The Oncologist®

Clinical Trial Results

Adapalene Gel 0.1% Versus Placebo as Prophylaxis for Anti-Epidermal Growth Factor Receptor-Induced Acne-Like Rash: A Randomized Left-Right Comparative Evaluation (APPEARANCE)

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Trial Information

- **UMIN Trial Identifier:** UMIN000016692
- **Sponsor:** Hyogo Prefecture Health Promotion
- **Principal Investigator:** Toru Mukohara
- **IRB Approved:** Yes

Lessons Learned

- The results of the APPEARANCE trial indicate that adapalene does not prevent acne-like rash over placebo when added to topical moisturizer and oral minocycline but instead may have a detrimental effect. Therefore, adapalene is not recommended as prophylaxis against acne-like rash induced by anti-epidermal growth factor receptor therapies.
- Given that acne-like rash was completely controlled with placebo in approximately half of patients, predictive measures to identify patients needing intensive prophylaxis are required.

Abstract

Background. Anti-epidermal growth factor receptor (EGFR) therapies are frequently associated with acne-like rash. To evaluate the prophylactic efficacy of adapalene, a topical retinoid used as first-line therapy for acne vulgaris, we conducted a randomized, placebo-controlled, evaluator-blinded, left-right comparative trial.

Methods. Patients with non-small cell lung, colorectal, or head and neck cancer scheduled to receive anti-EGFR therapies were randomly assigned to once-daily adapalene application on one side of the face, with placebo on the other side. All patients had topical moisturizer coapplied to both sides of the face, and received oral minocycline. The primary endpoint was the difference in total facial lesion count of acne-like rash at 4 weeks. Secondary endpoints included complete control rate (CCR) of acne-like rash (≤5 facial lesions) and global skin assessment (Investigator's Global Assessment [IGA] scale, grade 0–4) at 4 weeks. Two blinded dermatologists independently evaluated the endpoints from photographs.

Results. A total of 36 patients were enrolled, of whom 26 were evaluable. Adapalene treatment was associated with a greater lesion count than placebo at 4 weeks, although the difference was not statistically significant (mean, 12.6 vs. 9.8, p = .12). All four patients with a difference >10 in lesion count between face sides had a greater count on the adapalene-treated side. No significant differences were observed in CCR of acne-like rash (54% vs. 50%) or IGA scale (mean grade, 1.9 vs. 1.7) between the adapalene and placebo sides.

Conclusion. Adapalene is not recommended as prophylaxis against acne-like rash induced by anti-EGFR therapies. ***The Oncologist*** 2019;24:885–e413

Discussion

Acne-like rash is the most problematic skin toxicity induced by anti-EGFR therapies. Although the Multinational Association for Supportive Care in Cancer (MASCC) guideline

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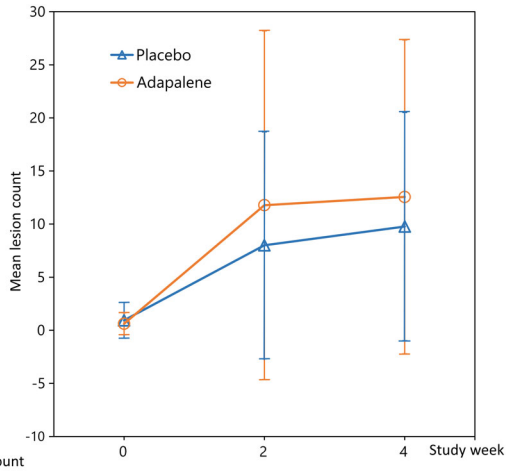

Mean lesion count	0	2	4
Placebo	0.9	8.0	9.8
Adapalene	0.6	11.8	12.6
Difference	0.3	−3.8	−2.8
p value	.17	.26	.12

Figure 1. Mean facial lesion count of acne-like rash at 0, 2, and 4 weeks of therapy.

