NU Study Number: *JNC06142016*
Other Study Numbers: STU00203631; NU 16D05

A Randomized Phase II Study of Topical Steroids as Preemptive Therapy for Epidermal Growth Factor Receptor Inhibitor-Induced Papulopustular Eruption

Principal Investigator: Jennifer Nam Choi, M.D.
Department of Dermatology
676 North St. Clair Street, Suite 1600
Chicago, IL 60611
Phone: (312) 695-8106
Fax:
Jennifer.choi@northwestern.edu

Biostatistician: Borko Jovanovic, Ph.D.
borko@northwestern.edu

Study Intervention(s): Triamcinolone 0.1% topical cream

Funding Source: Department of Dermatology

Version Date: January 25, 2021

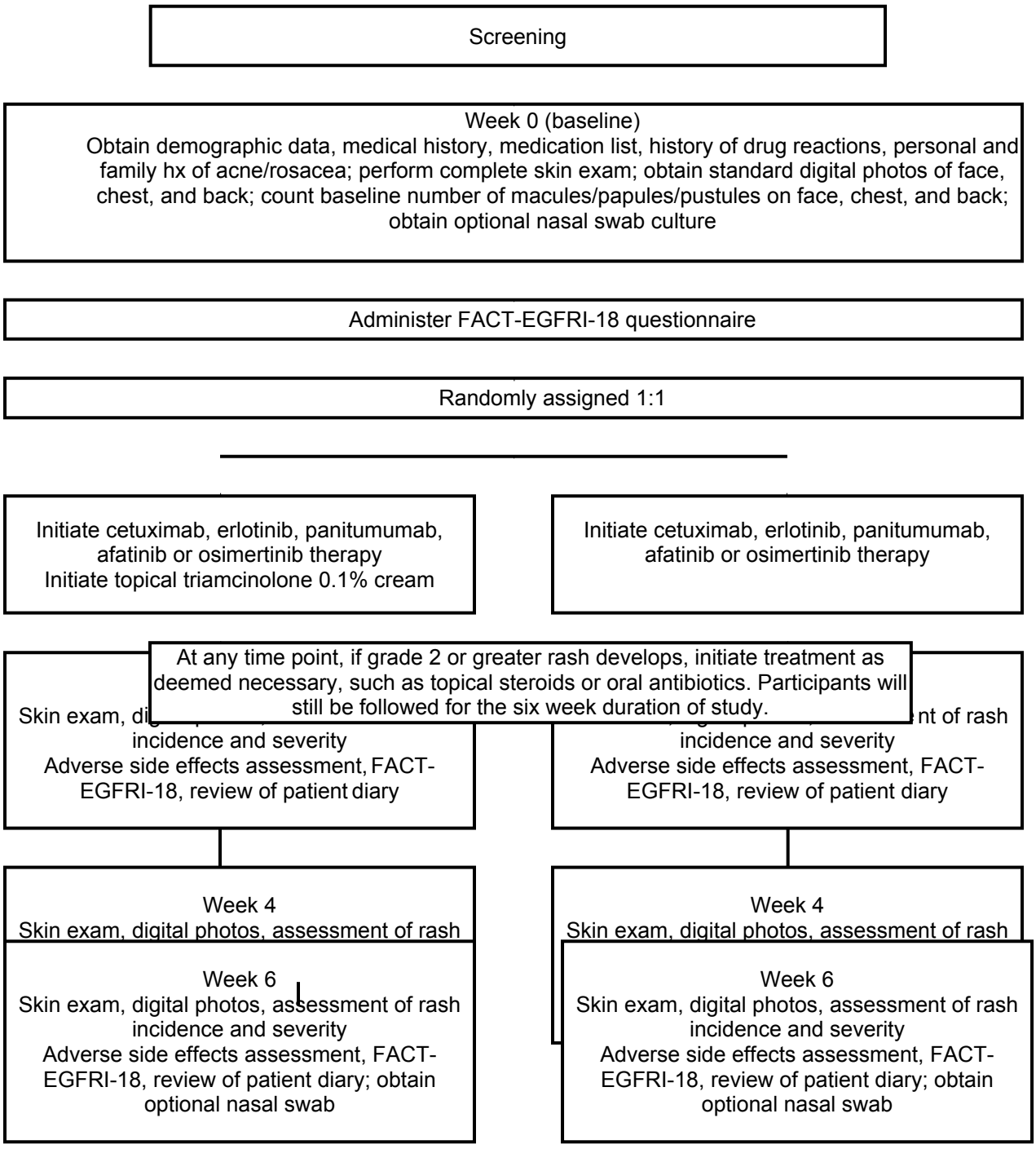
Protocol Number: JNC06142016

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
EGFR	Epidermal Growth Factor Receptor
EGFRI	Epidermal Growth Factor Receptor Inhibitor
IV (or iv)	Intravenously
SAE	Serious Adverse Event

STUDY SCHEMA



STUDY SUMMARY

Title	A Randomized Phase II Study of Topical Steroids as Preemptive Therapy for Epidermal Growth Factor Receptor Inhibitor-Induced Papulopustular Eruption
Short Title	A Study of Topical Steroids as Preemptive Therapy EGFR Inhibitor-Induced Papulopustular Eruption
Version	07-02-2019
Study Design	Randomized Control Trial
Study Center(s)	Robert H. Lurie Cancer Center
Objectives	To determine the efficacy of preemptive treatment with topical steroids (triamcinolone 0.1% cream for application to face, chest and back) when administered concomitantly for 6 weeks with erlotinib, cetuximab, panitumumab, afatinib or osimertinib to prevent papulopustular eruptions.
Sample Size	84
Diagnosis & Key Eligibility Criteria	Patients must have a histologically or cytologically confirmed cancer diagnosis for which EGFRI treatment is indicated, and must be starting treatment with cetuximab, erlotinib, panitumumab, afatinib or osimertinib.
Treatment Plan	This randomized, controlled, phase II clinical study is designed to assess the efficacy of preemptive treatment with topical steroids in preventing the papulopustular eruption induced by epidermal growth factor receptor inhibitor (EGFRI) treatment in cancer patients. Participants will be followed up for 6 weeks of twice daily application of triamcinolone cream to the face, chest, and back.
Statistical Methodology	For all analyses, a type I error of 5% (two-sided) will be used to test for statistical significance and will be performed using SAS v9.2 (SAS Institute, Cary, NC). Randomization will be stratified according to skin type.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

The epidermal growth factor receptor (EGFR) is a member of a family of membrane receptors with tyrosine kinase activity that is expressed in cells from all three embryonic layers, but particularly in cells of epithelial origin, including the skin, respiratory tract, gastrointestinal tract, urinary tract, and liver.[1] Because EGFR overexpression plays a role in the malignant behavior of cells and is overexpressed in human tumors of epithelial origin, several biologic agents targeting the EGFR have emerged over the past decade as a robust therapy against several malignancies, including non-small cell lung, colorectal, head and neck, and pancreatic carcinomas.[1] The first EGFR inhibitor was FDA-approved in 2004, and currently there are three tyrosine kinase inhibitors (TKIs) (erlotinib [Tarceva®], lapatinib [Tykerb®], afatinib [Gilotrif®]) and two monoclonal anti-EGFR antibodies (cetuximab [Erbitux®], panitumumab [Vectibix®]) that are commercially available.

