

Mechanisms and management of EGFR inhibitor-associated dermatologic toxicities

10th Annual Perspectives in Colorectal Cancer

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

- Genentech, Inc
- Hana Biosciences
- OSI Pharmaceuticals
- Amgen, Inc
- Glaxo Smith-Kline
- ImClone Systems, Inc
- Bristol Myers-Squibb
- Onyx Pharmaceuticals
- Lindiskin
- Bayer Pharmaceuticals

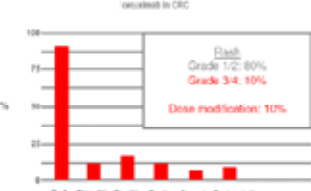
Major Toxicities: Chemotherapy vs EGFR-Targeted Agents

Traditional Chemotherapy	Myelosuppression, nausea/vomiting, neurotoxicity, organ toxicity
Anti-HER2	Cardiotoxicity, headache, nausea, dyspnea, pulmonary events
Anti-EGFR	Rash, diarrhea, fatigue, dyspnea, nausea/vomiting, infusion reaction

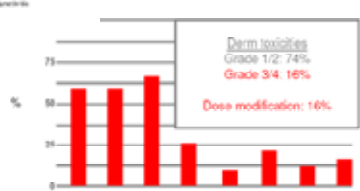
- Adverse events are different from standard chemotherapy but no less serious
- Discomfort or inconvenience experienced by patients might cause dose reduction or discontinuation of potentially life-prolonging therapy
- Some rare events are acutely life threatening

Dermatologic Toxicities to Monoclonal Antibodies in CRC

oculocutaneous in CRC



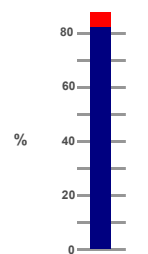
panniculomas in CRC



Cunningham et al. NEJM 2004; Hecht et al. 2006; Van Cutsem et al. J Clin Oncol 2007

Effects of EGFR-TI Combination on Skin Toxicity

This is NOT a head-to-head comparison, these are separate studies



■ Grade 1/2

■ Grade 3/4

BOND
Cunningham 2004

_____ cetuximab _____

Effects of Tumor Type on EGFR-TI Rash

- Meta-analysis of 16 phase II-III trials (1998-2008)
- 2,037 patients
- Risk ratio CRC v non-CRC: 1.9 (95% CI:1-3.6, p=0.049)

Category	Incidence (95% CI)	Relative risk (95% CI)
All grade skin rash	88.2% (84.8-91.0)	5.3 (4.2-7.3)
Acne-like skin rash	81.6% (75.4-86.6)	8.8 (3.8-13.2)
High-grade skin rash	11.3% (8.8-14.3)	21.8 (6.9-68.8)
Colorectal cancer	12.6% (9.7-16.4)	12.3 (4.3-33.4)
Non-colorectal cancer	6.6% (3.6-11.8)	17.8 (6.9-48.3)

Su et al. Oncology 2009

Papulopustular Eruption

- Red papulopustules in 45-100%
- Affects face + upper body
- Usually occurs within 8-10 days, peaks in 2 weeks
- Dose-dependent



NCI Common Terminology Criteria for Adverse Events relevant to EGFRi Rash

Adverse Event (Short name)	Grade 1	Grade 2	Grade 3	Grade 4
desquamation* or other lesions covering <50% of body surface area (BSA)			covering >50%	

COMMENTARY

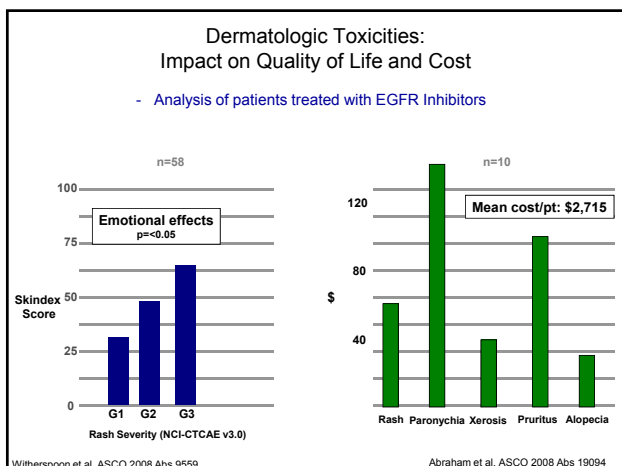
Is There Room for Improvement in Adverse Event Reporting in the Era of Targeted Therapies?