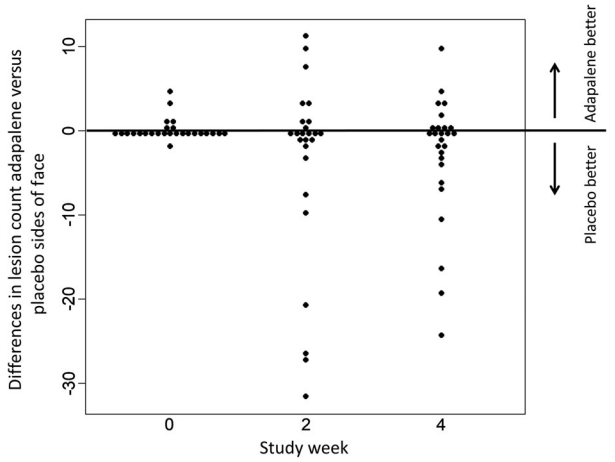

Figure 2. Scatter plot of differences in facial lesion count; each plot represents the difference in facial lesion count (placebo minus adapalene) in each case at 0, 2, and 4 weeks of therapy.

gives a grade A recommendation only for oral minocycline or doxycycline as prophylaxis for acne-like rash induced by anti-EGFR therapies, the development of more effective prophylactic measures is required. Because previous reports have suggested that adapalene is effective for the treatment of acne-like rash induced by anti-EGFR therapies, we conducted a placebo-controlled, evaluator-blinded, left-right comparative trial to clarify the prophylactic effect of adapalene against the particular type of acne-like rash.

We enrolled patients with advanced cancers, who were ≥20 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function, and who scheduled to receive treatment with an anti-EGFR drug (cetuximab, panitumumab, gefitinib, erlotinib, or afatinib) (Table 1).

Although there were no statistically significant differences in any of the efficacy endpoints between adapalene-treated and placebo-treated sides, there was a tendency for adapalene-treated sides to have worse outcome than placebo-treated sides (Figs. 1–4, Table 2). On the IGA scale, 15 of 26 patients scored equally between the placebo and adapalene sides, and 8 of the remaining 11 patients had a higher score on the adapalene side compared with the placebo side (Tables 3 and 4). Similarly, on the MASSC scale, whereas 16 of 26 patients had the same score for both sides, 8 of the remaining 10 patients had a greater score on the adapalene-treated side compared with the placebo-treated side (Tables 5 and 6).

The most commonly observed skin adverse events other than acne-like rash were dry skin, pruritus, pain, and erythema, and the overall incidence of each adverse event was similar between adapalene- and placebo-treated sides.

To the best of our knowledge, this is the first prospective and randomized study to evaluate the prophylactic effect of adapalene against acne-like rash induced by anti-EGFR therapies. In contrast to our hypothesis, our findings indicate that adapalene should not be recommended for the prevention of acne-like rash induced by anti-EGFR therapies, although its use for the treatment of the particular type of rash may still be considered.

Trial Information	
Diseases	Head and neck cancers, non-small cell lung cancer, and colorectal cancer
Stage of Disease/Treatment	Metastatic / Advanced
Prior Therapy	No designated number of regimens
Type of Study – 1	Phase II
Type of Study – 2	Randomized
Primary Endpoint	Left-right difference (the placebo side minus the adapalene side) in total rash count after 4 weeks of therapy
Secondary Endpoints	IGA scale after 4 weeks Incidence of grade ≥2 acne-like rash based on the MASCC scale after 4 weeks Interval to the occurrence of acne-like rash based on patient diaries Complete control rate of acne-like rash defined as number of facial lesions ≤5

	Incidence and severity of adverse events according to Common Terminology Criteria for Adverse Events version 4.0
	Adherence based on patient diaries