Because EGFR inhibitors (EGFRIs) specifically target pathways that are crucial for cancer cell growth and survival, as opposed to targeting all replicating cells, they are associated with different adverse systemic side effects in comparison with standard chemotherapeutic drugs.[2] Specifically, EGFRIs are associated with a distinct class-specific toxicity profile, most evident in tissues that are crucially dependent on EGFR signaling for normal function, including the skin and hair follicles.[3] Patients treated with EGFRIs experience cutaneous toxicities that can be severe, and these side effects often lead to reduction and even cessation of treatment. Depending upon the specific EGFRI and the dose, a characteristic papulopustular eruption can develop in as many as 45-90% of patients.[4,5] While it most frequently involves the sebaceous gland-bearing regions of the body, i.e. the scalp, face, chest and upper back, the eruption can extend to additional sites in severe cases.[5] The rash commonly starts as a sensory disturbance with erythema and edema (weeks 0 to 1), followed by a progression to an acne-like appearance with central pustule formation (weeks 1 to 3). Crusting then develops (weeks 3 to 5), and it often ends with erythematotelangiectatic changes (weeks 5 to 8).[6]

While the mechanisms that underlie EGFRI-associated cutaneous toxicities remain incompletely characterized, interference with the follicular and interfollicular EGFR signaling pathway is considered the critical component.[3] As EGFRs are primarily expressed in undifferentiated, proliferating keratinocytes in the basal and suprabasal layers of the epidermis and the outer layers of the hair follicle, inhibition of EGFR-mediated signaling pathways alters keratinocyte proliferation, differentiation, migration and attachment, as well as stimulates inflammation, all of which can lead to the distinctive cutaneous manifestations.[3]

Histologic studies of the EGFRI-induced rash have shown a mixed inflammatory infiltrate within the upper dermis (particularly around hair follicles), follicular rupture, and epithelial acantholysis.[3] The lesions are usually sterile, but the eruption can be complicated by secondary bacterial and viral infections in up to 30% of patients; there are even reports of associated bacteremia.[7,8] The cutaneous toxicity has been graded as moderate to severe in up to 55-60% of patients,[9,10] and it leads to significant discomfort and pruritus in one-third of patients.[5] Depending upon severity, up to a third of oncologists will discontinue EGFRI therapy.[4] In one study, only approximately 8% of providers obtained a dermatology consult to aid in management.[4]

Currently, the EGFRI-induced papulopustular eruption is most commonly assessed utilizing the grading system contained in the National Cancer Institute's Common Terminology Criteria for Adverse Events monograph (NCI-CTCAE; version 4.03) (see Table 1).[11]

Table 1: NCI-CTCAE, Version 4.03[11] Grading for Acneiform Rash

Grade 1	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
Grade 2	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
Grade 3	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated
Grade 4	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences

Several groups[12,13] have noted the shortcomings of the current grading system, primarily because it is based on two subjective measures (pain and physician assessment of whether intervention is needed) and total body surface area. In the EGFRI-induced rash, the face and upper trunk are the most commonly affected sites, and while involved total body surface area can be limited, severity of the affected areas can be high. It has been proposed that a more EGFRI-focused grading system would prove useful and be more appropriate for therapeutic decision-making in the clinical setting. Lacouture et al.[14] have proposed the following (see Table 2):

Table 2: Grading of EGFRI-induced papulopustular eruption by Lacouture et al.[14]

Adverse Event	**Grade 1**		**Grade 2**		**Grade 3**	
Papulopustular Eruption	1A Papules or pustules < 5; OR 1 area of erythema or edema < 1 cm in size	1B Papules or pustules < 5; OR 1 area of erythema or edema < 1 cm in size AND pain or pruritus	2A Papules or pustules 6-20; OR 2-5 areas of erythema or edema < 1 cm in size	2B Papules or pustules 6-20; OR 2-5 areas of erythema or edema < 1 cm in size AND pain, pruritus, or effect on emotions or functioning	3A Papules or pustules > 20; OR > 5 areas of erythema or edema < 1 cm in size	3B Papules or pustules > 20; OR > 5 areas of erythema or edema < 1 cm in size AND pain, pruritus, or effect on emotions or functioning

The EGFRI-induced papulopustular eruption could be considered the most clinically significant dermatologic toxicity in modern oncology.[7] There is evidence to suggest that the presence and severity of the skin rash may correlate with improved tumor response and survival. This was first demonstrated in a phase II study of patients with advanced non-small cell lung cancer (NSCLC) receiving erlotinib.[15] Patients with grade 0 rashes, as assessed by the NCI-CTC, had a median survival duration of 1.5 months. Those patients with a grade 1 rash had a median survival time of 8.5 months, while those with a grade 2-3 rash had a 19.6-month survival duration.[15] This correlation has been confirmed by retrospective analyses of several other phase II and III studies that used EGFRIs for NSCLC, colorectal cancer, head and neck cancer, ovarian cancer, and pancreatic cancer.[16] While these correlations need to be validated in prospective trials, the observations have led to the initiation of clinical trials with dose-escalation of EGFRIs in an attempt to elicit characteristic target rashes and to determine if the latter correlate with a better response. With similar reasoning, there has been potential patient concern that rash prevention or treatment may

limit tumor response to the EGFRI. To date, there is no evidence to suggest this reverse correlation exists.