Maureen Eggerly, Tito Fayo | J Natl Cancer Inst 2008;100:240-242

NCI Common Terminology Criteria for Adverse Events version 4.0

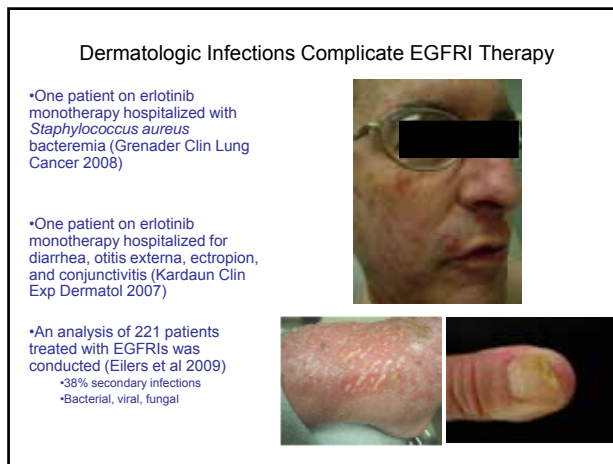
Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Death
Rash (acute)	erythema, papules, or pustules with symptoms of pruritus or tenderness	erythema, papules, or pustules with symptoms of pruritus or tenderness; limited self-care	erythema, papules, or pustules with symptoms of pruritus or tenderness; limited self-care; systemic symptoms	erythema, papules, or pustules covering >30% of BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive hospitalization or with antitumor treatment discontinuation	Death



Dermatologic Infections Complicate EGFRi Therapy

- One patient on erlotinib monotherapy hospitalized with *Staphylococcus aureus* bacteremia (Grenader Clin Lung Cancer 2008)
- One patient on erlotinib monotherapy hospitalized for diarrhea, otitis externa, ectropion, and conjunctivitis (Kardaun Clin Exp Dermatol 2007)
- An analysis of 221 patients treated with EGFRi was conducted (Eilers et al 2009)
 - 38% secondary infections
 - Bacterial, viral, fungal



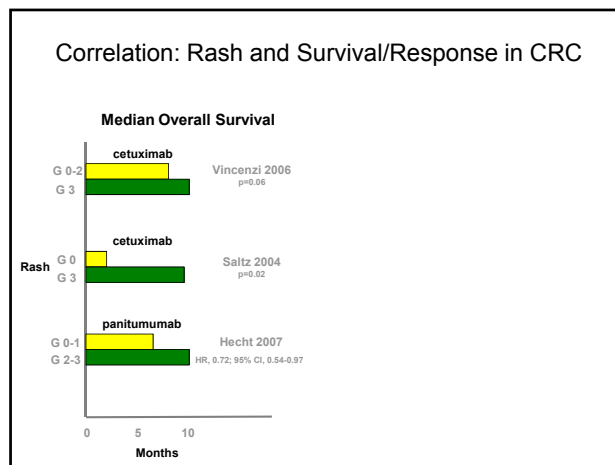
Incidence and Classification of Infection in 84 Infected Patients

Bacterial, Fungal, and Viral Infections Agent*	Bacterial Infections	Fungal Infections	Viral Infections
Methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA)	35		
<i>Candida Oryziformis</i>		13	
Tetracycline-resistant MRSA (T4-MRSA)	0		
Tetracycline-resistant MRSA (T4-MRSA)	8		
Herpes Simplex			7
<i>Pseudomonas aeruginosa</i>	7		
Tinea Pedis		7	
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	5		
<i>Serratia marcescens</i>	5		
Enterococci aerogenes	4		
Herpes Zoster			4
<i>Enterococcus faecalis</i>	3		
<i>Klebsiella oxytoca</i>	3		
<i>Klebsiella pneumoniae</i>	3		
β -hemolytic <i>Streptococcus</i> , Lancefield Group D	2		
<i>Staphylococcus epidermidis</i>	2		
Tinea Cruris		2	
<i>Asiaticobacter Daumanni</i> Complex	1		
<i>Candida Albicans</i>		1	
<i>Corynebacterium</i> Species	1		
Enterococci cloacae	1		
<i>Staphylococcus lugdunensis</i>	1		
<i>Stenotrophomonas</i> (Karthomonas); maltophilia	1		
Tinea Oral (Candidosis)			1
Tinea Corporis			1
Tinea Unguium			1