Additional Details of Endpoints or Study Design

The total facial lesion count at 4 weeks following prophylactic treatment with 100 mg oral minocycline for acne-like rash was previously reported to be an average of 61. For the evaluation of half-faces in the present study, the lesion count for a half-face following oral treatment with minocycline was estimated to be 30, with reduction of the rash count to 15 per half-face with concomitant adapalene treatment judged clinically significant. A sample size of 26 has 80% power to detect the mean of paired differences of 15 with an estimated SD of differences of 25 and a significance level of 0.05 using a Wilcoxon signed-rank test. Therefore, the target sample size was set at 30, accounting for several patient discontinuations. The difference between placebo and adapalene sides in rate of complete control of acne-like rash and incidence of grade 2 or higher acne-like rash based on the MASCC scale and dermatologist global assessment using the IGA scale was evaluated using McNemar's tests and a Wilcoxon signed-rank test, respectively. A *p* value less than .05 was considered to be statistically significant.

Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information

Drug 1

Generic/Working Name	Adapalene gel 0.1%
Trade Name	Differin Gel 0.1%
Company Name	Galderma
Drug Type	Topical retinoid
Route	Topical application

Schedule of Administration

Patients were randomly assigned to once-daily adapalene application on one side of the face and placebo on the other side before bedtime. All patients also applied topical moisturizer to both sides of the face twice a day and received oral minocycline 100 mg once a day. Topical and oral treatments were started on the same day as initiation of anti-EGFR therapy.

Patient Characteristics

Number of Patients, Male	21
Number of Patients, Female	15
Age	Median (range): 65 (47–82)
Performance Status: ECOG	0 — 12 1 — 21 2 — 3 3 — 0 Unknown — 0
Other	Anti-EGFR drug: cetuximab, 12; panitumumab, 7; afatinib, 11; erlotinib, 4; gefitinib, 2. Concurrent therapy: cytotoxic agent, 18; bevacizumab, 2; monotherapy, 16
Cancer Types or Histologic Subtypes	Non-small cell lung cancer, 17; colorectal cancer, 14; head and neck cancer, 5

Primary Assessment Method

Title	Primary analysis
Number of Patients Screened	36
Number of Patients Enrolled	36
Number of Patients Evaluable for Toxicity	35

Number of Patients Evaluated for Efficacy	26
Evaluation Method	Left-right difference (the placebo side minus the adapalene side) in total rash count after 4 weeks of therapy
Outcome Notes	Mean lesion count, adapalene-treated versus placebo-treated sides, 12.6 versus 9.8, $p = .12$

Adverse Events: Adapalene Side

	Of Special Interest, for 4 Weeks of Therapy						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Rash acneiform	51%	43%	6%	0%	0%	0%	49%
Dry skin	43%	54%	3%	0%	0%	0%	57%
Pruritus	77%	23%	0%	0%	0%	0%	23%
Pain of skin	77%	20%	3%	0%	0%	0%	23%
Erythema multiforme	80%	17%	3%	0%	0%	0%	20%

Although the overall incidence of each adverse event was similar between adapalene- and placebo-treated sides, some grade 2 events were observed only on adapalene-treated sides.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Adverse Events: Placebo Side

	Of Special Interest, for 4 Weeks of Therapy						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Rash acneiform	48%	49%	3%	0%	0%	0%	52%
Dry skin	46%	54%	0%	0%	0%	0%	54%
Pruritus	86%	14%	0%	0%	0%	0%	14%
Pain of skin	80%	20%	0%	0%	0%	0%	20%
Erythema multiforme	86%	14%	0%	0%	0%	0%	14%

Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Anti-epidermal growth factor receptor (EGFR) therapies, either anti-EGFR monoclonal antibodies (MABs) or EGFR tyrosine kinase inhibitors (TKIs), are commonly used to treat patients with colorectal, non-small cell lung, pancreatic, and head and neck cancers. The acne-like rash that develops mainly on the face and trunk is a particularly problematic toxicity of anti-EGFR therapies because it occasionally leads to diminished quality of life in patients and treatment interruption [1, 2]. Additionally, the severity of the acne-like rash has been reported to correlate with the therapeutic effects of anti-EGFR drugs in some types of cancer [3, 4]. It is therefore critical to optimize the prophylactic management of the acne-like rash induced by these treatments.