Both the physical discomfort and psychological effects of the EGFRI-induced rash are believed to affect patients' health-related quality of life (HRQL). Physical discomfort, including pain, burning and skin sensitivity, can lead to restriction of daily activities and independence.[17] Given that the EGFRI-induced papulopustular eruption occurs predominantly on the scalp, face and upper trunk, i.e. cosmetically sensitive areas, the visible consequences of this rash can also produce a high degree of psychological distress. For example, these side effects may lead to anxiety and have a negative impact on self-image and self-esteem, which can then result in social isolation and depression.[17] Such a profound impact on the patient's psychological wellness can lead to a decision by the patient or the oncologist to dose-reduce, interrupt, or discontinue EGFRI therapy.

While the EGFRI-induced rash can be quite severe, it is rarely life-threatening. A systemic review of 8,998 cancer patients enrolled in 117 trials of EGFRIs did not find any skin rash-related deaths.[18] As a result, the general consensus by expert panels is to continue drug therapy with symptomatic management (based on the severity of the rash) before any dose reduction is made.[19] The goal in managing EGFRI-induced skin toxicity is to minimize the detrimental effects of the rash on patients' quality of life and treatment course, thereby allowing optimal clinical benefit from continued and uninterrupted use of EGFRIs when possible. Experts emphasize that, in the majority of cases, there is no clinical need to withdraw EGFRI treatment, and that the EGFRI-induced skin toxicity should be viewed as manageable.[19]

To our knowledge, there are very few controlled clinical trials that have investigated either preemptive or reactive treatment regimens for EGFRI-associated cutaneous toxicities. Current interdisciplinary guidelines for management are based primarily upon qualitative evidence, anecdotal reports, and expert opinion. Anecdotal reports of simple interventions include topical emollients, sunscreens, avoidance of UV radiation, topical analgesics, topical antibiotics, topical corticosteroids, topical cyclosporine analogs, and topical pimecrolimus and tacrolimus.[20,21] Systemic treatment of the eruption has consisted primarily of oral antibiotics, in particular tetracycline, doxycycline and minocycline, and there have been two placebo-controlled trials and one preemptive versus reactive treatment trial of these oral antibiotics. As for topical corticosteroids, they have primarily been used concomitantly with oral antibiotics as treatment after rash onset and have not previously been investigated as preemptive rash treatment.

1.2 Intervention Background & Overview

Oral antibiotics
The first published randomized controlled clinical trial that prospectively evaluated a systemic therapy for the EGFRI-induced papulopustular eruption investigated the use of oral minocycline (100 mg daily) versus placebo for 8 weeks, beginning on the same day as the initiation of cetuximab therapy (n = 48 patients; 24 in each arm).[22] Patients also received topical tazarotene daily to one side of the face. Overall the number of lesions increased rapidly during the first 4 weeks of therapy and then stabilized by week 8. Patients treated with minocycline had significantly lower log lesion counts than those in the placebo group from weeks 1 through 4 ($p = 0.005$). This difference was apparent by week 1, peaked at weeks 2 and 4, and then tapered by week 8. At week 4, there were a lower proportion of patients in the minocycline arm who reported moderate to severe itch than in the placebo arm. Additionally, there was a trend toward a lower frequency of a moderate to severe rash in patients in the minocycline arm (20%) compared with those receiving placebo (42%) ($p = 0.13$). Tazarotene did not have any significant benefit and was associated with significant irritation. While there was no statistically significant difference in moderate to severe rashes between the minocycline and placebo arms, possible explanations include a sub-therapeutic dose of minocycline. In acne vulgaris, minocycline is frequently used at a dosage of 100 mg twice daily to provide maximal benefit.[23]

In a second placebo-controlled trial conducted by the North Central Cancer Treatment Group (NCCTG),[9] this phase III trial examined 61 patients who had begun treatment with an EGFRI within 7 days of study entry and had not yet developed rash. The patients were randomized to oral tetracycline (500 mg twice daily) versus placebo for 4 weeks. There was no difference in rash incidence at 4 weeks; however, tetracycline lessened the rash severity. Seventeen percent of tetracycline-treated patients had a grade 2 or worse rash at 4 weeks compared with 55% of placebo-treated patients ($p = 0.04$). Additionally, the tetracycline arm was associated with improvements in pruritus according to Skindex-16 scores. (Skindex-16 is a previously validated questionnaire used as a dermatologic quality-of-life instrument relevant to rash development and its implications on symptoms, emotions, and functioning.[24])

Most recently, a phase II Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial investigated the effectiveness of oral doxycycline (100 mg twice daily) by randomizing 95 patients with metastatic colorectal cancer to either: (1) preemptive therapy (started 24 hours prior to initiation of panitumumab plus irinotecan or FOLFIRI [leucovorin, 5-fluorouracil, irinotecan], and continued daily through week 6); or (2) reactive therapy (started when symptoms of dermatologic toxicity first appeared).[10] In addition to the doxycycline, the treatment regimen consisted of topical hydrocortisone 1% cream twice daily, sunscreen when going outdoors, and moisturizer to areas of xerosis. At week 6, preemptive treatment reduced the incidence rate of grade 2 or greater skin toxicities by over 50% when compared to reactive treatment.[10] The incidence of grade 2 or greater skin toxicities during the 6-week skin treatment period was 29% and 62% for the preemptive and reactive groups, respectively. Additionally, the time to severe skin toxicity was significantly delayed by preemptive skin treatment. At 6 weeks, the event- (grade 2 or greater skin toxicity) free probabilities were 70% and 38% for the preemptive and reactive arms, respectively.

Overall, two of these three controlled studies suggest that the tetracycline derivatives can lessen the severity, and possibly prevent, EGFRI-induced papulopustular eruptions. The beneficial effects of tetracyclines can be attributed to their anti-inflammatory effects, as well as their tissue-protective properties, such as their inhibition of neutrophil and eosinophil chemotaxis[25]. In addition, tetracyclines may have antineoplastic properties. In *in vitro* studies, doxycycline has been shown to have anti-angiogenic properties and induces apoptosis in colorectal cancer cells.[26] Thus, it is theoretical that doxycycline may have beneficial effects against tumor activity.

Currently, the standard of care according to current interdisciplinary guidelines for management of the EGFRI-associated papulopustular eruption includes initiation of either oral doxycyline 100 mg twice daily or oral minocycline 100 mg twice daily at the onset of grade 2 or greater severity of rash.[19] The most common side effects associated with the tetracycline antibiotics are nausea, vomiting, and diarrhea. Often times, these gastrointestinal-related side effects may lead to cessation of treatment with these antibiotics.