*The number of infectious agents outnumbered the number of infected patients because the infections are often polymicrobial

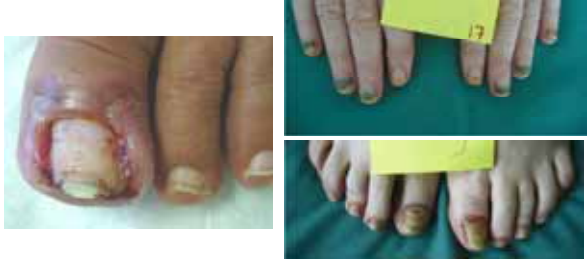
38% of patients treated with EGFRi developed infections at sites of toxicity

Eilers et al, AAD Annual Meeting 2009



Periungual and Nail Alterations

- Develops in 12-58%
- Paronychia begins in lateral nail folds
- Usually occur after 4-8 weeks of therapy
- Associated with tenderness, impairing ADLs



Suh et al, Br J Dermatol 2007; Winther et al, Support Care Cancer 2008

Xerosis

- Dry skin reported in approx 12-58% of patients
- Appearance after week 3
- Fissures in digit tips or heels
- Dysregulated epidermal proliferation/differentiation



Roe et al, J Am Acad Dermatol 2006; Agha et al, Oncology 2007

Regulatory Abnormalities of Hair Growth and Texture

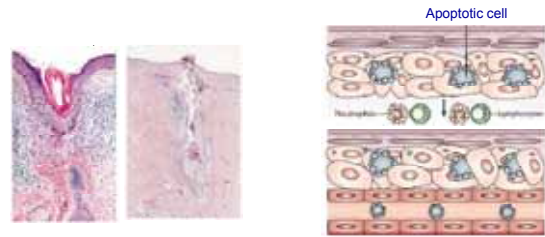
- Appearing >100d after EGFRi initiation
- Scalp and body alopecia with curling in 5%
- Facial hypertrichosis/eyelash trichomegaly in 20% (Roe et al, 2006)



Lai and Lacouture, Br J Dermatol 2006

EGFR is essential in epidermis

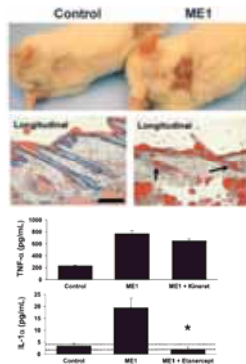
- EGFR is constitutively expressed in the epidermis, follicle, sebaceous, eccrine glands, dendritic APCs
- EGFR inhibition leads to negative effects in skin:
 - apoptosis, inflammation, atrophy, telangiectasias, ↓ photoprotection



Lacouture ME, Nat Rev Cancer 2006; Busam et al, Br J Dermatol 2005

Experimental Correlates of EGFRi Skin Toxicity

- SCID mice treated with ME1
- Alterations:
 - Wavy, decreased hair
 - Yellow skin crusting
 - Follicular plugging, neutrophils
 - Increased sebum
- Increased IL-1, TNFα in skin
- Anakinra (anti-IL1)
- Etanercept (anti-TNFα)