Several randomized trials have shown that tetracyclines such as doxycycline and minocycline are useful as prophylaxis against skin toxicity caused by anti-EGFR therapies [5, 6]. For example, prophylaxis with a topical steroid and oral doxycycline was shown to reduce the incidence of grade ≥2 skin toxicities induced by panitumumab, compared with the same treatment given in a reactive manner in the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial [6]. Based on these findings, the Multinational Association for Supportive Care in Cancer (MASCC) guideline gives a grade A recommendation for the use of oral minocycline 100 mg daily or doxycycline 100 mg twice daily as prophylaxis for acne-like rash induced by anti-EGFR therapies [7]. However, the recommendation for prophylaxis with topical hydrocortisone 1% cream remains at grade C [7]. Because regular use of topical corticosteroids can cause various forms of skin toxicity such as skin atrophy and telangiectasia, development of other prophylactic therapies is required.

Adapalene, a naphthoic acid derivative that is used to treat acne vulgaris, has high affinity toward retinoic acid receptors β and γ and may normalize keratinocyte proliferation and differentiation and reduce inflammation [8]. Some case reports and case series have shown that adapalene is effective for the treatment of acne-like rash induced by anti-EGFR therapies [9–11]. In a Japanese phase II trial, the incidence of grade ≥2 skin toxicities during 6 weeks of prophylactic

therapy with topical adapalene and oral minocycline in patients receiving panitumumab was 29.2%, and it was similar to that in the STEPP trial [12]. To date, however, the prophylactic effect of adapalene has not been adequately evaluated, and we therefore conducted the present study. Adapalene unexpectedly did not demonstrate a prophylactic effect on acne-like rash induced by anti-EGFR therapies when coadministered with topical moisturizer and oral minocycline, but instead appeared to have a detrimental effect compared with placebo.

The study design comparing the sides of a patient's face can eliminate background differences and enable the sample size to be minimized. We used the base of the 0.1% adapalene gel (Differin Gel, Galderma, La Defense, France) as the placebo. Because tiny particles of adapalene can be visualized in the gel, this study was not strictly double-blinded but instead was evaluator-blinded. The dermatologists evaluated the skin condition based on photographic images without seeing the patients and thus minimized the risk of bias.

A somewhat detrimental effect of topical retinoic acid receptor-specific retinoid as prophylaxis for acne-like rash was not entirely unexpected. In a previous study, tazarotene 0.05% cream, another retinoid, was applied to one half of the face only, starting from initiation of cetuximab treatment [5]. Although there were fewer skin eruptions, on average, in the tazarotene group, global assessment by a dermatologist at week 4 was equivalent for both sides in 87% of patients but worse for tazarotene-treated sides in 10% of patients. However, in 14 out of 43 patients (32.6%), tazarotene application was interrupted because of local irritation. We therefore suggest that the unsuccessful outcome of tazarotene prophylaxis might have been attributable to skin-irritating toxicity. We used adapalene in the present study because it is less irritating than tazarotene [13], and evidence of its effect on EGFR inhibitor-induced acne-like rash is accumulating [10–12]. Based on our results, however, adapalene might still have had an irritating effect and render the skin more susceptible to acne-like rash compared with placebo. Our findings, however, do not negate the effect of adapalene for the treatment of acne-like rash induced by anti-EGFR therapies. When used for the treatment of acne-like rash, adapalene is applied as a dot onto each lesion rather than in a planar fashion, as used for prophylactic purposes, and therefore might not irritate normal skin around the lesion.

We estimated that there would be 30 facial lesions on the placebo side based on a study with mainly white subjects, but there were fewer lesions in our study, with a mean of 9.8. Additionally, the complete control rate on the placebo side was 50%, and 42% and 46% of patients had grade 0 or 1 IGA scale and grade 1A or 1B MASCC scale on the placebo side, respectively. This may indicate that East Asians are less susceptible to anti-EGFR therapies, and that a topical moisturizer and oral minocycline may be sufficient treatment for approximately half of the patients. However, the remaining patients may still require prophylactic measures to prevent the development of an acne-like rash.