Topical Steroids
Though antibiotics are commonly used to treat EGFRI-induced papulopustular rash, there are several reasons why an alternative treatment, such as topical steroids, may be more appropriate. Firstly, while tetracyclines were first suggested as a possible treatment given its similarity to acne vulgaris, the EGFRI-induced rash differs in that it lacks comedones, is predominantly pustular, and histopathologically spares the sebaceous glands.[13] A history of acne or rosacea is not a risk factor for the eruption[27], and anti-acne agents have not been shown to be clearly effective.[3,28] Secondly, the eruption is not due to an infectious process, but more likely an inflammatory one, suggested by the presence of a mixed inflammatory infiltrate on histologic examination. An *in vitro* study done with keratinocytes showed that EGFR inhibitor treatment leads to effects on pro-inflammatory cytokines.[29] In particular, EGFRI treatment was found to lead to decreased levels of CXCL8 and increased levels of CCL5 and CCL2. CXCL8 is also known as interleukin-8 and is a chemokine that has been identified to induce angiogenesis and metastasis in several cancers, and subsequent inhibition by EGFRI may contribute to antineoplastic effects. On the other hand, CCL5 and CCL2 are chemokines that recruit macrophages, T cells, and dendritic cells to sites of inflammation. While this may be important for inducing immune responses against tumors, this

also suggests that there may be pro-inflammatory mechanisms induced by EGFRI treatment that could explain its side effects. Though the mechanism underlying EGFRI-induced rashes remains to be completely characterized, there is undoubtedly an inflammatory component that can be targeted by the administration of corticosteroids.

In retrospective studies designed to identify treatment regimens used for EGFRI-induced rashes, topical steroids were often used in combination with other therapies, including oral antibiotics. A chart review of 15 cases of patients taking erlotinib showed a papulopustular eruption in 80% (12/15) of patients.[30] These patients were treated with submicrobial doses of doxycycline in addition to topical anti-inflammatory agents. High-potency topical steroids, such as fluocinolone, clobetasol, and betamethasone, were the most commonly used agents, followed by topical tacrolimus and pimecrolimus. The majority of subjects improved with treatment after an average period of 3 months. Of 11 patients who developed papulopustular rash and had follow up, 6 patients experienced total improvement of cutaneous lesions and 4 patients had partial improvement.

A second retrospective, uncontrolled comparative study looked at 49 patients to identify three established treatment regimens, each including topical steroids, for the management of EGFRI-associated rashes.[31] Patients in this study were treated using one of three strategies for a total of three weeks: 1) sole topical anti-inflammatory agent (mometasone furoate cream), 2) combined topical anti-inflammatory agent (prednicarbate 0.25% cream) and antibiotics (nadifloxacin cream), and 3) combined topical anti-inflammatory agent (prednicarbate cream), antibiotics (nadifloxacin) as well as concomitant systemic isotretinoin therapy. Rash severity in patients was assessed using the EGFRI-induced rash severity score (ERSS or WoMoScore), a skin-specific scoring system introduced in 2008.[32] The ERSS score ranges from 0 to 100 and is calculated from body involvement, facial involvement and clinical grading of erythema, papulation, pustulation and scaling/crusts. All three treatment approaches were found to be effective and significantly reduced the severity of the rash over a period of 3 weeks. The statistically most significant effects were achieved with topical mometasone furoate cream, although statistical comparison of the different regimens was limited due to variations in patient numbers and rash severity in each of the three test groups. Mometasone furoate (Class 4) is a more potent corticosteroid as compared to prednicarbate (Class 5), which may suggest increased efficacy with higher potency steroids.

These findings led to the decision to use triamcinolone 0.1% cream for application to the face, chest, and back daily as the preemptive treatment arm in this study. To our knowledge, there are no prospective randomized clinical trials to date that have evaluated use of topical corticosteroids alone for the preemptive treatment of EGFRI-induced papulopustular rash. The STEPP trial as described above did use a treatment regimen that included a very low potency hydrocortisone 1% cream, but focused more on the use of oral antibiotics. Given the inflammatory nature of the EGFRI-induced rash and the proven efficacy of topical steroids in case reports and retrospective studies, it is likely that higher-potency topical steroids may represent a simple and convenient prophylactic treatment that can reduce the incidence or severity of EGFRI-associated rashes, improve patient quality of life, and ensure adherence to oncologic treatment.

1.3 Rationale for the Current Study

As the adverse side effect of a papulopustular rash is very prevalent in patients taking EGFR inhibiting drugs, and often interferes with the ability to continue treatment, this trial seeks to identify a treatment that will diminish or eliminate the incidence of the rash. The randomized control design will allow us to compare the control group with the treatment group, to effectively analyze the impact of the treatment. The dosing regimen (twice daily on face, chest, and back), will ensure that a systemic dose of steroids is not administered, while effectively covering the areas of most likely rash outbreak.

In this study, the FACT-EGFRI-18 questionnaire will be used to assess impact of rash on the health-related quality of life (HRQL) of the patients. This is a questionnaire developed specifically to assess the changes in emotional, physical, and social function that are caused by EGFRI treatment.[33] It is similar to the Skindex-16 questionnaire used in previous studies, but

more specific to reactions of EGFRIs. This questionnaire was developed through a process of interviews with patients undergoing EGFRI treatment for colorectal, lung, pancreatic, and adenocarcinoma cancers. See appendix 1 for questionnaire questions.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

To assess the difference in percentage of participants who develop a grade 2 or greater rash in the control group as compared to the case group of preemptive treatment with topical steroids (triamcinolone 0.1% cream for application to face, chest and back) when administered concomitantly for 6 weeks with erlotinib, cetuximab, panitumumab, afatinib or osimertinib to prevent papulopustular eruptions.

2.2 Secondary Objectives & Endpoints

2.2.1 To assess the difference in maximum severity of rash between the preemptive treatment group and the reactive treatment group.

2.2.2 To assess the difference in change in quality-of-life due to rash between the two treatment groups.

2.2.3 To determine whether there is a difference in adherence to chemotherapy between the two treatment groups.

2.2.4 To determine if the results of baseline nasal swab cultures are associated with rash development or rash severity.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with a histologically or cytologically confirmed cancer diagnosis for which EGFRI treatment is indicated. This will be single-center trial conducted at the Robert H. Lurie Cancer Center of Northwestern University.