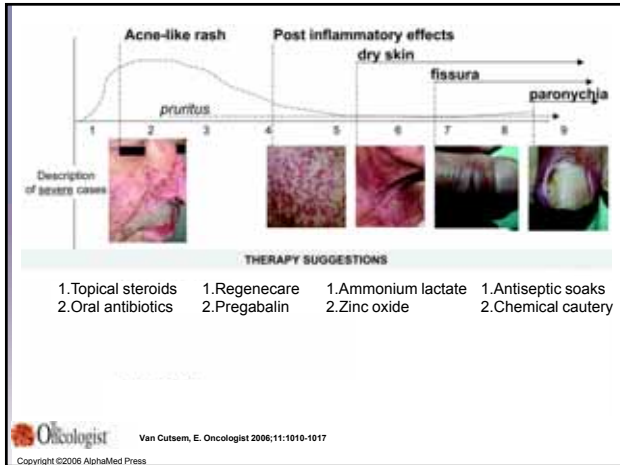


Surguladze et al, Cancer Res 2009

Clinical Trials on EGFRi Derm Toxicities

Intervention	Type/Design	Study size	Open date	Status
Doxycycline	Pilot, PK analysis	30	Sep 2008	Open
SERIES Algorithm	Interventional/Phase III, reactive vs. prophylactic	120	Jan 2008	Open
Histopathological characterization	Retrospective	32	June 2007	Open
Menadione	Phase I, topical, split face, with PK analysis	24	April 2008	Open
Regenecare gel	Observational, rash control	20	July 2006	Open
Regenecare gel	Observational, symptom control	20	April 2006	Complete
Tetracycline	Randomized, Double-Blind, Placebo Control	126	December 2004	Open
Sunscreen	Randomized, Double-Blind, Placebo Control	110	October 2006	Open
Minocycline + Lotion (clindamycin 2% Hydrocortisone 1%)	Randomized, Open Label, Active Control	150	June 2007	Open
Metronidazole	Non-Randomized, Open Label	34	Feb 2008	Open
Creams Versutex, Eritex and Fisiogel	Randomized, Open Label	312	October 2008	Not recruiting
STEPF (Skin Toxicity Evaluation Protocol to Panitumumab)	Interventional Phase 2, Open Label, Randomized	100	April 2006	Complete

Lacouture, Oncology 2009 (www.clinicaltrials.gov (Accessed 10/28/08))



N03CB: Tetracycline for Rash Prevention

Eligibility: patients with cancer who had started EGFR inhibitor therapy within 7 days
No rash
No recent tetracycline
N=61

- Tetracycline 500 mg orally twice a day x 1 month
- Placebo orally twice a day x 1 month

- Primary endpoint: rash incidence
- Secondary endpoint: rash severity
- Assessment
 - CTCAE v3.0 monthly physician reports x 8 weeks
 - Weekly patient reports x 8 weeks (questionnaires, Skindex-16)

Jatoi et al, Cancer 2007

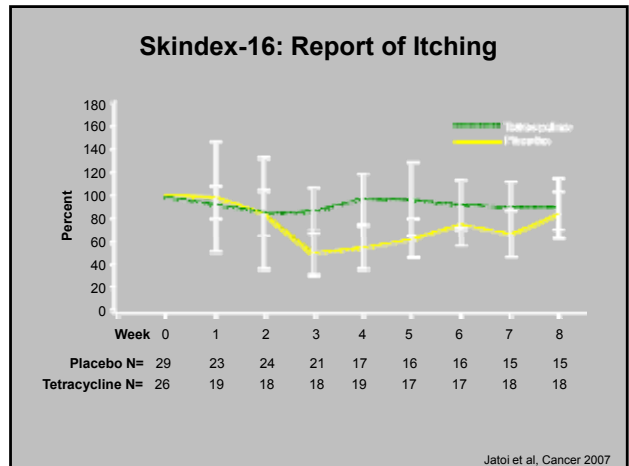
Tetracycline for Rash Prevention: Results

Assessment	Physician-Reported Rash Incidence, %		
	Tetracycline N=31	Placebo N=30	P Value
4 Weeks	70%	76%	0.61

Assessment	Grade ≥2 Physician-Reported Rash Severity, N (%)		
	Tetracycline	Placebo	P Value
4 Weeks	4 (17)	16 (55)	0.009

- Patient reports similar to physician results
- 3 patients in each arm stopped EGFR inhibitor treatment early

Jatoi et al, Cancer 2007



Tazarotene and Minocycline for Rash Prevention

Cetuximab therapy for CRC

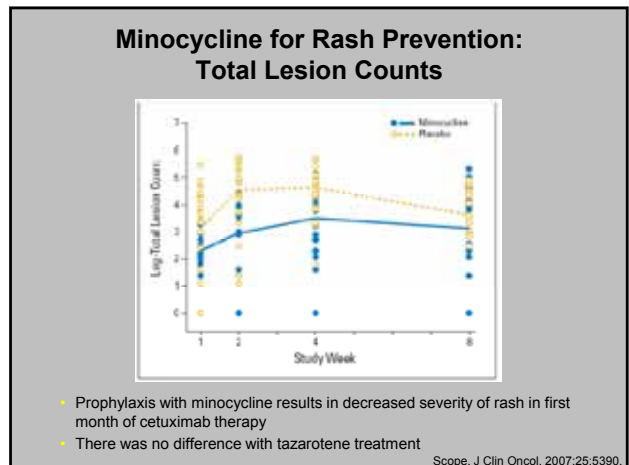
Randomize

Minocycline 100 mg Daily N=24		Daily Placebo N=24	
0.05% tazarotene cream daily to left half of face N=12	0.05% tazarotene cream daily to right half of face N=12	0.05% tazarotene cream daily to left half of face N=12	0.05% tazarotene cream daily to right half of face N=12