Our study had several limitations. First, although we evaluated patients who received different EGFR-TKIs and EGFR-MABs together, pathology and the response to adapalene may differ between acne-like rashes depending on the causative agent. In our study, three of four patients with a facial lesion count of >10 on the adapalene-treated side compared with the placebo-treated side received an EGFR-TKI (afatinib for one patient and erlotinib for two patients). Second, because there is no standardized method for lesion counting, the generalizability of our results is limited. However, there was a high consistency in the lesion count by the two evaluators in the present study (Cronbach's coefficient alpha >0.9).

In conclusion, our findings indicate that adapalene should not be recommended for the prevention of acne-like rash induced by anti-EGFR therapies. Predictive measures to identify patients needing intensive prophylaxis over topical moisturizer and oral minocycline are required. There is also a requirement for more effective and less toxic prophylactic agents than topical corticosteroids.

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Disclosures

Toru Mukohara: Chugai Pharmaceutical (RF); **Naomi Mizuta:** Eli Lilly Japan KK (E [spouse]); **Yoshihiro Nishimura:** AstraZeneca (H); **Hironobu Minami:** Novartis, Asahi-Kasei Pharma, Astellas, AstraZeneca, Bayer, Behringer, Bristol-Myers Squibb, Celgene, Chugai, DaiichiSankyo, DaiNihonSumitomo, Eizai, Janssen, Kowa, Kyowa-Kirin, Eli Lilly & Co., Merck Serono, Merck Sharp & Dohme, Nihon Shinyaku, Nippon Chemiphar, Eizai, Ono Yakuhin, Ohtsuka, Pfizer, Sanofi, Shire Japan, Taiho, Taisho-Toyama, Takeda, Teijin Pharma, Yakult, Genomic Health, CSL Behring, Nihon Kayaku (RF, including personal fees and clinical trial support). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

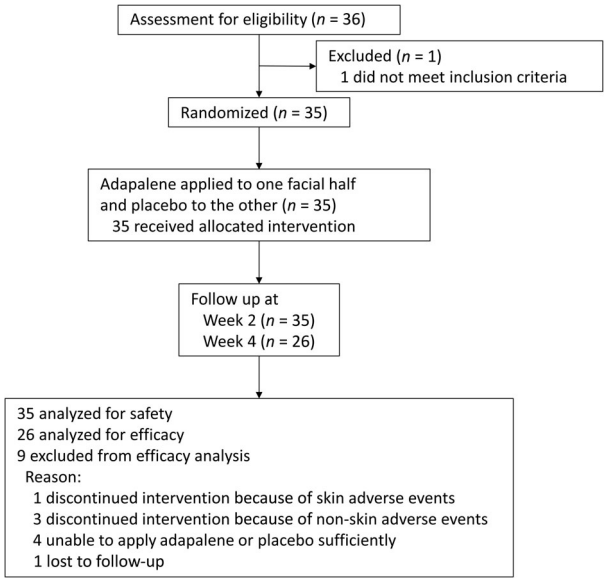

Figure 3. Consolidated Standards of Reporting Trials diagram.

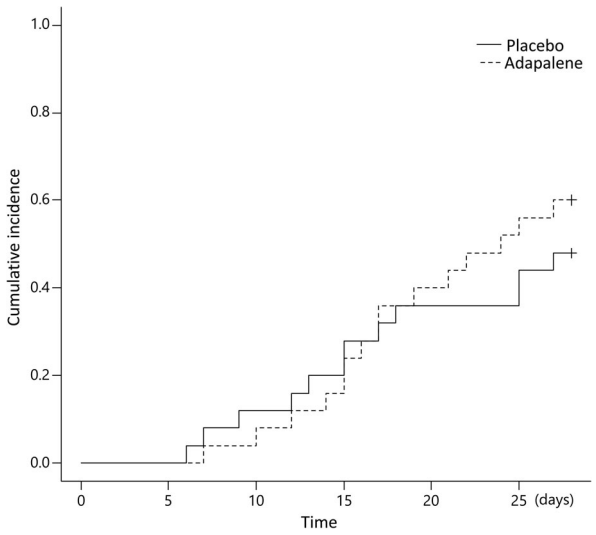

Figure 4. Interval until the occurrence of acne-like rash.