A total of 84 subjects will be needed for this trial. Approximately 10 potentially eligible patients are seen per month, and it is anticipated that at least 4 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Jennifer Choi at (312) 695-8106.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a histologically or cytologically confirmed cancer diagnosis for which EGFRI treatment is indicated

3.1.2 Initiation of topical steroids or control treatment within 7 days of initiation of cetuximab, erlotinib, panitumumab, afatinib or osimertinib

3.1.3 Patients must be age ≥ 18 years.

3.1.4 Life expectancy of greater than 6 weeks

3.1.5 Patient able to use topical medications reliably and complete questionnaires with assistance if needed

3.1.6 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients who have used systemic or topical steroids within 7 days of trial registration, or start systemic or topical steroids for reasons unrelated to trial during the 6-week follow up period. Systemic steroids as part of chemotherapy regimen are allowed.

3.2.2 Patients who have used antibiotics within 7 days of trial registration, or start antibiotics for other conditions during the 6-week follow up period

3.2.3 History of allergic reactions to topical steroids

3.2.4 Patients with any rash at the time of study registration

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.0 TREATMENT PLAN

4.1 Overview

The treatment in this study will include a twice daily application of 0.1% triamcinolone topical cream, applied to the face, chest, and back. In addition, all patients will be instructed to adhere to the same skin treatment regimen, regardless of whether they are in the preemptive or control arm, which will be administered beginning day -3 to day 7(three days before the administration of the first EGFRI dose until 7 days after the administration of the first EGFRI dose) and will be continued through week 6. This regimen will include daily moisturizers as well as use of broad spectrum sun protection before going outdoors.

Patients will be followed every 2 weeks for 6 weeks total, and at each visit will fill out a FACT-EGFRI-18 questionnaire. Optional nasal swab cultures to check for bacterial and fungal growth will be taken at the first and last visit, in addition to any time a culture of the skin is taken. If the patient agrees to the culture and there is bacterial colonization, they will be treated as standard of care. Standard of care is not to treat a positive nasal swab. If an infection develops, this will be treated with antibiotics that cover the bacteria isolated in the culture. In addition, standardized photographs will be taken at each visit, and graded by two blinded dermatologists, if any rash appears. These photos may be used in the future for academic purposes. If they are used outside of the study, the eyes of the participants will be blacked out to help maintain confidentiality. Patients will be given the option to conduct the visits in-person or remotely. If the visit will be conducted remotely, then all required study documentation, diaries, questionnaires, and photography will be submitted to the study team prior to the remote visit for review. For remote visits, the study coordinator will call the subject at the appointment time to review the protocol, answer questions, and review diaries, questionnaires, and AEs.

4.2 Treatment Administration

4.2.1 Treatment arm: Triamcinolone 0.1% Cream

Eligible patients will be randomly assigned to either the treatment group to receive topical triamcinolone 0.1% cream for application to the face, chest and back, or will be assigned to the control group to receive no preemptive treatment. Patients will be assigned to either group in a randomized manner, stratified according to Fitzpatrick skin type. Stratification group 1 will consist of patients with Fitzpatrick skin type I-III. Stratification group 2 will consist of patients with Fitzpatrick skin type IV-VI. The Fitzpatrick skin typing test is a numerical classification schema for human skin color, as explained below (Fitzpatrick TB. The validity and practicality of sun reactive skin types i through iv. 1988. Archives of Dermatology. 124(6):869-871.)

- **Type I** (scores 0–6) always burns, never tans (pale white; blond or red hair; blue eyes; freckles)

- **Type II** (scores 7–13) usually burns, tans minimally (white; fair; blond or red hair; blue, green, or hazel eyes)
- **Type III** (scores 14–20) sometimes mild burn, tans uniformly (cream white; fair with any hair or eye color)

- **Type IV** (scores 21–27) burns minimally, always tans well (moderate brown)
- **Type V** (scores 28–34) very rarely burns, tans very easily (dark brown)
- **Type VI** (scores 35–36) Never burns, never tans (deeply pigmented dark brown to darkest brown)

If the patient is randomized to the treatment group, then the study team has the option to distribute the study drug either in person during a clinic visit or by shipping the study drug to the patient after success registration. If shipping the study drug to the patient, then we will use a courier such as FEDEX that provides tracking information and overnight shipments are preferred. The packaging will be secure and tamper proof, and the patient's name and address information will be verified.

If in the preemptive arm, treatment with topical steroids will start within 3 days of initiation of the EGFR inhibitor drug and continue for 6 continuous weeks. Patients will be instructed to apply the topical steroid twice daily over the face, chest and back. Patients will document each day administration of their EGFRI drug (if a tyrosine kinase inhibitor, i.e. home oral administration) and study topical medication, as well as a daily chart indicating potential medication adverse effects, in a study diary. Upon enrollment in the study, patients will be given an instruction sheet (see Appendix 3) for application of the topical cream.

All patients will be instructed to adhere to the same skin treatment regimen, regardless of whether they are in the treatment or control arm, which will be administered beginning up to 3 days before EGFRI initiation until up to 7 days after EGFRI initiation and will be continued through week 6. The skin treatment regimen will consist of skin moisturizer applied to the face, chest and back daily in the morning on rising and nightly at bedtime; and sunscreen (PABA free, at least SPF 15, UVA and UVB protection) applied to exposed skin areas before going outdoors. Participants will track their application in a daily diary (see Appendix 2).

4.2.2 Control arm

Participants in the control arm will be asked to follow the daily skin treatment regimen of skin moisturizer and sun protection before going outdoors, and to chart their applications in a daily diary.

4.3 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Any patient who develops any of the side effects listed in section 8.1.9 will be taken off of treatment with triamcinolone cream, but will be followed through the study for six weeks.

4.4 Concomitant Medications/Treatments

Patients must be on one of the following EGFR inhibitor drugs: erlotinib, cetuximab, panitumumab, afatinib or osimertinib.

4.5 Duration of Therapy

Patients will receive treatment for 6 weeks. If any patient is in the control arm and develops a papulopustular rash, they will be treated with topical triamcinolone 0.1% cream and or antibiotic treatment, oral doxycycline 100 mg or oral minocycline 100 mg twice daily, as is the standard of care. These participants will still be followed for the 6 week duration of study.

4.6 Duration of Follow Up

Patients will be enrolled in the study for 6 weeks. They will be followed in clinic every 2 weeks with the option for remote visits instead of in-person visits by submitting the required documentation and photography to the study team ahead of the remote visit for review. The

remote visit will happen using telephone to review the protocol, answer questions and concerns, and review diaries, questionnaires, and AEs.

