Skin toxicity is a frequently-reported side effect of monoclonal antibodies against the EGFR and TKIs in large, randomized controlled trials with these agents. Adverse effects typically reported include an acneiform rash, folliculitis, xerosis, pruritus, exfoliation, fissures, erythema, paronychia, hypertrichosis, and hyperpigmentation. While the EGFR is expressed in various tumors, it also plays specific roles in normal healthy epithelial cells of the skin. EGFR is expressed in keratinocytes located in specific layers of the epidermis, outer sheath cells in hair follicles, sebaceous glands of the pilosebaceous unit, dermal arteries, and eccrine sweat glands. Therefore, cutaneous toxicity may be caused by direct inhibition of the EGFR in healthy skin. This theory is supported by the observation that EGFR inhibition induces the expression of chemokines that enhance skin inflammation through leukocyte recruitment, vascular dilation, and edema. Activated neutrophils then release proteases that cause loss of epidermal intracellular attachments, basal keratinocyte degeneration, and damage to the basement membrane. These events likely contribute to the development of papules and pustules characteristic of the acneiform eruption seen in EGFR inhibitor therapy. Finally, disruption in the skin barrier due to such inflammation may facilitate secondary bacterial infection of the typically sterile lesions.

ACNEIFORM ERUPTION
Clinical Presentation. The acneiform eruption typically occurs after one week of treatment with the monoclonal antibodies and is usually seen in the seborrheic areas of skin including the face, scalp, neck, posterior auricular area, shoulders, and chest. Involvement of the lower trunk, extremities, and buttocks has been reported with worsening clinical progression of the rash. The eruption commonly presents as erythematous follicular papules and pustules without comedones. Additional features associated with the acne-like rash include telangiectasias and pruritus, which is not characteristic of other types of drug-induced acne. The severity of skin eruptions ranges from grade 1 to grade 5 according to the earlier National Cancer Institute Common Toxicity Criteria version 2.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0), and current NCI CTCAE v4.0. Skin toxicity of grade 3 or higher during therapy is an indication for dose reduction or interruption, which may lead to reduced efficacy or loss of response to treatment. While spontaneous remission of the rash despite continued treatment has been reported, recrudescence following each infusion may occur, and partial resolution with continued administration can
also be seen.\textsuperscript{15,16} Therefore, preventing or adequately managing skin toxicity is necessary to ensure maximal therapeutic benefit and patient quality of life.\textsuperscript{17}

The Burden of the Acneiform Eruption During EGFR-inhibitor Treatment. The incidence and severity of the acneiform-like eruption differs between classes of EGFR inhibitors.\textsuperscript{16,18} The monoclonal antibodies typically exhibit a more severe and widespread reaction compared to the TKIs.\textsuperscript{10,16} Cetuximab has a reported severe skin toxicity of 12-20 percent as monotherapy, five percent to nine percent with adjunct chemotherapy and up to 50 percent in combination with radiation.\textsuperscript{7,15} As a result, nearly half of patients may require dose adjustments to cetuximab infusions during cancer treatment. An acneiform eruption of any severity has been reported in 75 to 100 percent of patients undergoing cetuximab treatment.\textsuperscript{14} In comparison, up to 35 percent of patients receiving panitumumab monotherapy or combination therapy have reported severe skin toxicity.\textsuperscript{7,15} The incidence of an acneiform rash of any severity is 57 percent among patients treated with panitumumab monotherapy, which is significantly less than with cetuximab treatment.\textsuperscript{15} Among all TKIs, grade 3 skin toxicity is significantly lower with a reported one percent to nine percent incidence rate in two recent systematic reviews.\textsuperscript{7,15}