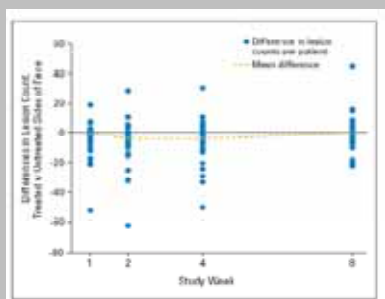
18 Analyzed 2 Months 17 Analyzed

Total lesion count each side of face

Scope, J Clin Oncol. 2007;25:5390.



Tazarotene and Minocycline for Rash Prevention: Difference in Lesion Counts per Patient

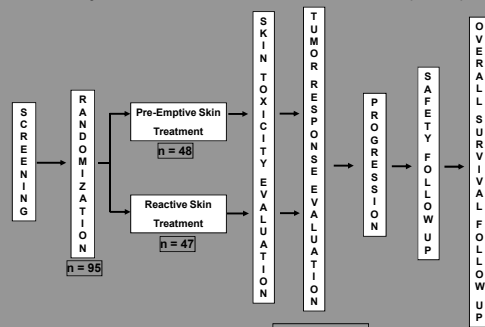


• Tazarotene application showed no clinical benefit

Scope. *J Clin Oncol*. 2007;25:5390.

STEPP Study Schema

Phase 2, open-label study of pre-emptive versus reactive skin toxicity treatment in metastatic colorectal cancer (mCRC)



Mitchell et al, ASCO 2009

Skin Treatment

- Prophylactic skin treatment regimen administered weeks 1 to 6 (beginning day 1):
 - Skin moisturizer – apply to face, hands, feet, neck, back, and chest daily in the morning upon rising
 - Sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection) – apply to exposed skin areas before going outdoors
 - Topical steroid (1% hydrocortisone cream) – apply to face, hands, feet, neck, back, and chest at bedtime
 - Doxycycline 100 mg BID
- Per investigator discretion, a reactive skin treatment was administered anytime during weeks 1-6
- From week 7 and thereafter, investigators had the option to continue patients on the assigned skin treatment regimen

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Table 1: Patient Disposition

	Prophylactic Skin Treatment n = 48	Reactive Skin Treatment n = 47
Patients who ended second-line treatment – n (%)	48 (100)	47 (100)
Reason for ending treatment – n (%)		
Disease progression	30 (63)	28 (60)
Adverse event	5 (10)	5 (11)
Patient request	5 (10)	6 (13)
Death	3 (6)	2 (4)
Other	5 (10)	6 (13)
Median follow-up time ¹ , weeks	31.0	40.7

¹ Follow-up time is calculated as the randomization date to the last on-study or long-term follow-up visit.

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Table 1: Demographics and Disease Characteristics (cont'd)

	Prophylactic Skin Treatment n = 48	Reactive Skin Treatment n = 47
Sex – n (%)		
Men	32 (67)	26 (55)
Race – n (%)		
White or Caucasian	34 (71)	40 (85)
Black or African American	6 (13)	5 (11)
Hispanic or Latino	5 (10)	1 (2)
Other	3 (6)	1 (2)
Age – years, median (min, max)	60 (24, 84)	61 (40, 86)
ECOG performance status – n (%)		
0	34 (71)	30 (64)
1	12 (25)	17 (36)
2	2 (4)	0 (0)
Primary tumor type – n (%)		
Colon	34 (71)	28 (60)
Rectal	14 (29)	19 (40)
Number of metastatic sites – n (%)		
1	18 (38)	17 (36)
> 1	30 (63)	30 (64)

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Primary Endpoint - Incidence of Grade 2 or Higher Skin Toxicities¹ in Prophylactic vs Reactive Skin Treatment Arms (During the Skin Treatment Period, Final Analysis)