They will not be followed up after the final visit during the 6th week, when they will terminate the drug regimen.

4.7 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity as determined by either the patient's physician or by the patient himself
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

5.0 STUDY PROCEDURES

	Screening	On Treatment		
Time Period	Baseline	Week 2	Week 4	Week 6
Assessment or Activity				
Informed Consent	X			
Obtain history[1]	X			
Complete skin exam[2]	X	X	X	X
Standardized digital photos of face, chest, and back	X	X	X	X
FACT-EGFRI-18 Questionnaire	X	X	X	X
Assess for adverse side effects		X	X	X
Review of patient diary		X	X	X
Application of topical triamcinolone 0.1% cream	X	X	X	
Nasal Swab[3]	X			X

[1]Includes demographic data, medical history, medication list, history of drug reactions, personal and family history of acne/rosacea
[2]Includes baseline count of any macules, papules, or pustules present on face, chest, and back at baseline.
[3] A nasal swab will be optional for the patient at the first and last treatment and at any time a rash with pustules develops. If the optional nasal swab is positive for bacterial colonization, this will be treated per standard of care.

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

A grade 2 rash is defined in Table 1 (p. 5) as papules and/or pustules covering 10-30% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (iADL).

6.2 Primary Endpoint

The study endpoint is defined as the percentage of patients who develop a grade 2 or greater rash between the control group as compared to the case group of preemptive treatment with topical steroids (triamcinolone 0.1% cream for application to face, chest and back) when administered concomitantly for 6 weeks with erlotinib, cetuximab, panitumumab, afatinib or osimertinib to prevent papulopustular eruptions.

6.3 Secondary Endpoints

6.3.1 The difference in maximum severity of rash between the preemptive treatment group and the reactive treatment group
6.3.2 The difference in change in quality of life due to rash between the two treatment groups.
6.3.3 The difference in adherence to chemotherapy between the two treatment groups.
6.3.4 The association of baseline nasal swab cultures and development of rash or rash severity.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern. The level of risk attributed to this study requires moderate intensity monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those

who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. Because AEs associated with EGFR- inhibitor treatment are monitored by the treating oncology physician, for the purposes of this study, only AEs that were possibly, probably, or definitely related to triamcinolone 0.1% cream will be collected, including those symptoms listed in section 8.1.9 will be reported. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.

- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- Results in death.
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- Is life-threatening.
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events that are determined to be possibly, probably, or definitely related to study treatment should be reported on the adverse event (AE) Case Report Form (CRF) within NOTIS Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study’s phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of

treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any

other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

8.0 DRUG INFORMATION

8.1 Triamcinolone 0.1% topical cream

8.1.1 Other names: Aristocort, Aristogel, Flutex, Kenalog, Triacet, Triacort, Triatex, Triderm, Trymex

8.1.2 Classification: topical steroid

8.1.3 Mode of action: Induce inhibitory proteins to the production of phospholipase A2, preventing the release of arachidonic acid in the inflammatory pathway.

8.1.4 Storage and stability: store away from moisture and light, at room temperature.

8.1.5 Protocol dose specifics

Application of triamcinolone 0.1% cream to 25% BSA will result in sub-pharmacological dosing that mimics physiologic equivalent of corticosteroids. Topical application of triamcinolone 0.1% cream is not likely to result in significant systemic absorption that will produce hypothalamic-pituitary-adrenal axis suppression and therefore, will not pose a risk for glucocorticosteroid insufficiency after withdrawal of treatment.

8.1.6 Preparation

The patient will apply approximately 5 grams total (1 teaspoon) to the face, chest, and back twice a day.

8.1.7 Route of administration for this study: topical cream application

8.1.8 Availability & Supply

This drug will be provided by the Northwestern Research Pharmacy, and will be stored at 676 St. Clair in suite 1600 in a locked storage room of the Dermatology Department. The drug will be stored with the investigational drug log.

8.1.9 Side effects

- Blistering, burning, crusting, dryness, or flaking of the skin
- Thinning of the skin with easy bruising
- Itching, scaling, severe redness of the skin
- Redness and scaling around the mouth
- Acne or pimples
- Burning and itching of the skin with blisters
- Burning, itching, and pain in hairy areas, or pus at root of hair
- Increased hair growth on forehead, back, arms, legs
- Lightening of normal skin color
- Lightening of treated areas of dark skin
- Reddish purple lines on arms, face, legs, trunk, or groin
- Softening of the skin

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This study is a randomized control trial with a control arm and a treatment arm. The primary study endpoint is defined as the percentage of patients developing a grade 2 rash or greater.

9.2 Sample Size and Accrual

A total of 80 patients will be enrolled in the study. Assuming a low 3% lost to follow-up rate, we will aim for a sample size of 84 patients (42 patients per treatment group), which will provide 80% power to detect a difference in rash incidence of 30% between the steroid arm and control group (i.e. 45% in the steroid arm versus 75% in the control group).

9.3 Data Analyses Plans

The primary objective will be to assess and compare the incidence of rash in patients treated preemptively with topical steroids and control patients.

Proportions experiencing EGFRI-induced papulopustular eruption (any severity) by 6 weeks will be estimated and compared using the Mantel-Haenszel Chi-Square test to account for the stratification factor in the randomization procedure. A test for homogeneity will be performed to assess the adequacy of a common odds ratio (OR). Results will be summarized using an OR and 95% confidence interval. Supportive analysis will use a generalized estimating equations (GEE) approach, which will allow modeling of the proportion of patients with rash over time. Fixed factors for treatment group, time and the treatment group by time interaction will evaluate time differences in the proportion of patients with rash between the two treatment arms while accommodating repeated measures over time.

The secondary objective, maximum grade severity during the 6-week study period will be tabulated by treatment group and compared using the Cochrane Armitage test for trend.

Secondary endpoints will also include comparisons across the study arms to assess changes in quality-of-life scores from baseline, as measured by the FACT-EGFRI-18 questionnaire. FACT-EGFRI-18 scores will be presented as the median percentage from baseline. Scores at 6 weeks will be compared using the nonparametric Van Elteren test, which combines stratum-specific Wilcoxon Rank-Sum statistics with weights inversely proportional to stratum sizes. Differences in adherence to chemotherapy treatment over the 6 weeks will be compared across the two study arms using the Mantel-Haenszel Chi-Square test. The incidence of adverse events will also be compared across treatment arms with a Fisher exact test.