An acneiform rash of any severity may compromise continued treatment with EGFR inhibitors, according to survey data from US oncology practices. While adverse effects data from clinical trials and the experience of the oncology practitioners surveyed support that a majority of patients experience a rash of grade 1 or 2, the survey results revealed that 32 percent discontinued EGFR inhibitors completely due to a rash and 76 percent interrupted treatment for up to three weeks for skin toxicity.\textsuperscript{19} Despite this severity, oncology practitioners infrequently referred these patients to dermatologists: just eight percent referred a patient with skin toxicity to a dermatology clinic and some survey respondents reported concerns that dermatologists were not capable of providing effective therapeutic interventions for the skin toxicity.\textsuperscript{19}

Treatment of the Acneiform Eruption. While the cutaneous toxicities of EGFR inhibitors are well described in clinical trials and case reports, there is a paucity of primary studies examining regimens for the management of the acneiform eruption seen with these agents. Therefore, best practice guidelines for the prophylaxis and treatment of the acneiform eruption have been difficult to develop. In 2011, the first-generation expert opinion recommendations from the Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group panel were published to guide clinicians in the prevention and management of the EGFR inhibitor-associated skin toxicity.\textsuperscript{20}

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|}
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EGFR Inhibitor & Therapy & Duration & Outcome & Study Type \\
\hline
Cetuximab & Minocycline 100mg daily\textsuperscript{21} & 8 weeks, prophylaxis & Decreased lesion count* & RCT \\
 & Nadifloxacin and Prednicarbate cream\textsuperscript{12} & 6 weeks, treatment & Skin Score (character and extent of lesions)** & Uncontrolled trial \\
 & Vitamin K1 0.1% containing cream\textsuperscript{7} & 8 weeks, prophylaxis & Incidence and severity of skin toxicity*** & Uncontrolled trial \\
Panitumumab & Doxycycline 100mg twice daily, Hydrocortisone 1% cream daily, sunscreen, and skin moisturizer\textsuperscript{17} & 6 weeks, prophylaxis & Decreased grade 2 or greater skin toxicity* & RCT \\
All & Alcohol-free skin emollients, avoidance of hot, frequent, or lengthy showers, sun avoidance and broad-spectrum sunscreen use\textsuperscript{15} & Prior to and during treatment, prophylaxis & Decrease skin toxicity & N/A \\
 & Alclometasone 0.05% cream daily, Fluocinonide 0.05% cream twice daily\textsuperscript{20} & NR, treatment & Decrease lesion count & N/A \\
\hline
\end{tabular}
\caption{Acneiform eruption: prophylaxis and treatment considerations}
\end{table}

*Statistically significant at endpoint of treatment **Significant decrease in severity reported however, severity not specified ***No grade 3 or 4 skin rashes compared with a 20\% incidence for first-line therapy in mCRC

EGFR = Epidermal growth factor receptor; N/A = Not applicable; NR = Not reported
Prior to the start of EGFR inhibitor therapy, designing a prophylactic management plan incorporating lifestyle modifications and providing patient education is recommended. Specific interventions include using a thick, alcohol-free emollient as a skin moisturizer, avoidance of hot, frequent, or lengthy showers, and the use of a broad-spectrum sunscreen and sun avoidance.15,18 Oral antibiotics, topical vitamin A derivatives, topical immunomodulators, topical steroids, and sunscreen have been evaluated in randomized controlled trials for prophylaxis of cutaneous toxicities associated with EGFR inhibitors. Cetuximab-induced cutaneous toxicity was significantly decreased with prophylactic minocycline 100mg daily compared to placebo during the first eight weeks of treatment while topical tazarotene 0.05% in the same cohort of patients was not superior to placebo in reducing lesion counts on the face after eight weeks.21 Minocycline prophylaxis prevented the development of severe acneiform rashes, and fewer patients reported moderate-to-severe itch during the initial eight weeks of cetuximab treatment.15 In a second trial for patients initiated on cetuximab treatment, prophylactic topical pimecrolimus 1% applied to the face significantly reduced lesion count after five weeks of twice-daily treatment. Interestingly, the total lesion counts of both sides of the face decreased significantly by the endpoint at five weeks so the results were determined to not be clinically relevant.7 Panitumumab related cutaneous toxicity of grade 2 or higher was significantly decreased after a six-week regimen of prophylactic oral doxycycline 100mg twice daily, topical hydrocortisone 1% once daily, sunscreen, and skin moisturizer compared to sunscreen and skin moisturizer alone.17 Management of non-specified EGFR inhibitor toxicity was not significantly different with the use of prophylactic oral tetracycline 500mg twice daily for four weeks or SPF 60 sunscreen applied twice daily for four weeks.7 The MASCC Skin Toxicity Study Group published Grade A recommendations for prophylactic systemic minocycline and doxycycline 100mg daily for up to eight weeks after initiating EGFR-inhibitor therapy.20 Patients may benefit from medium- to high-potency topical corticosteroids such as alclometasone 0.05% cream daily or fluocinonide 0.05% cream twice daily for the treatment of the acneiform eruption.20 Novel therapies for the management of skin toxicity have been investigated in uncontrolled studies and case reports. A trial of nadifloxacin and prednicarbate cream for the treatment of facial lesions in patient undergoing cetuximab treatment was reported to significantly improve the severity of skin toxicity at one, two, and six weeks when assessed using the Skin Score.22 A 0.1% Vitamin K1 containing cream was evaluated for prophylaxis of skin toxicity during the first eight weeks of cetuximab plus chemotherapy for the treatment of mCRC. After the eight week treatment period, no grade 3 or grade 4 toxicities were seen and just 65 percent of patients experienced any grade of skin toxicity.7 Regenecare gel, a mixture of lidocaine, marine collagen, aloe vera, and sodium alginate, applied prophylactically to the right side of the face for one week in patients treated with various EGFR inhibitors was reported to improve itch on the treated side.7 However, the authors did not report any other objective measures of improvement in skin toxicity. In a recent case series, topical recombinant human epidermal growth factor (rhEGF) spray was investigated for the treatment of acneiform lesions in patients receiving TKIs.23 Two patients on erlotinib who developed an acneiform rash that was not responsive to topical steroids or oral minocycline were treated for four weeks with topical rhEGF twice daily. At the conclusion of therapy, both patients had significant improvement in the number of pustules and flattening of remaining lesions.23 The prevention and treatment of secondarily infected skin lesions is discussed in an expert opinion article based on clinical experience and available clinical trials. Intranasal mupirocin is recommended for prevention of secondary infection and a short course of oral antibiotics in the tetracycline class may be effective for secondarily infected skin.24 Agents that are discouraged in the management of skin toxicity have also been reported in expert opinion recommendations.15 Topical medications that are traditionally used in acne treatment, including benzoyl peroxide, have not been shown to be efficacious in the treatment acneiform eruptions caused by EGFR inhibitors and may worsen dry skin, irritation, and burning associated with this adverse side effect.24 Consensus guidelines have recently been published for the management of an acneiform eruption coexisting with radiation dermatitis in patients with SCCHN undergoing combination radiotherapy and EGFR inhibitor treatment have been published, which is particularly helpful for an acneiform eruption that coexists with a grade 2 or higher radiation dermatitis.25

CONCLUSION
Cutaneous toxicity with EGFR inhibitor treatment is a common adverse effect that may affect a patient’s ability to continue anti-cancer treatment and can negatively affect a patient’s quality of life. Management strategies for prophylaxis and treatment of the acneiform eruption associated with these EGFR inhibitors have been evaluated in a limited number of randomized controlled trials without comparable or consistent results. Interventions to prevent and treat EGFR inhibitor-induced skin toxicity are needed and can be best investigated with further large, randomized studies for each class of EGFR inhibitors. The available data suggests that oral tetracyclines may have therapeutic benefit in preventing acneiform eruptions during treatment with the monoclonal antibodies (Table 1). A multi-disciplinary team of dermatologists and oncologists may optimize patient care during EGFR inhibitor treatment through surveillance and management of cutaneous skin reactions.
Increased awareness of the skin toxicities associated with these targeted therapeutics by dermatologists is necessary to accurately diagnose and treat these patients.

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