Table 1. Patient demographic and baseline disease characteristics

Demographics and Characteristics	Patients, *n* (%) *n* = 36	Evaluable patients, *n* (%) *n* = 26
Age, median (range), years	65 (47–82)	63 (47–82)
Gender, male	21 (58.3)	17 (65.4)
ECOG performance status		
0	12 (33.3)	10 (38.5)
1	21 (58.3)	5 (19.2)
2	3 (8.3)	1 (3.8)
Tumor type		
Non-small cell lung	17 (47.2)	13 (50.0)
Colorectal	14 (38.9)	9 (34.6)
Head and neck	5 (13.9)	4 (15.4)
EGFR inhibitor		
Cetuximab	12 (33.3)	7 (26.9)
Panitumumab	7 (19.4)	6 (23.1)
Afatinib	11 (30.6)	8 (30.8)
Erlotinib	4 (11.1)	3 (11.5)
Gefitinib	2 (5.6)	2 (76.9)
Concurrent therapy		
Cytotoxic agent	18 (50.0)	12 (46.2)
Bevacizumab	2 (5.6)	2 (76.9)
Monotherapy	16 (44.4)	12 (46.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table 2. Rates of complete control of acne-like rash[a]

Time point	*n*	Placebo side, *n* (%)	Adapalene side, *n* (%)	*p* value[b]
Week 2	25	15 (60)	14 (56)	.56
Week 4	26	13 (50)	14 (54)	.32

[a]Determined as (the number of faces with an acne-like rash count of 5 or less) / (total number of faces in the efficacy analysis population).
[b]Based on a McNemar's test.

Table 3. Dermatologists' global assessment using the IGA scale

	Placebo side *n* (%)	Adapalene side *n* (%)
IGA scale		
Grade 0	4 (15)	4 (15)
Grade 1	7 (27)	8 (27)
Grade 2	6 (23)	2 (8)
Grade 3	9 (35)	10 (38)
Grade 4	0	2 (8)
Mean grade	1.7	1.9
p value[a]		.43

[a]Based on a Wilcoxon signed-rank test.
Abbreviation: IGA, Investigator's Global Assessment.

Table 4. Investigator's Global Assessment Scale for acne vulgaris

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe; greater than grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

Table 5. Incidence of grade 2 or higher acne-like rash based on the Multinational Association for Supportive Care in Cancer scale

	Placebo side *n* (%)	Adapalene side *n* (%)
Patients with grade 2 or higher	14 (54)	13 (50)
p value[a]		.56
Grade 1A	4	4
Grade 1B	8	9
Grade 2A	3	1
Grade 2B	8	4
Grade 3A	2	2
Grade 3B	1	6

[a]Based on a McNemar's test.

Table 6. Multinational Association for Supportive Care in Cancer scale for papulopustular eruption by epidermal growth factor receptor inhibitors

Grade		Description
Grade 1	Grade 1A	Papules or pustules <5; OR 1 area of erythema or edema <1 cm in size
	Grade 1B	Papules or pustules <5; OR 1 area of erythema or edema <1 cm in size AND pain or pruritus
Grade 2	Grade 2A	Papules or pustules 6–20; OR 2–5 areas of erythema or edema <1 cm in size
	Grade 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
Grade 3	Grade 3A	Papules or pustules >20; OR more than 5 areas of erythema or edema <1 cm in size
	Grade 3B	Papules or pustules >20; OR more than 5 areas of erythema or edema <1 cm in size; AND pain, pruritus, or effect on emotions or functioning