	Prophylactic Skin Treatment n = 48	Reactive Skin Treatment n = 47
Patients with grade 2 or higher skin toxicity – n (%) ²	14 (29)	29 (62)
Odds Ratio ³ (95% CL)	0.3 (0.1, 0.6)	
Grade 2 – n (%)	11 (23)	19 (40)
95% CI	11 - 35	26 - 54
Grade 3 – n (%)	3 (6)	10 (21)
95% CI	0 - 13	10 - 33

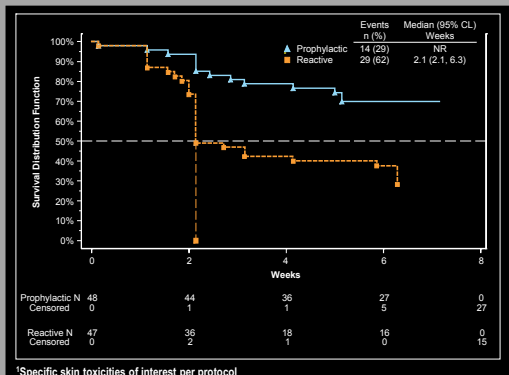
¹ Specific skin toxicities of interest per protocol

² There were no grade 4 skin toxicities during the skin treatment period

³ Odds ratio is estimated from a logistic regression model including treatment (prophylactic vs reactive) that includes an adjustment for chemotherapy stratum (Q2W vs Q3W)

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Probability of Grade 2 or Higher Skin Toxicity by Time on the Study



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Best Overall Response¹ and Progression-free Survival By Skin Treatment Group

	Central Review	
	Prophylactic n = 48	Reactive n = 47
Best overall response - n (%)	7 (15)	5 (11)
Complete response	0 (0)	0 (0)
Partial response	7 (15)	5 (11)
Stable disease	24 (50)	25 (53)
Disease control	31 (65)	30 (64)
Disease progression	9 (19)	10 (21)
Not done or unevaluable	8 (17)	7 (15)
Progression free survival - KM Median (95% CI) Months	4.7 (2.9 - 6.0)	4.1 (2.9 - 6.2)

¹By independent central review and confirmed by a follow-up assessment no less than 28 days after the criteria for response were first met

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Best Overall Response¹ and Progression-free Survival by KRAS Status and Skin Treatment Group²

Central Review	Wild-type KRAS		Mutant KRAS	
	Prophylactic (N = 23)	Reactive (N = 26)	Prophylactic (N = 21)	Reactive (N = 17)
	Best overall response - n (%)	4 (17)	4 (15)	2 (10)
Complete response	0 (0)	0 (0)	0 (0)	0 (0)
Partial response	4 (17)	4 (15)	2 (10)	1 (6)
Stable disease	13 (57)	13 (50)	11 (52)	10 (59)
Disease control	17 (74)	17 (65)	13 (62)	11 (65)
Disease progression	3 (13)	7 (27)	5 (24)	1 (6)
Not done or unevaluable	3 (13)	2 (8)	3 (14)	5 (29)
Progression free survival - KM Median (95% CI) Months	6 (4 - 9)	5 (2 - 8)	3 (3 - 5)	3 (3 - 9)

¹Responses were confirmed via central review and confirmed 28 days after the criteria for response was first met.

²This was an unplanned analysis

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Adverse Events of Interest¹ Week 1 Through the Safety Follow-up

	Prophylactic Skin Treatment - n = 48			Reactive Skin Treatment - n = 47		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Pts with any event - n (%)	48 (100)	20 (42)	5 (10)	47 (100)	25 (53)	10 (21)
Dermatitis acneiform	37 (77)	2 (4)	0 (0)	40 (85)	10 (21)	0 (0)
Pruritus	30 (63)	1 (2)	0 (0)	32 (68)	5 (11)	0 (0)
Pustular rash	13 (27)	2 (4)	0 (0)	19 (40)	8 (17)	0 (0)
Paronychia	8 (17)	0 (0)	1 (2)	17 (36)	3 (6)	0 (0)
Nausea	32 (67)	3 (6)	0 (0)	26 (55)	4 (9)	0 (0)
Vomiting	22 (46)	3 (6)	0 (0)	17 (36)	4 (9)	0 (0)
Fatigue	29 (60)	5 (10)	0 (0)	27 (57)	5 (11)	0 (0)
Diarrhea	27 (56)	7 (15)	0 (0)	40 (85)	15 (32)	0 (0)
Neutropenia	9 (19)	3 (6)	1 (2)	20 (43)	8 (17)	4 (9)
Hypomagnesemia	7 (15)	1 (2)	1 (2)	13 (28)	2 (4)	1 (2)
Dehydration	6 (13)	3 (6)	0 (0)	16 (34)	8 (17)	0 (0)

¹There were no grade 5 adverse events of interest

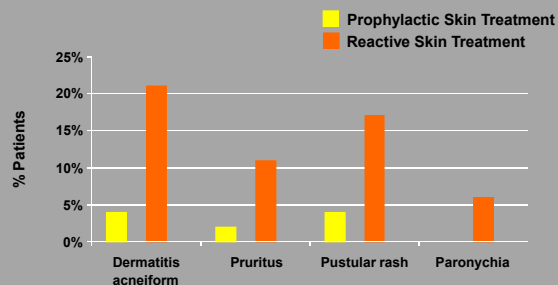
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Treatment Exposure

	Prophylactic Skin Treatment	Reactive Skin Treatment
Total number of panitumumab doses ¹	325	333
Total panitumumab doses delayed during the study ¹ - n (%)	12 (4)	21 (6)

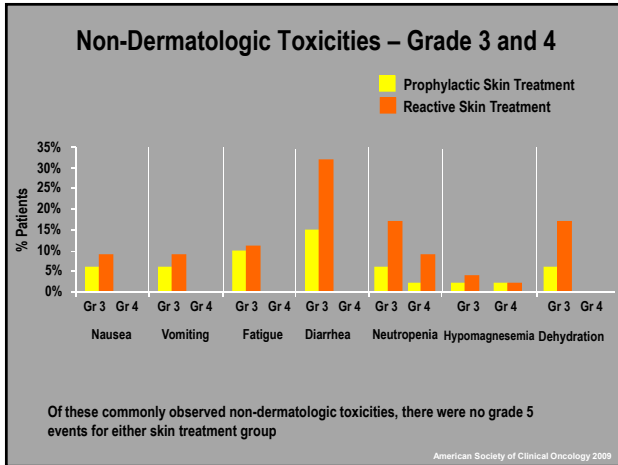
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Dermatologic Toxicities - Grade 3



Of these commonly observed dermatologic toxicities, there were no grade 4 or 5 events for either skin treatment group

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Mean (SD) DLQI Score Change from Baseline to Week 3 and Week 7¹

	Prophylactic Skin Treatment n = 46	Reactive Skin Treatment n = 44
Mean (SD) DLQI change from baseline to week 3 – points	1.3 (2.6)	4.2 (5.8)
Mean (SD) DLQI change from baseline to week 7 – points	2.0 (2.8)	2.6 (4.4)

¹Based on the PRO Analysis Set defined as patients who had a baseline and at least 1 post-baseline DLQI score

Patients in the prophylactic skin treatment group reported improved quality of life, especially during weeks 2 to 3 when the median time to first ≥ grade 2 skin toxicity of interest was reached in the reactive skin treatment group

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Topical Menadione restores EGFR signaling in the skin

- Rash believed to be due to EGFR inhibition in normal skin
- Menadione not expected to affect EGFRi anti-tumor activity
- Potential to address similar toxicities with other TKIs
- Non-greasy, non-staining, odorless lotion

Perez-Soler, R et al., ASCO 2006, abstract #3036

Phase 1 may provide proof-of-concept

TREATMENT EMERGENT GROUP
EGFRi-treated patients with early rash (n = 12)

TREATMENT PRE-EMERGENT GROUP
Patients scheduled to begin an EGFRi (n = 12)

Twice-daily topical menadione to half of the face/neck and upper torso

Twice-daily excipient lotion to the other half of the face/neck and upper torso

Safety assessments including close primary tumor monitoring

Pharmacokinetic and bioavailability profiling

Visual and biopsy assessment of activity

Conclusions

- Dermatologic toxicities are amenable to study and treatment
- Clinical trials are underway in interdisciplinary setting
- Improved/consistent reporting and grading of toxicities is critical
- Characterization of dermatologic toxicities will increase in importance
 - Adjuvant setting
 - Dose escalation/combination studies
 - Survivorship issues

Malignancy associated

Treatment-related

Late events

Agha et al, Oncology 2007

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