10.0 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the

implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion. This may be completed electronically or in-person on an IRB approved paper consent form.

10.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

10.3 Registration Procedures

10.3.1 Registering a Patient to the Phase II Portion of the Study

Patients will be registered by either Shikha Walia (phone: 312-503-4347) or Dr. Jennifer Choi (phone: 312-695-8106) at the time of screening. Patients will fill our registration forms which will be kept on file in the Department of Dermatology. Participants may contact Shikha Walia or Katherine Bagnowski with questions regarding eligibility forms and registration procedures.

For potential patients for the phase II portion of this study, study team will inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, the following items will be completed to confirm eligibility and receive a subject identification number:
• Eligibility eCRF (complete in NOTIS)
• Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
• Signed and dated informed consent document (upload in NOTIS)
• Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

10.4 Data Submission

Data Collection: Raw data consists of paper copies of the FACT-EGFRI-18 Questionnaire and subject diary. Raw data and signed consent forms will be collected by the research team.

Confidentiality Issues: Raw data questionnaires, diaries, and source document data collection sheets contain no identifying information. Consent forms will be stored separately from the raw data. A Coded ID List with Subject's name and participant code will be stored separately from the data set as coded information. Data confidentiality is addressed through data storage and data sharing sections below.

Data Storage: Data from questionnaires and daily diaries are de-identified; each subject will be given a unique code and codes with identifiers will be maintained on password protected computers, in password protected network folders per FSM Data Security Policy. Identifiers to be stored are name only. Data will be stored in a secure drive (U: drive for NM) which is maintained by Northwestern Memorial. De-identified dataset will be created and stored properly as above.

Quantitative research data will be entered into an Excel database and paper copies of questionnaires and daily diaries will be scanned to PDF. Electronic data will be stored in a secure drive (U: drive for NM) which is maintained by Northwestern Memorial. Paper source documents will be kept in the Northwestern University Dermatology office located at: 676 N. St. Clair St., Suite 1600, Chicago, IL 60611 in a locked file cabinet. Access to locked cabinets will be granted only to the PI and authorized study personnel. All regulatory documentations will be managed by NUCATS.

Records Retention: Archival of study documents will be stored indefinitely upon study completion at Iron Mountain, a document storage facility. All study records are archived indefinitely per Iron Mountain's policies and procedure.

10.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires moderate intensity risk level as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the NOTIS for additional data submission instructions.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

10.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

10.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

10.8 Publication Policy

This section should be removed if the trial is not rated as a high intensity trial.

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

REFERENCES

1 Lage, A., Crombet, T. & Gonzalez, G. Targeting epidermal growth factor receptor signaling: early results and future trends in oncology. *Ann Med* **35**, 327-336 (2003).
2 Dancey, J. & Sausville, E. A. Issues and progress with protein kinase inhibitors for cancer treatment. *Nature Reviews Drug Discovery* **2**, 296-313, doi:10.1038/nrd1066 (2003).
3 Lacouture, M. E. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nature Reviews Cancer* **6**, 803-812, doi:10.1038/nrc1970 (2006).
4 Boone, S. L. *et al.* Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology* **72**, 152-159, doi:10.1159/000112795 (2007).
5 Li, T. & Perez-Soler, R. Skin toxicities associated with epidermal growth factor receptor inhibitors. *Target Oncology* **4**, 107-119, doi:10.1007/s11523-009-0114-0 (2009).
6 Lacouture, M. E. & Lai, S. E. The PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) syndrome. *British Journal of Dermatology* **155**, 852-854, doi:10.111/j.1365-2133.2006.07452.x (2006).
7 Lacouture, M. E. The growing importance of skin toxicity in EGFR inhibitor therapy. *Oncology* **23**, 194, 196 (2009).
8 Li, J., Peccerillo, J., Kaley, K. & Saif, M. W. Staphylococcus aureus bacteremia related with erlotinib skin toxicity in a patient with pancreatic cancer. *Journal of the Pancreas* **10**, 338-340 (2009).
9 Jatoi, A. *et al.* Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group *Cancer* **113**, 847-853, doi:10.1002/cncr.23621 (2008).
10 Lacouture, M. E. *et al.* Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *Journal of Clinical Oncology* **28**, 1351-1357, doi:10.1200/JCO.2008.21.7827 (2010).
11 Vol. 4 (ed U.S. Department of Health and Human Services) (National Cancer Institute, National Institutes of Health, 2009).
12 Solomon, B. M. & Jatoi, A. Rash from EGFR inhibitors: Opportunities and challentes for palliation. *Current Oncology Reports* **10**, 304-308 (2008).
13 Perez-Soler, R. *et al.* HER1/EGFR Inhibitor-Associated Rash: Future Directions for Management and Investigation Outcomes from the HER1/EGFR Inhibitor Rash Management Forum. *The Oncologist* **10**, 345-356 (2005).
14 Lacouture, M. E. *et al.* A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Supportive Care in Cancer* **18**, 509-522 (2010).
15 Perez-Soler, R. *et al.* Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *Journal of Clinical Oncology* **22**, 3238-3247, doi:10.1200/JCO.2004.11.057 (2004).
16 Perez-Soler, R. & Saltz, L. Cutaneous Adverse Effects With HER1/EGFR-Targeted Agents: Is There a Silver Lining? *Journal of Clinical Oncology* **23**, 5235-5246 (2005).
17 Wagner, L. I. & Lacouture, M. E. Dermatologic toxicities associated with EGFR inhibitors: the clinical psychologist's perspective. Impact on health-related quality of life and implications for clinical management of psychological sequelae. *Oncology* **21**, 34-36 (2007).
18 Jatoi, A. & Nguyen, P. L. Do patients die from rashes from epidermal growth factor inhibitors? A systematic review to help counsel patients about holding therapy. *The Oncologist* **13**, 1201-1204 (2008).
19 Lynch, T. *et al.* Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *The Oncologist* **12**, 610-621 (2007).
20 Lorusso, P. Toward Evidence-Based Management of the Dermatologic Effects of EGFR Inhibitors. *Oncology* **23**, 186-194 (2009).

21 Lacouture, M. E., Basti, S., Patel, J. & Benson, A. r. The SERIES clinic: an interdisciplinary approach to the management of toxicities of EGFR inhibitors. *Journal of Supportive Oncology* **4**, 236-238 (2006).

22 Scope, A. *et al.* Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *Journal of Clinical Oncology* **25**, 5390-5396, doi:10.1200/JCO.2007.12.6987 (2007).

23 Del Rosso, J. Q. & Kim, G. Optimizing use of oral antibiotics in acne vulgaris. *Dermatologic Clinics* **27**, 33-42 (2009).

24 Chren, M., Lasek, R., Sahay, A. & Sands, L. Measurement properties of Skindex-16: a brief quality of life measure for patients with skin diseases. *Journal of Cutaneous Medicine and Surgery* **5**, 105-110 (2001).

25 Sapadin, A. N. & Fleischmajer, R. Tetracyclines: nonantibiotic properties and their clinical implications. *Journal of the American Academy of Dermatology* **54**, 258-265 (2006).

26 Onoda, T., Ono, T., Dhar, D. K., Yamanoi, A. & Nagasue, N. Tetracycline analogues (doxycycline and COL-3) induce caspase-dependent and -independent apoptosis in human colon cancer cells. *International Journal of Cancer* **118**, 1309-1315 (2005).

27 Balagula, Y. *et al.* Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. *International Journal of Dermatology* **50**, 129-146, doi:10.111/j.1365-4632.2010.04791.x. (2011).

28 Shah, N. T. *et al.* Practical management of patients with non-small-cell lung cancer treated with gefitinib. *Journal of Clinical Oncology* **23**, 165-174, doi:10.1200/JCO.2005.04.057 (2005).

29 Paul, T. *et al.* Cytokine regulation by epidermal growth factor receptor inhibitors and epidermal growth factor receptor inhibitor associated skin toxicity in cancer patients. *European Journal of Cancer* **50**, 1855-1863 (2014).

30 Wnorowski, A., de Souza, A., Chachoua, A. & Cohen, D. The management of EGFR inhibitor adverse events: a case series and treatment paradigm. *International Journal of Dermatology* **51**, 223-232, doi:10.1111/j.1365-4632.2011.05082 (2012).

31 Gerber, P. A. *et al.* Management of EGFR-inhibitor associated rash: a retrospective study in 49 patients. *European Journal of Medical Research* **17**, doi:10.1186/2047-783X-17-4 (2012).

32 Wollenberg, A., Moosmann, N., Klein, E. & Katzer, K. A tool for scoring of acneiform skin eruptions induced by EGF receptor inhibition. *Experimental Dermotology* **17**, 790-792, doi:10.1111/j.1600-0625.2008.00715.x (2008).

33 Wagner, L. I. *et al.* The development of a Functional Assessment of Cancer Therapy (FACT) questionnaire to assess dermatologic symptoms associated with epidermal growth factor receptor inhibitors (FACT-EGFRI-18). *Supportive Care in Cancer* **21**, 1033-1041, doi:10.1007/s00520-012-1623-4 (2013).

APPENDICES

Appendix 1: FACT-EGFRI-18 Questionnaire[33]
Subject ID number:_____Date:_____

		Not at all	A little bit	Somewhat	Quite a bit	Very much
ST4	My skin or scalp feels irritated	0	1	2	3	4
ST5	My skin or scalp is dry or “flaky”	0	1	2	3	4
ST6	My skin or scalp itches	0	1	2	3	4
ST7	My skin bleeds easily	0	1	2	3	4
ST9	I am bothered by a change in my skin’s sensitivity to the sun	0	1	2	3	4
ST32	My skin condition interferes with my ability to sleep	0	1	2	3	4
ST22	My skin condition affects my mood	0	1	2	3	4
ST17	My skin condition interferes with my social life	0	1	2	3	4
ST24	I am embarrassed by my skin condition	0	1	2	3	4
ST37	I avoid going out in public because of how my skin looks	0	1	2	3	4
ST26	I feel unattractive because of how my skin looks	0	1	2	3	4
ST34	Changes in my skin condition make daily life difficult	0	1	2	3	4
ST38	The skin side effects from treatment have interfered with household tasks	0	1	2	3	4
ST16	My eyes are dry	0	1	2	3	4
ST15	I am bothered by sensitivity around my fingernails or toenails	0	1	2	3	4
ST29	Sensitivity around my fingernails makes it difficult to perform household tasks	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
ST11	I am bothered by increased facial hair	0	1	2	3	4

Appendix 2: Daily Diary

Subject ID Number: _____

Fill in the date and time each time you apply the medication.
Write in any side effects that you have while taking the medication.
Please bring this drug diary with you to your follow up appointments.

Drug A:	0.1% topical triamcinolone cream	**Your oncologist:**	
How often:	Twice daily	**Phone:**	
How much:	Apply to face, chest, and upper back	**Your dermatologist:**	Dr. Jennifer Choi
When:	Once in the morning and once in evening	**Phone:**	(312) 695-8106

Special instructions: Remember to rub the cream in completely before engaging in daily activities. Please remember to apply broad spectrum sunscreen before going outside, and to use daily moisturizer. If you skip or miss a dose of the triamcinolone, please write “skipped” or “missed” under Time applied.

Day	Date		Time applied	Is a rash present?	Symptoms and Location of Symptoms
Ex:	1/2/2016		8:15am	☑Yes ☐No	Itching, redness, pustules or bumps
1				☐Yes ☐No	
1				☐Yes ☐No	
2				☐Yes ☐No	
2				☐Yes ☐No	
3				☐Yes ☐No	
3				☐Yes ☐No	
4				☐Yes ☐No	
4				☐Yes ☐No	
5				☐Yes ☐No	

5				☐Yes ☐No	
6				☐Yes ☐No	
6				☐Yes ☐No	
7				☐Yes ☐No	
7				☐Yes ☐No	
8				☐Yes ☐No	
8				☐Yes ☐No	
9				☐Yes ☐No	
9				☐Yes ☐No	
10				☐Yes ☐No	
10				☐Yes ☐No	
11				☐Yes ☐No	
11				☐Yes ☐No	
12				☐Yes ☐No	
12				☐Yes ☐No	
13				☐Yes ☐No	
13				☐Yes ☐No	
14				☐Yes ☐No	
14				☐Yes ☐No	
15				☐Yes ☐No	
15				☐Yes ☐No	
16				☐Yes ☐No	

Appendix 3: Instructions Sheet

Instructions for Triamcinolone 0.1% cream application

Your Dermatologist: Dr. Jennifer Choi

Phone: (312) 695-8106

Apply about one teaspoon (5g) total of the cream to evenly cover your face, upper chest, and upper back. It may be necessary to ask someone to help you apply the cream to your back. It is important that the cream is evenly spread over the following areas of your body: