New and Emerging Drug Reactions

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Disclosures

- None

New and Emerging Drug Reactions

"There are some remedies worse than the disease"

Publilius Syrus (c.42 BC)

Cutaneous Drug Reactions

- Most common side effect of medications
  - 30% of all ADR
  - 2.25 million pts./year in US
  - 1-3% of hospitalized patients

"Mrs. Nortman just sent in this fax of a rash that she's got on her stomach."

Cutaneous adverse event diagnosis

- Dermatologist (Allergist?) as psychic
  - Polypharmacy
  - Murky drug exposure history
  - Inaccurate drug 'allergy' history
  - Skin biopsy "to identify offending agent"

Is the eruption a drug reaction?

- **Known** reaction to the drug in question?
- **Previous** exposure to drug?
- **Exclude** other causes (e.g. viral exanthem)?
- **Temporal** relationship between drug use and reaction?
- **Improvement** following drug cessation?
- **Reactivation** upon drug re-challenge?

Cutaneous adverse event diagnosis

- Dermatologist (Allergist?) as psychic
  - Polypharmacy
  - Murky drug exposure history
  - Inaccurate drug 'allergy' history
  - Skin biopsy "to identify offending agent"

- References
  - ePocrates
  - Litt's Drug Eruption & Reaction Manual
  - www.pubmed.gov

Naranjo criteria

Table 2: The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total	

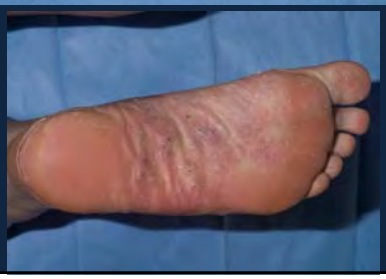
Scoring: 0: doubtful 1-4: possible 5-8: probable 9 or >: definite

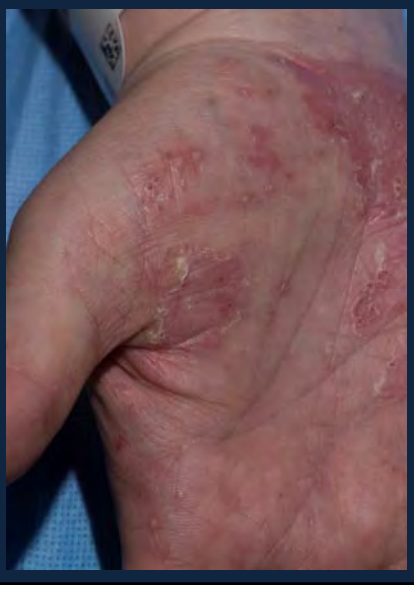
https://www.biomedcentral.com/content/.../1471-2318-9-5-s2.doc

Case 1

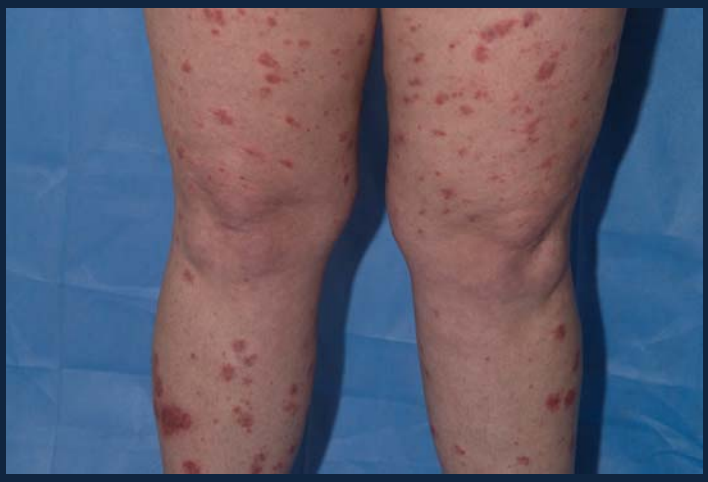
- Iatrogenic vs. innate?

40 year old with palmo-plantar psoriasis





1 month after starting adilimumab: Is this eruption a drug reaction?



- Generalized pustular psoriasis following treatment with adalimumab for palmo-plantar disease

Table I. Psoriasis associated with anti–tumor necrosis factor-α therapy: General features of patients in current study compared with 120 other cases

Feature	Current study (N = 56)*	Wollina et al† (N = 120)
Female	41 (73%)	67%
Age at onset, mean (range), y		
Total	48.1 (17-86)	42.3 (13-78)
Women	46.7 (17-86)	
Men	51.8 (28-68)	
Diagnosis	22 (39%) CD	51% RA
	14 (25%) RA	8% AS
	9 (16%) PS	8% PS
	5 (9%) PA	7% CD
	6 (11%) Others‡	16% Others
Personal history of PS		
Yes	16 (29%) (mean age at onset, 19.5 y; range, 1-40 y)	21%
No	31 (55%)	73%
Unknown	9 (16%)	6%
Family history of PS		
Yes	13 (23%)	7%
No	30 (54%)	55%
Unknown	13 (23%)	38%
TNF-α inhibitor		
Infliximab	30 (54%)	53% Infliximab§
Adalimumab	19 (34%)	22% Adalimumab§
Etanercept	7 (12%)	31% Etanercept§
Timing of cutaneous adverse effects, mean (range), mo		
Overall	17.1 (1-96)	9.5 (0-63)
Infliximab	17.6 (1-60)	
Etanercept	27.1 (1-54)	
Adalimumab	12.1 (1-96)	
Cutaneous presentations of PS	25 (45%) Palmoplantar pustulosis	NA
	7 (12%) Generalized pustular PS	
	2 (4%) Erythrodermic PS	
	27 (48%) Plaque PS	
	2 (4%) Inverse PS	
	12 (21%) Scalp PS	

J Am Acad Dermatol 2012;67:e179-85.

Anti-TNF "Paradoxical"Autoimmunity

Medicine • Volume 86, Number 4, July 2007

TABLE 1. Registry of Autoimmune Diseases Associated With Anti-TNF Agents*

Disease	Total No. of Cases Reported
Cutaneous leukocytoclastic vasculitis	79
Lupus-like syndrome	48
Systemic lupus erythematosus	37
Interstitial lung disease	18
Cutaneous necrotizing vasculitis	8
Isolated cutaneous lupus	7
Peripheral neuropathy	6
Rapidly progressive glomerulonephritis	5
Cutaneous lymphocytic vasculitis	4
Sarcoidosis	3
Henoch-Schönlein purpura	2
Pulmonary hemorrhage	2
Inflammatory myopathies	2
Antiphospholipid syndrome	2
Polyarteritis nodosa	1
Temporal arteritis	1
Urticarial vasculitis	1
Bronchiolitis obliterans organizing pneumonia	1
Other type of vasculitis	6
Total	**233**

*Last update: December 31, 2006.

Naranjo criteria

Table 2: The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
			Total	3

Scoring: 0: doubtful 1-4: possible 5-8: probable 9 or >: definite

https://www.biomedcentral.com/content/.../1471-2318-9-5-s2.doc

Table 1 Collective Data of 207 Patients Who Developed Psoriasis During TNF Antagonist Treatment

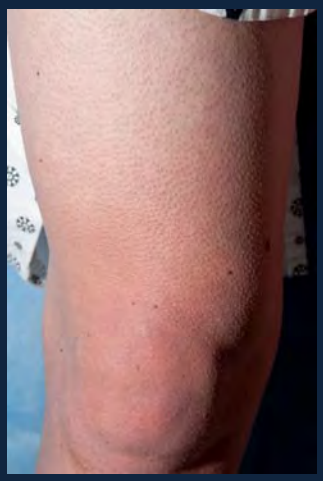
	Total	RA	SN	IBD	Psoriasis	Other
Number of patients	207	88	53	41	13	12
Men (%)	64 (35%)	9 (12%)	30 (57%)	12 (36%)	6 (55%)	7 (58%)
Women (%)	119 (65%)	65 (88%)	23 (43%)	21 (64%)	5 (45%)	5 (42%)
Sex unknown	24	14	0	8	2	0
Age, mean (SD)	44.9 (14.6)	53.6 (12.1)	42.6 (12.1)	30.1 (9.6)	45.3 (13.3)	40.5 (13.6)
Age unknown	30	14	5	8	2	1
Infliximab (%)	121 (59%)	40 (45%)	33 (62%)	37 (90%)	3 (23%)	8 (66%)
Etanercept (%)	40 (19%)	19 (22%)	11 (21%)	0	8 (62%)	2 (17%)
Adalimumab (%)	46 (22%)	29 (33%)	9 (17%)	4 (10%)	2 (15%)	2 (17%)
Pustular	110 (56%)	46 (59%)	31 (58%)	20 (49%)	4 (30%)	9 (75%)
Plaque	98 (50%)	35 (45%)	29 (55%)	25 (61%)	3 (23%)	6 (50%)
Guttate	23 (12%)	10 (13%)	4 (7%)	2 (5%)	7 (53%)	0
New onset (%)	165 (85%)	79 (90%)	37 (70%)	39 (95%)	n/a	10 (83%)
Exacerbation (%)	29 (15%)	9 (10%)	16 (30%)	2 (5%)	n/a	2 (17%)
Resolved off anti-TNF (%)	50 (24%)	13 (15%)	10 (19%)	19 (46%)	5 (38%)	3 (25%)
Partial or no resolution off anti-TNF (%)	11 (5%)	3 (4%)	2 (4%)	4 (10%)	0	2 (17%)
Resolved on anti-TNF (%)	53 (26%)	30 (34%)	14 (26%)	7 (17%)	2 (15%)	0
Partial resolution on anti-TNF(%)	52 (25%)	21 (24%)	17 (32%)	7 (17%)	5 (38%)	2 (17%)
No reoccurrence with change of anti-TNF (%)	13 (6%)	8 (9%)	3 (6%)	0	1 (8%)	1 (8%)
No resolution on anti-TNF (%)	2 (1%)	2 (2%)	0	0	0	0
Resolved off anti-TNF, reoccurred with reintroduction (%)	4 (2%)	2 (2%)	0	0	0	2 (17%)
Resolved off anti-TNF, reoccurred with reintroduction of different anti-TNF (%)	12 (6%)	7 (8%)	2 (4%)	3 (7%)	0	0
Outcome unknown (%)	10 (5%)	2 (2%)	5 (9%)	1 (2%)	0	2 (17%)

Semin Arthritis Rheum 2010;40:233-240

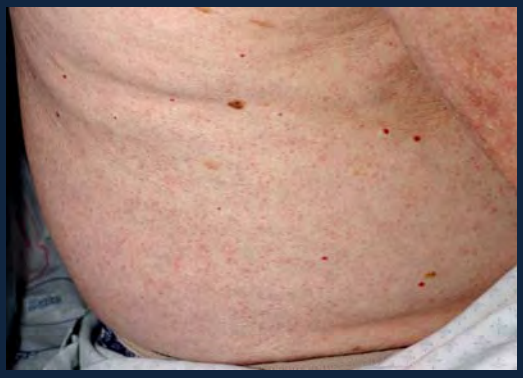
The challenge(s) of cutaneous drug reactions in 2016

- Not typical 'immunologic' (Type I-IV) hypersensitivity reactions
- Targeted therapies: very specific pathways/mechanisms involved → poorly understood reactions (paradoxical)
- Anti-neoplastic reactions: long-term AE management
  - Management of skin toxicity: $1920/pt.
- 'Class effect' with targeted agents: Anti-TNF, EGFRi

Raf-associated follicular hyperkeratosis



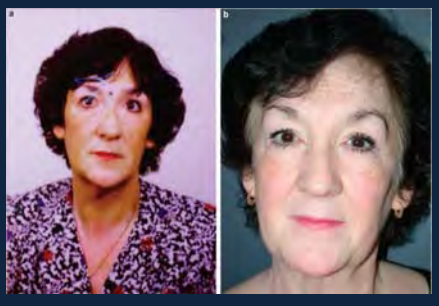
Vemurafenib
(BRAF inh.)



Sorafenib
(Multikinase RAF inh.)

Imatinib and cabozantinib: pigment dilution

Imatinib: bcr-abl, c-kit, PDGFR



Vitiligo before and during imatinib Tx

Br J Dermatol. 2005 Sep;153(3):691-2.
JAMA Dermatol. 2015 Feb;151(2):170-7.

Cabozantinib: C-MET, RET, VEGFR, AXL, TKR A/B, c-kit

During treatment

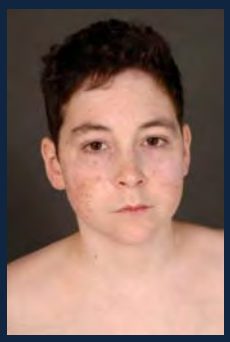
3 weeks after discontinuing drug

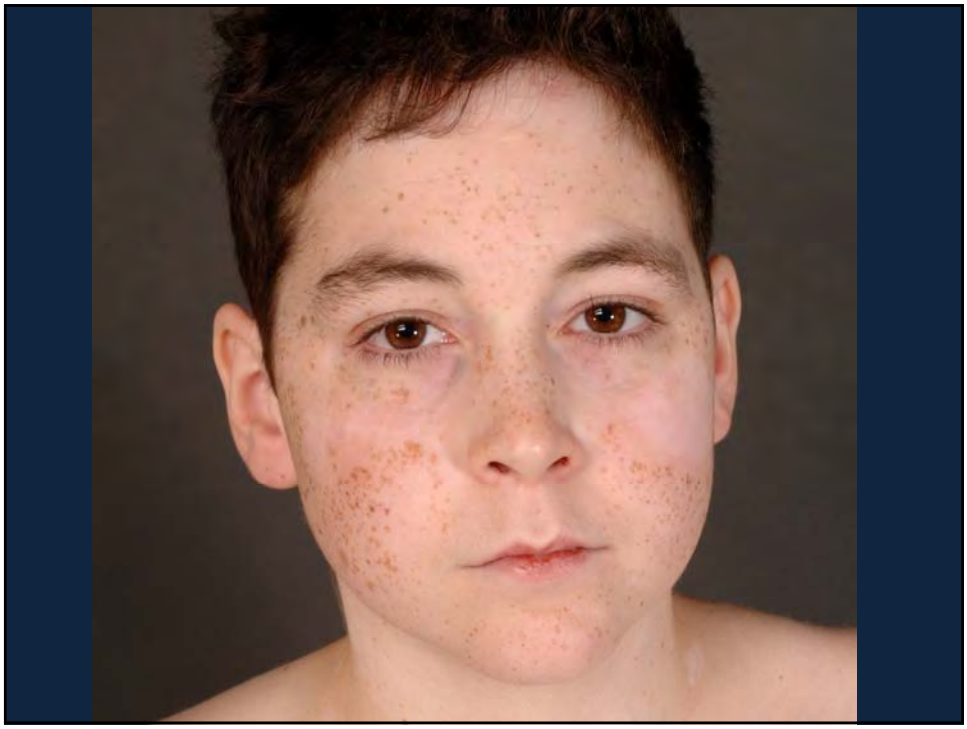
Case 2

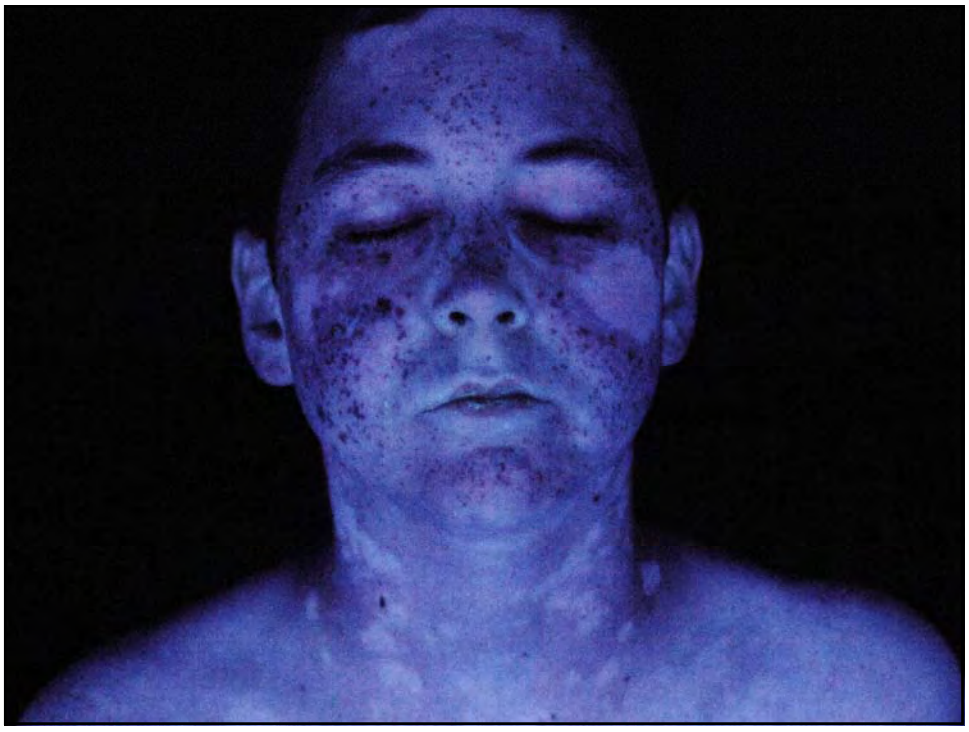
- Sunburn vs. GVHD in a child

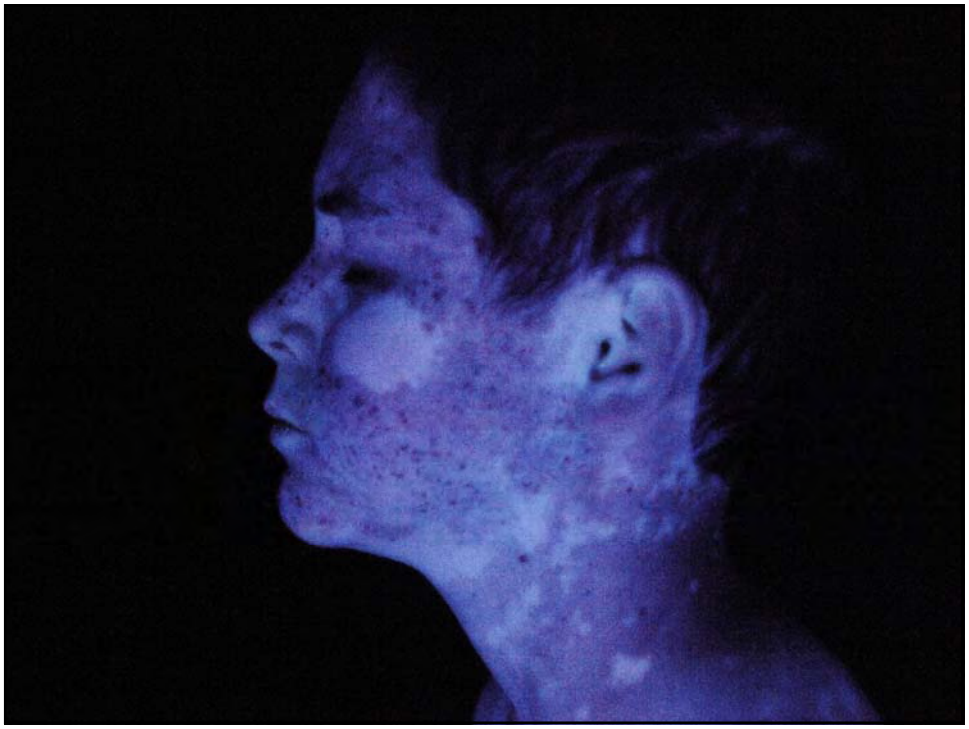
Patient 1: 15 year old boy

- Age 6:
  - Metastatic rhabdomyosarcoma
- Age 12: nonmyeloablative PBSCT
  - Day 8: acute skin GVHD
  - Day 100: lichen planus-like cGVHD
  - 20 months: vitiligo-like depigmentation

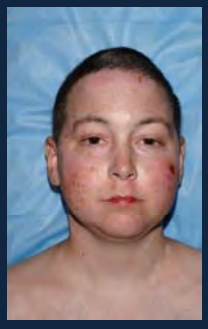




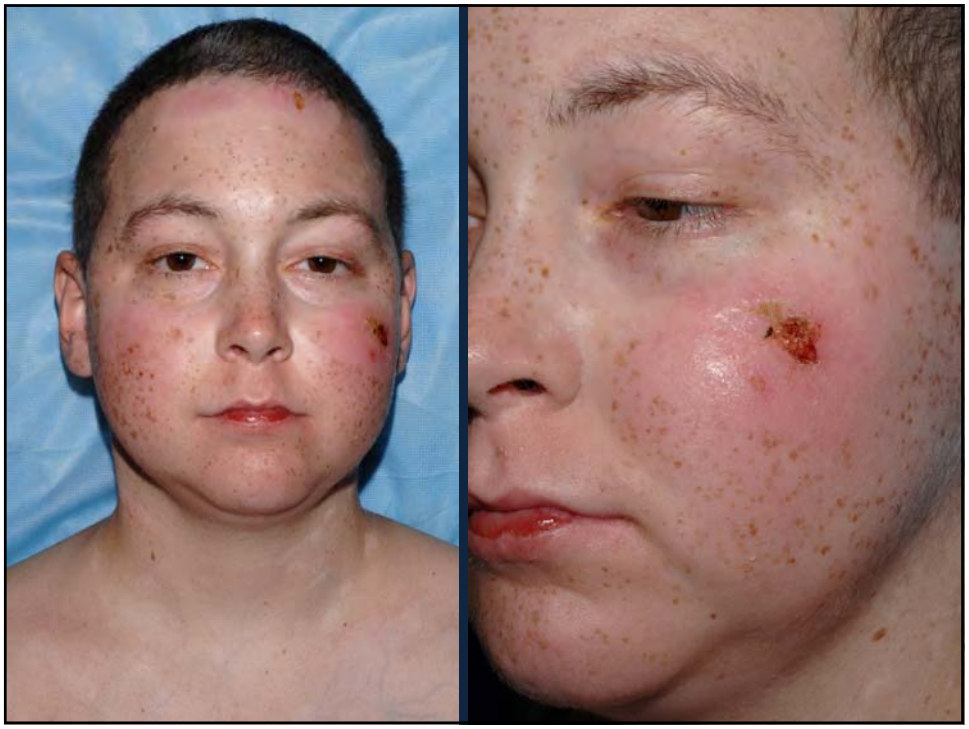


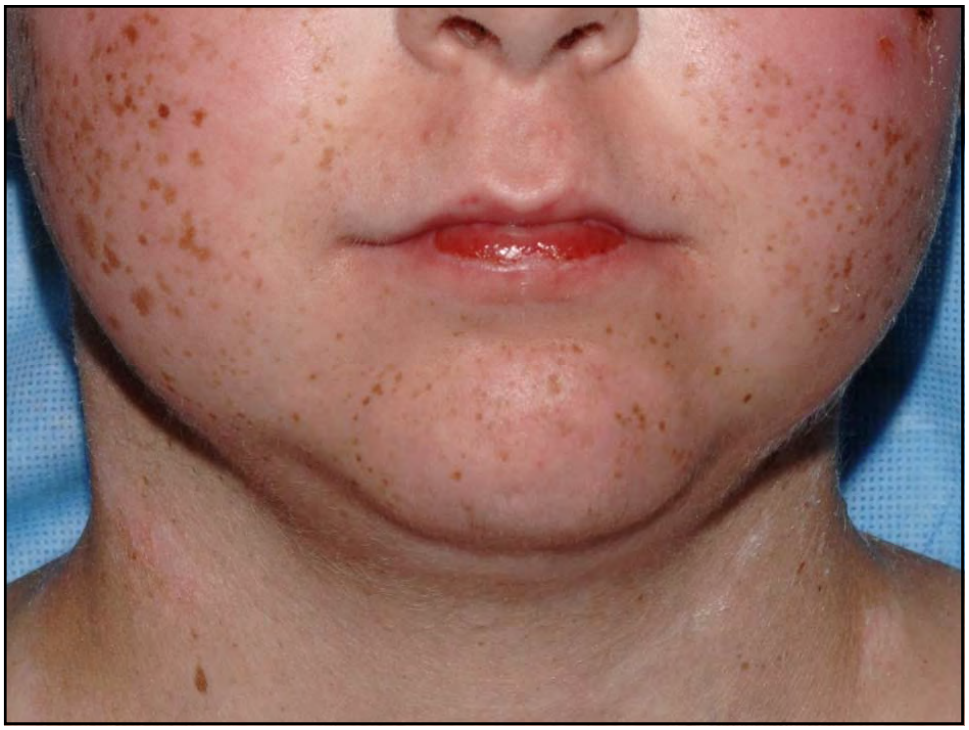


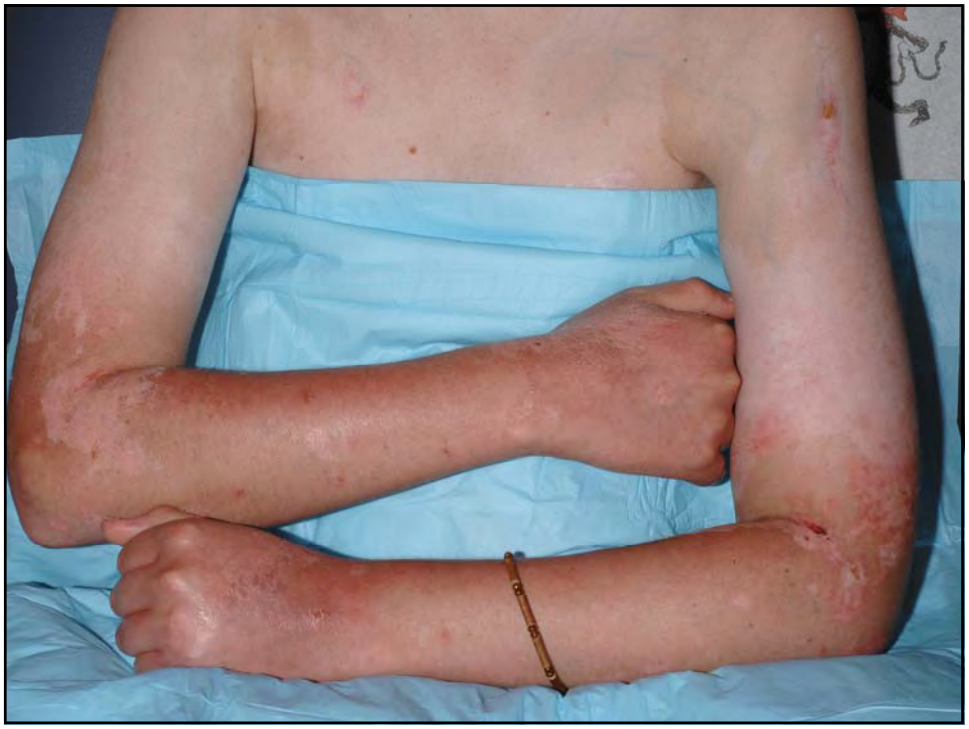
Patient 1: 15 year old boy

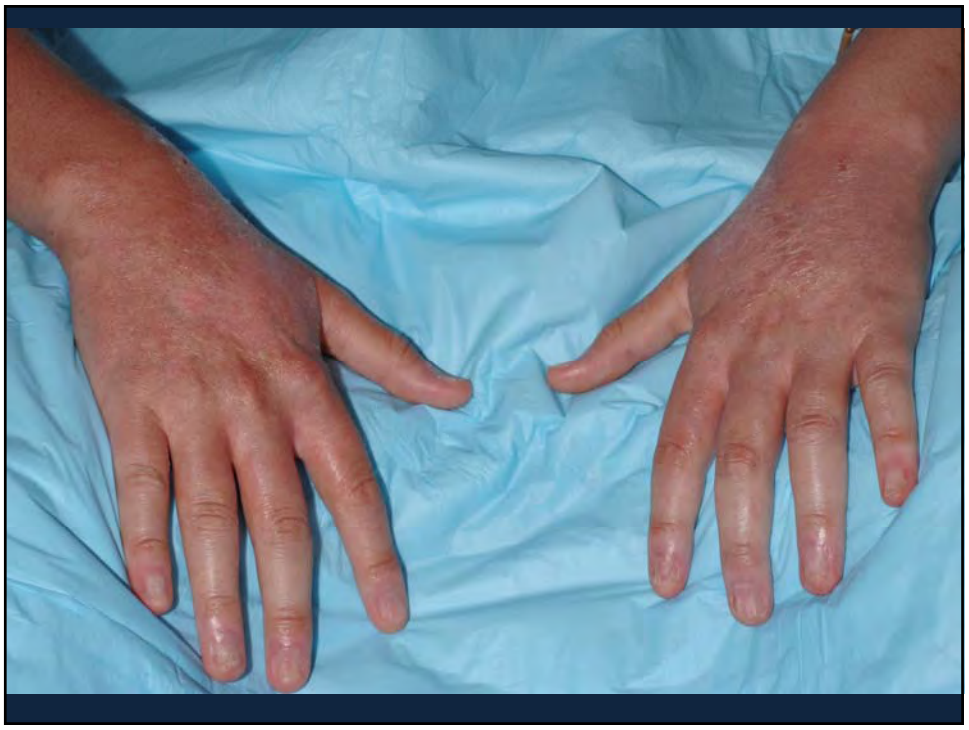


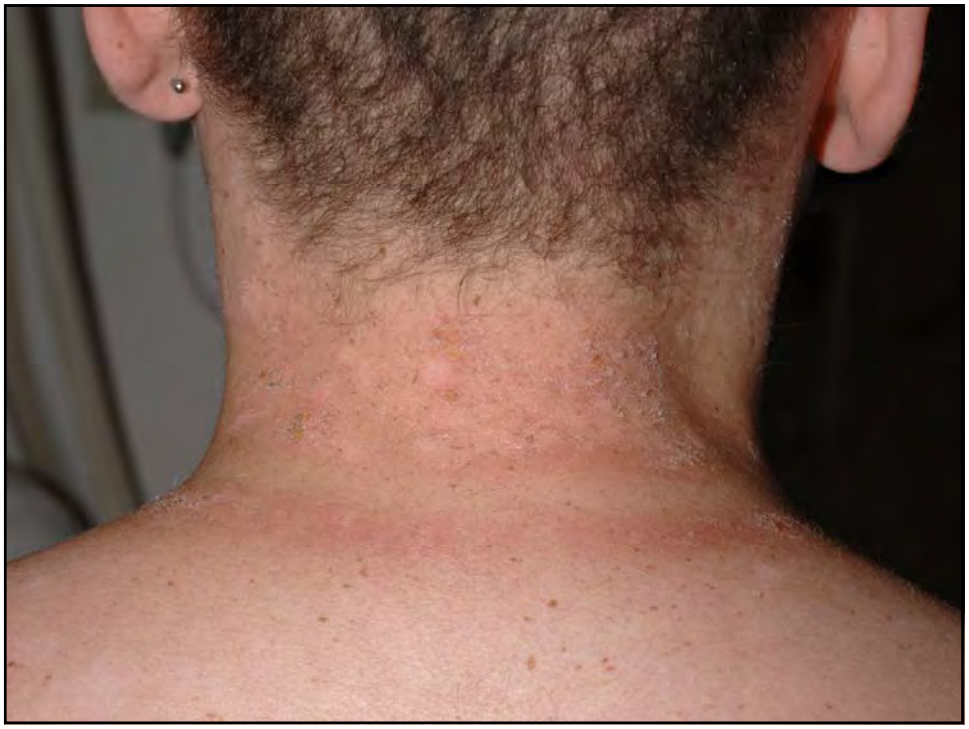
- Age 6: metastatic alveolar rhabdomyosarcoma
- Age 12: nonmyeloablative PBSCT
  - Day 8: acute skin GVHD
  - Day 100: lichen planus-like cGVHD
  - 20 months: vitiligo-like depigmentation
  - 34 months: intense erythema of forehead, malar cheeks, upper extremities and feet
  - Returns to NIH for presumed flare of cGVHD

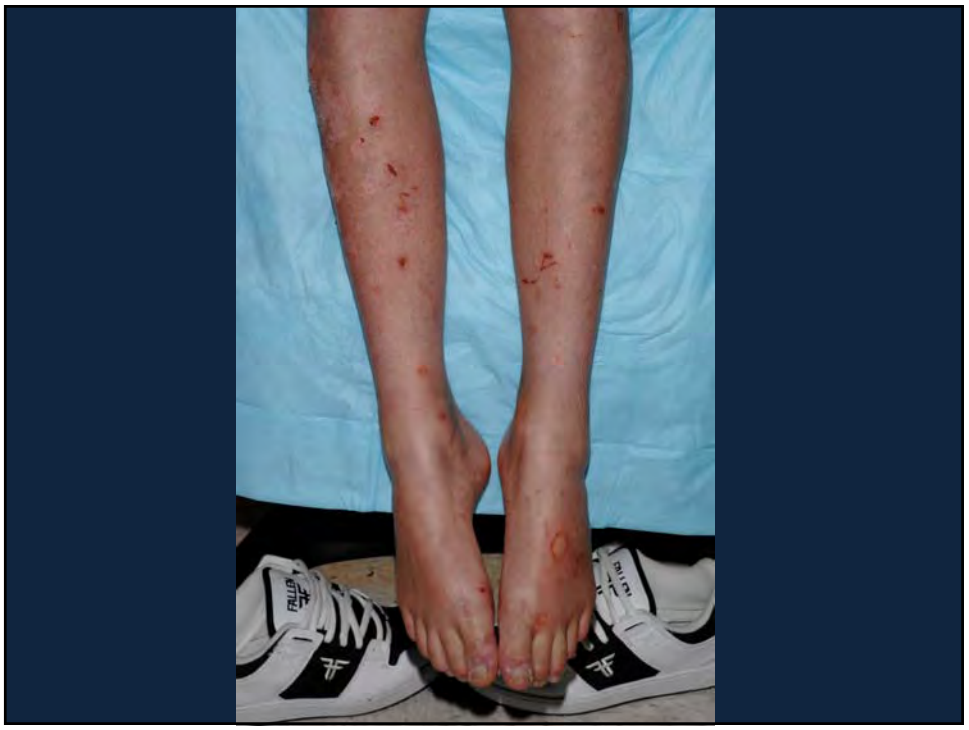


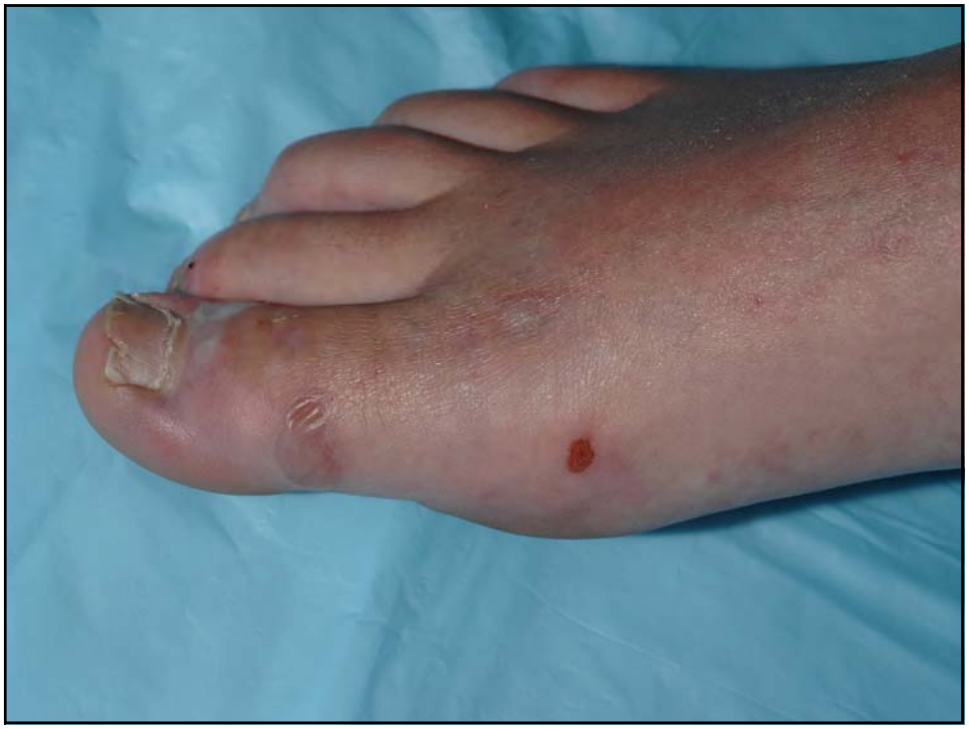










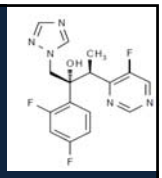


Voriconazole-induced phototoxicity

- Voriconazole 200mg QD two weeks prior to onset for presumed pulmonary aspergillosis

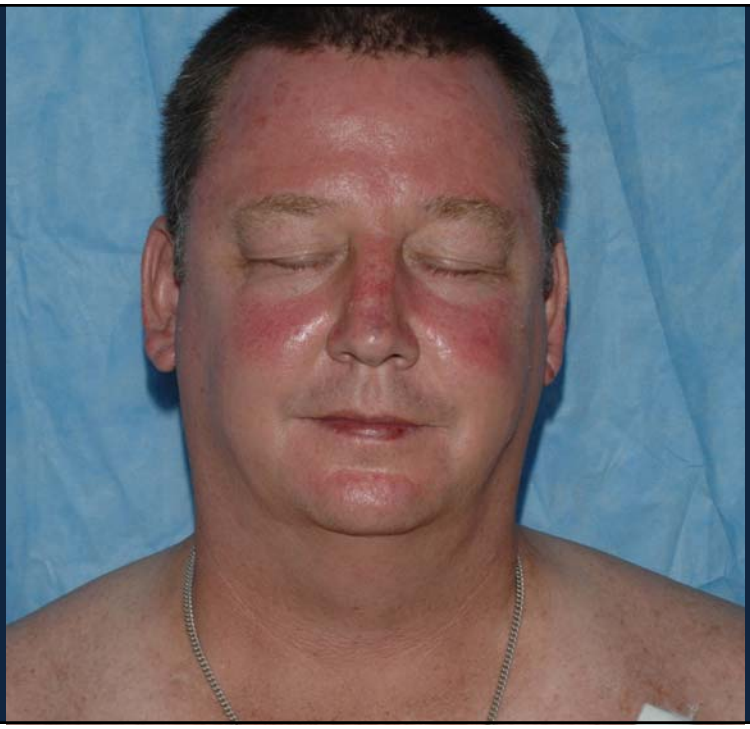
- Dx: phototoxicity/pseudoporphyria cutanea tarda
- Tx: voriconazole replaced with posaconazole
  - Strict photoprotection instituted
  - F/u 3 weeks later: resolution of bulle/erythema improved

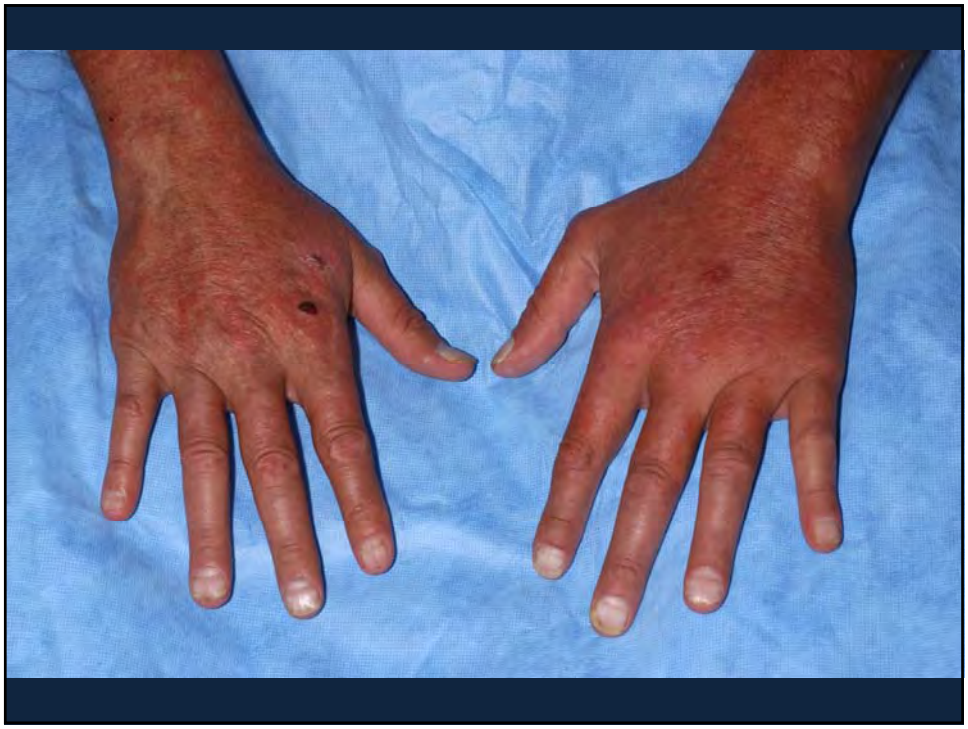
Voriconazole (Vfend®)



- 2nd generation orally bioavailable triazole
- FDA approval 2001
  - Invasive aspergillosis
  - Candidemia, esophageal and disseminated candidiasis
- Side effect profile
  - Vision changes (20%)
  - Hallucinations (15%)
  - Hepatic enzyme abnormalities (12-20%)
  - "Skin reactions" (attributable to drug: 7%)
    - Photosensitive rash (2%)

Vfend (Voriconazole, Oral and Intravenous Formulations), NDA 21-267, Briefing Document for FDA Antiviral Drugs Advisory Committee Meeting, 4 October 2001. Pfizer Inc. [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_01_Pfizer.pdf





Photodermatol Photoimmunol Photomed 2007; 23: 29–31
Blackwell Munksgaard

Photodermatology
Photoimmunology
& Photomedicine

Brief communication

Voriconazole-induced pseudoporphyria

J P Tolland[1], P P McKeown[2], J R Corbett[3]

[1]*Departments of Dermatology, Belfast City Hospital Trust, Royal Hospitals Trust Belfast,* [2]*Department of Cardiology, Royal Hospitals Trust Belfast, and* [3]*Department of Dermatology, Royal Hospitals Trust Belfast*

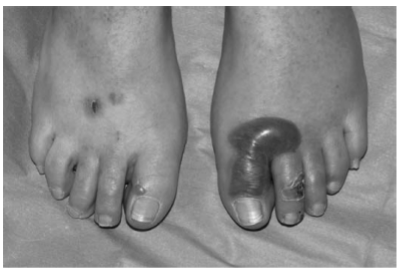


Fig. 1. Bullae and erosions on the dorsal aspects of the feet.

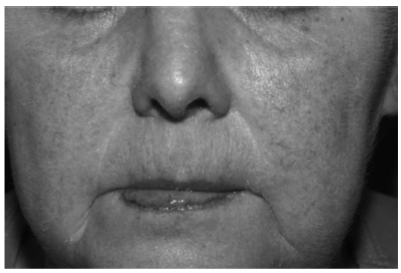
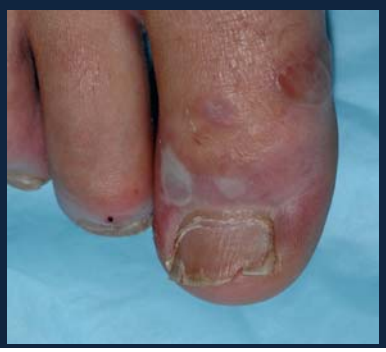
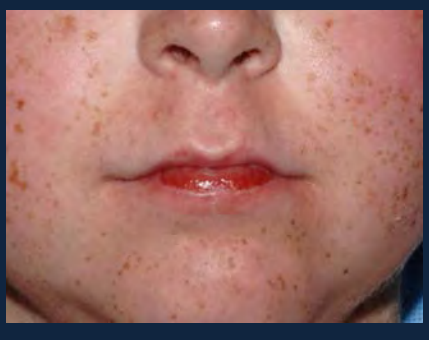
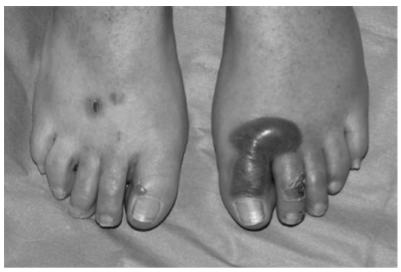


Fig. 2. Erosive lesions on lips.







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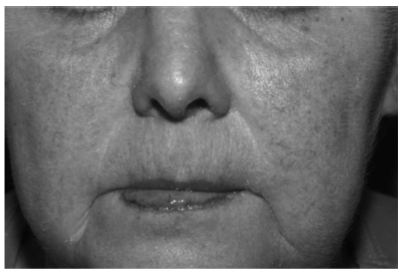


Fig. 2. Erosive lesions on lips.

ASBMT
American Society for Blood and Marrow Transplantation

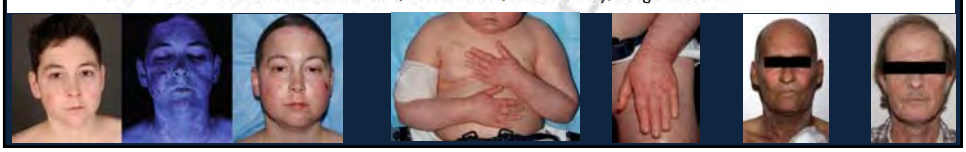
Voriconazole-Induced Phototoxicity Masquerading as Chronic Graft-versus-Host Disease of the Skin in Allogeneic Hematopoietic Cell Transplant Recipients

Asha R. Patel,[1] Maria L. Turner,[1] Kristin Baird,[2] Juan Gea-Banacloche,[3] Sandra Mitchell,[4] Steven Z. Pavletic,[3] Barbara Wise,[2] Edward W. Cowen[1]

Systemic fungal infections pose a significant risk to patients following allogeneic hematopoietic cell transplantation (alloHCT). Voriconazole (Vfend®, Pfizer) is an oral second-generation triazole antifungal agent that offers a broad spectrum of coverage against fungal species and is frequently utilized in the post-HCT setting. Herein, we describe 5 patients who were initially believed to be experiencing a flare of cutaneous chronic graft-versus-host disease (cGVHD), but who were actually exhibiting phototoxicity caused by voriconazole. A high index of suspicion for this adverse reaction in the post-alloHCT setting will prevent misdiagnosis and avoid inappropriate therapy for cGVHD.

Biol Blood Marrow Transplant ■: 1-7 (2008)

KEY WORDS: Graft-versus-host disease, Voriconazole, Phototoxicity, Fungal infection



Photoaging and phototoxicity from long-term voriconazole treatment in a 15-year-old girl

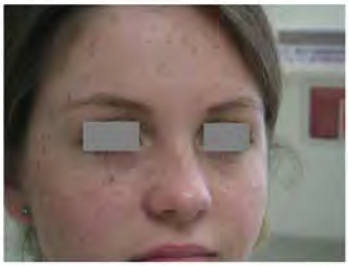


Fig 1. Numerous solar lentigines and ephelides on face 4 weeks after discontinuation of voriconazole treatment.

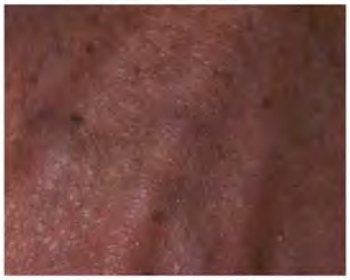
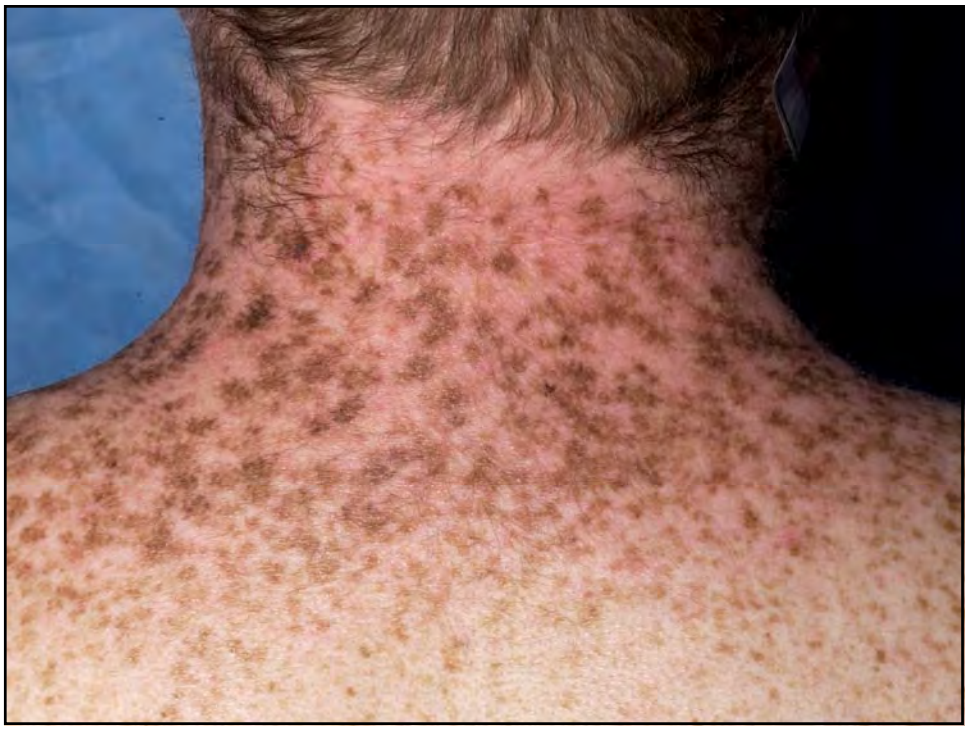
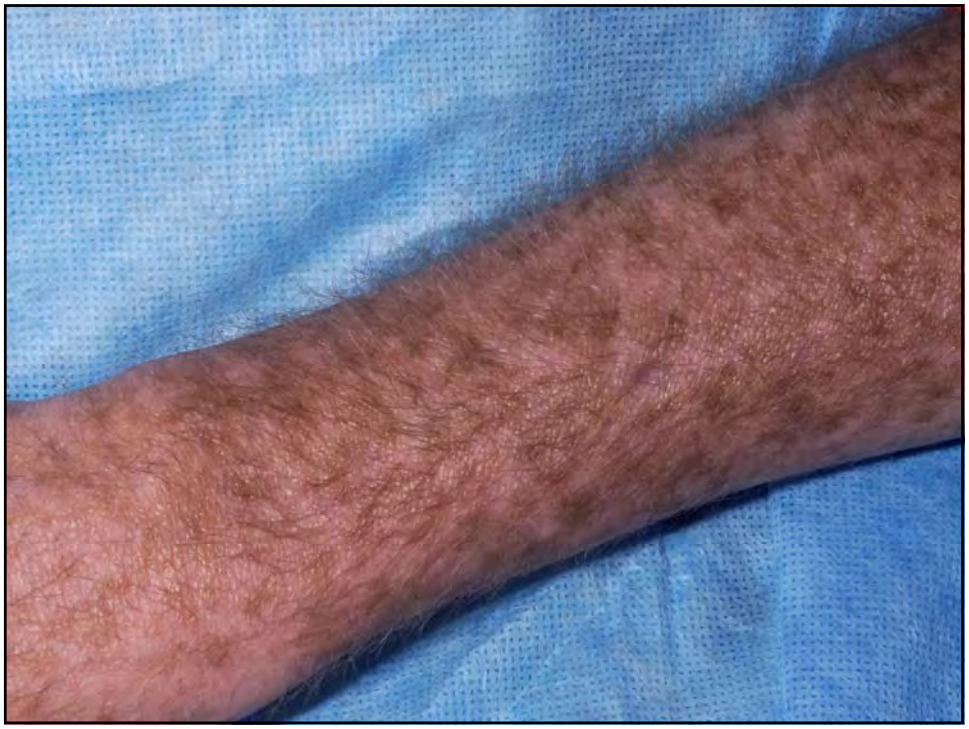
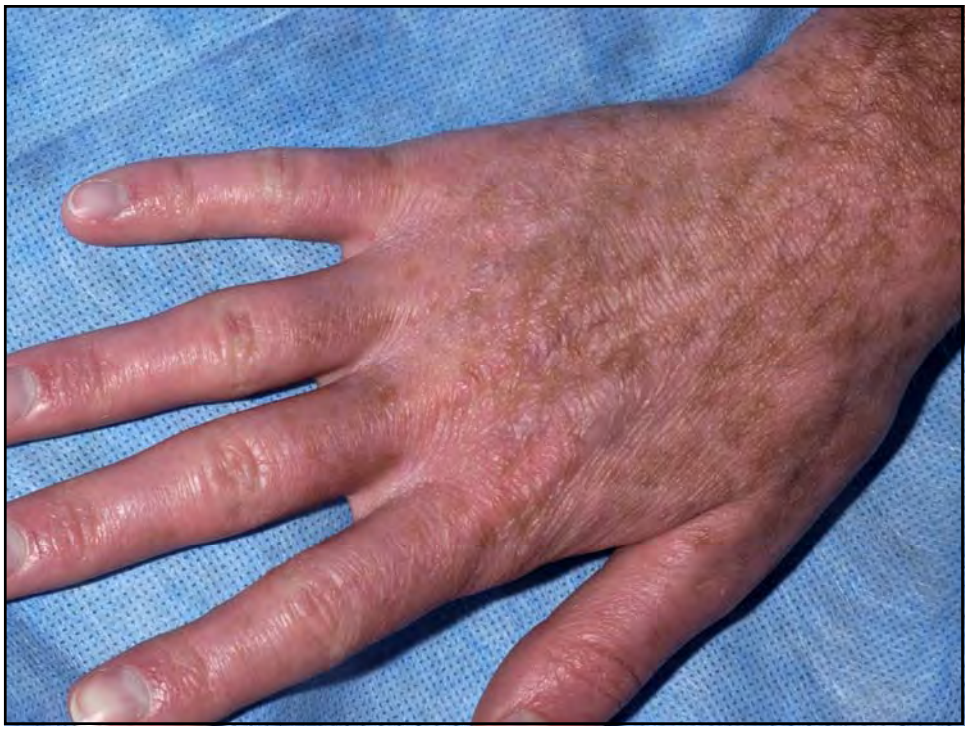


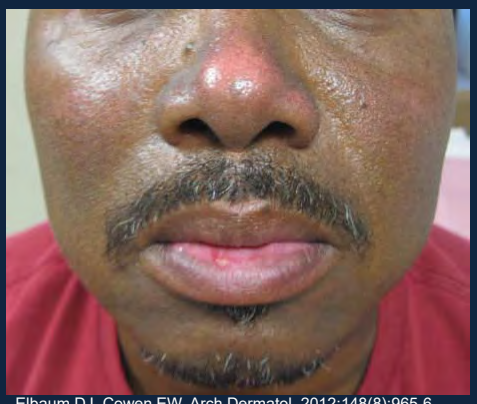
Fig 2. Solar elastosis and lentigines on back of left hand immediately after discontinuation of voriconazole treatment.



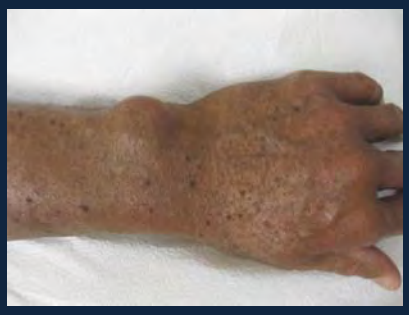


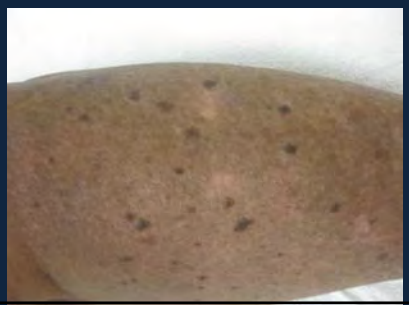


Voriconazole phototoxicity/photoaging in an AA-male with coccidiomycosis



Elbaum DJ, Cowen EW. Arch Dermatol. 2012;148(8):965-6.





What is the true incidence of voriconazole-induced phototoxicity?

- Product labeling not generalizable to current Tx population
- Phototoxicity requires **both** drug and sufficient UV exposure
  - FDA trial data: critically ill inpts → limited outdoor exposure
  - NIH population: ambulatory outpt. population with chronic immunodeficiency (CGD, Job syndrome, cGVHD)
- The incidence of voriconazole-associated phototoxicity in the **ambulatory** (UV-exposed) population likely higher than described in product label

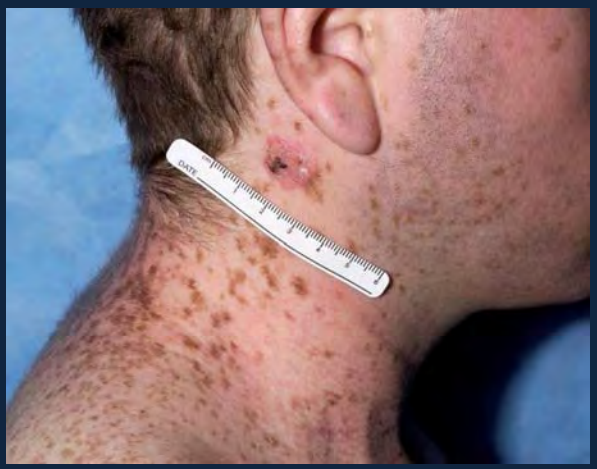
High frequency of voriconazole-related phototoxicity in patients with cystic fibrosis

TABLE 1 Description of the whole population exposed to voriconazole and comparison regarding photosensitivity groups

	Total population	Photosensitivity	No photosensitivity	p-value
Subjects n	31	18	13	
Photosensitivity	18 (58.1)	18	0	
Age yrs	15.8 (4–35)	13.5 (4–26.1)	16.8 (6.75–35)	0.08
Age <18 yrs	19 (61.3)	12 (66.7)	7 (53.8)	0.28
Sex male/female n	15/16	8/10	8/5	0.60
Weight kg	44 (10.6–77)	41 (10.6–57)	50 (17.3–77)	0.03
CFTR mutation (ΔF508)				0.004
ΔF508/ΔF508	13 (41.9)	12 (66.7)	1 (7.7)	
ΔF508/other	16 (51.6)	5 (27.8)	11 (84.6)	
Other/other	2 (6.5)	1 (5.6)	1 (7.7)	
CFTR mutation (class II)				0.024
Class II/class II	18 (58.1)	14 (77.8)	4 (30.8)	
Class II/other	11 (35.5)	3 (16.7)	8 (61.5)	
Other/other	2 (6.5)	1 (5.6)	1 (7.7)	
Pancreatic insufficiency	27 (87.1)	17 (94.4)	10 (76.9)	0.36
Daily dose of voriconazole				
mg	400 (120–400)	400 (120–400)	400 (200–400)	
mg·kg^{-1}	8 (5.0–24.2)	9 (1.3–28)	8 (2.5–64)	0.10
Time of drug exposure months	6.5 (1.3–64)	6.5 (1.3–28)	15 (2.5–64)	0.44
Treatment interruption in relation with skin reactions	11 (35.5)	11 (61.1)	0	

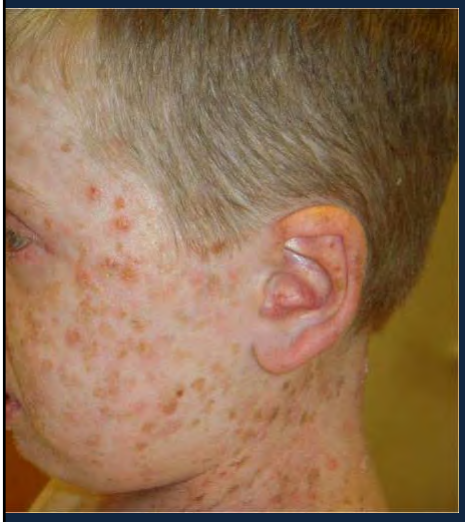
Eur Respir J. 2012 Mar;39(3):782-4.

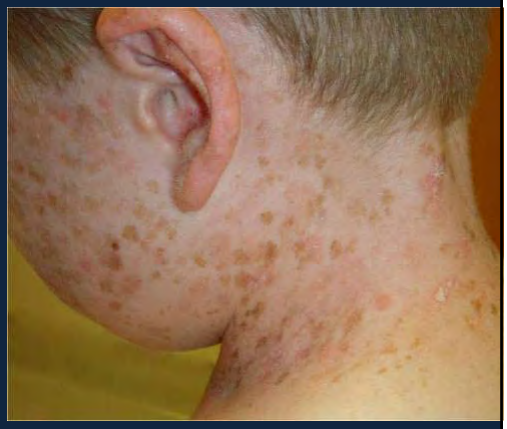
Voriconazole-associated phototoxicity/SCC



22 yo HIV+ pt. with Bowens disease (SCC *in situ*) on chronic voriconazole

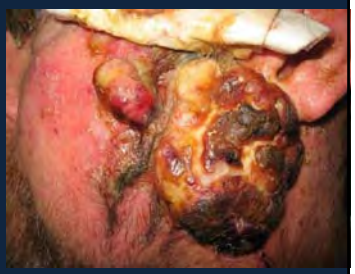
9 yo with cGVHD with 2 SCC on chronic voriconazole





Voriconazole and SCC

- 51 SCC/8 immunocompromised pts with chronic voriconazole-associated phototoxicity (age 9-54 yrs)
- Duration of immunosuppression
  - Median 51 mos (range 13-122 mos)
- Duration of voriconazole Tx
  - Median 46.5 mos (range 13-60 mos)
- "High-risk" immunocompr. Population
  - Correlation vs. causation



Metastatic SCC on chronic voriconazole

J Am Acad Dermatol 2010;62:31-7.

ORIGINAL CLINICAL SCIENCE

J Heart Lung Transplant 2010;29:1240-4.

Voriconazole exposure and geographic location are independent risk factors for squamous cell carcinoma of the skin among lung transplant recipients

Aniket Vadnerkar, MD,[a] M. Hong Nguyen, MD,[a] Dimitra Mitsani, MD,[a] Maria Crespo, MD,[a] Joseph Pilewski, MD,[a] Yoshiya Toyoda, MD, PhD,[b] Christian Bermudez, MD,[b] Eun J. Kwak, MD,[a] Fernanda P. Silveira, MD,[a] and Cornelius J. Clancy, MD[a,c]

From the Departments of [a]Medicine and [b]Cardiothoracic Surgery, University of Pittsburgh Medical Center; and the [c]Department of Medicine, Pittsburgh VA Healthcare System, Pittsburgh, Pennsylvania.

- Retrospective case: control study (2003-08)
  - SCC 3.1% (17/543)
  - Median f/u: 36 mo; median time to SCC: 19.1 months
  - 94% sun exposed surfaces
- Multivariate analysis
  - Duration of voriconazole: HR 2.1 (p = 0.04)
  - High sun exposure residence: HR 3.8 (p = 0.0004)

Voriconazole (VFEND®) product labeling

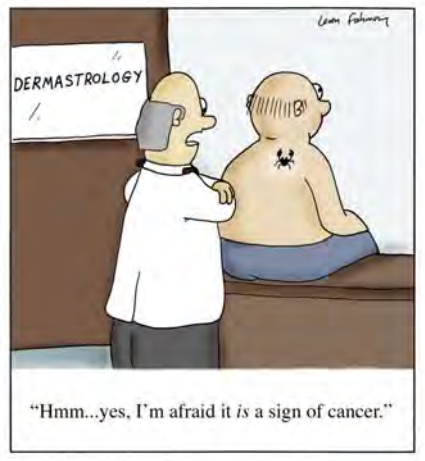
"If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, VFEND® should be discontinued."

Case 3

- Immunobullous disease from anti-neoplastic therapy

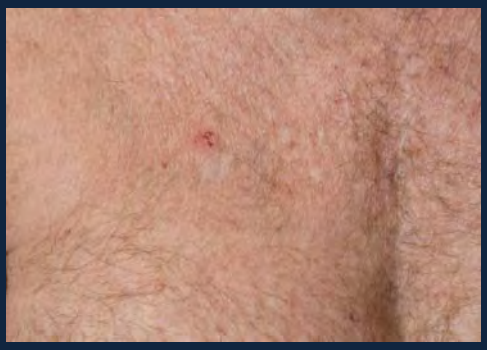
Skin Reactions from New Anti-Cancer Therapies

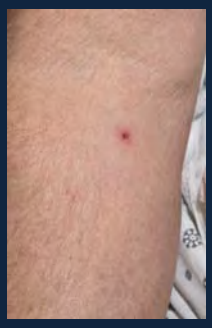
- Classes
  - **CTLA-4, PD-1/L1 inhibitors**
  - EGFR inhibitors
  - Multikinase inhibitors
  - VEGFR inhibitors
  - BRAF inhibitors
  - MEK inhibitors
- Dermato-oncology 'supportive care'



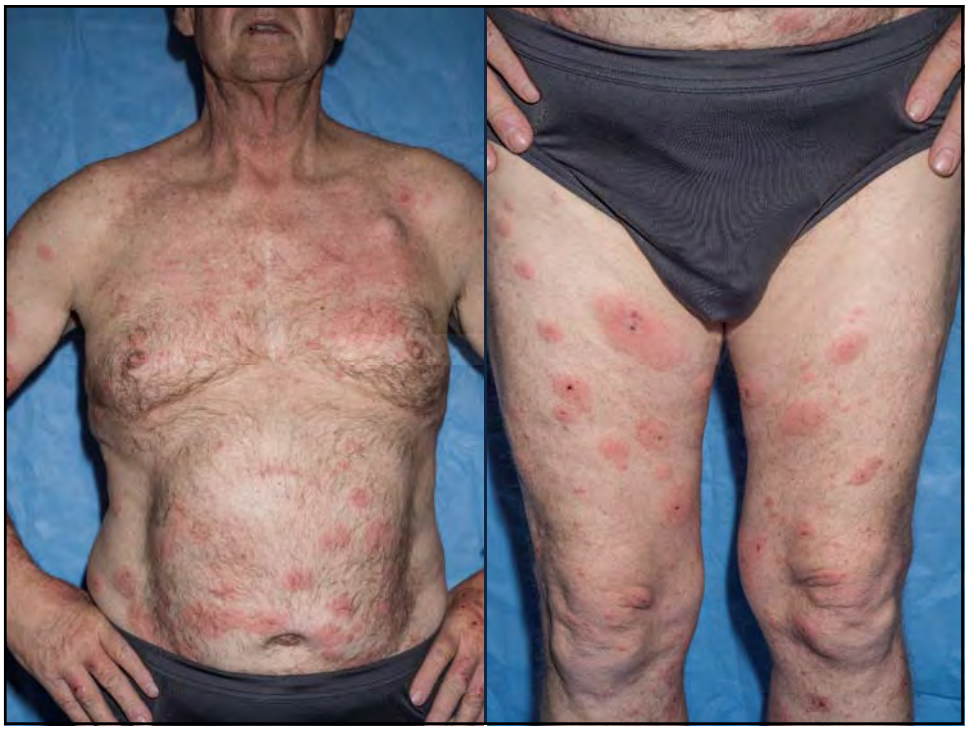
Case 3

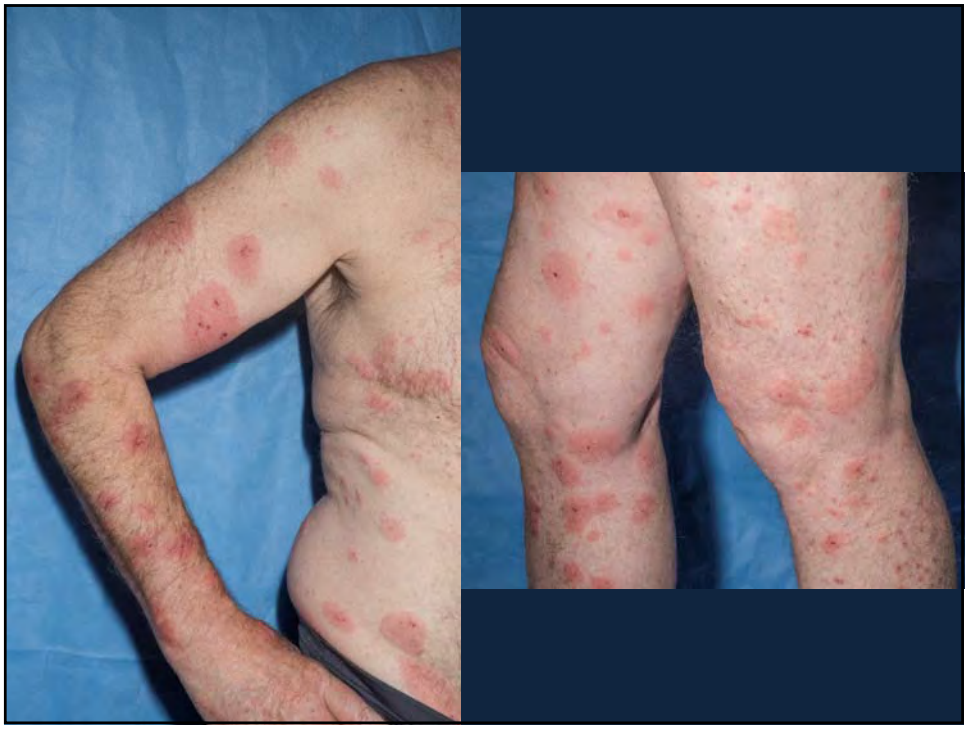
- 51 year old male metastatic pancreatic CA
- Localized small pruritic papules/plaques (PD-L1/anti-TGFb)

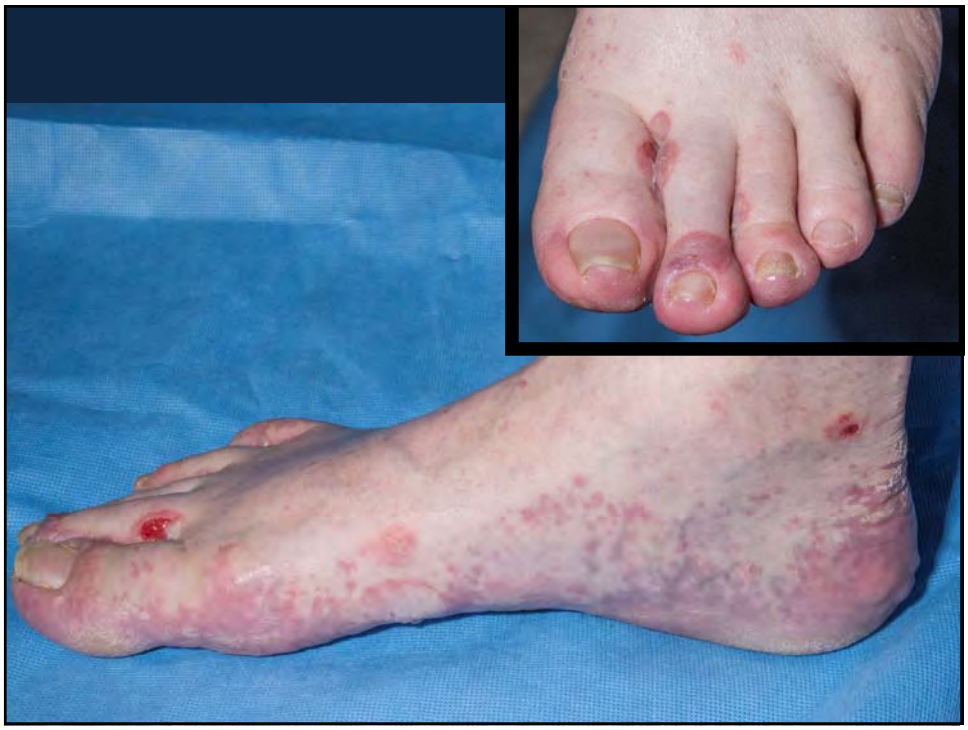




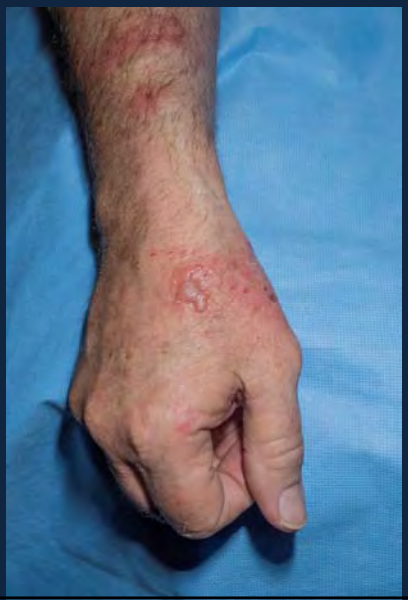
- Skin bx: lichenoid dermatitis
- Dx: Drug-induced rash secondary to anti-PD-L1
- Resolution with topical steroids

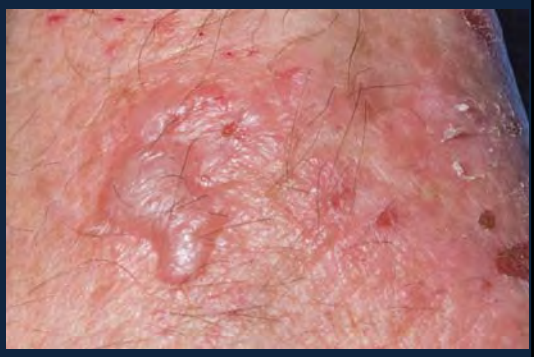






Case 3





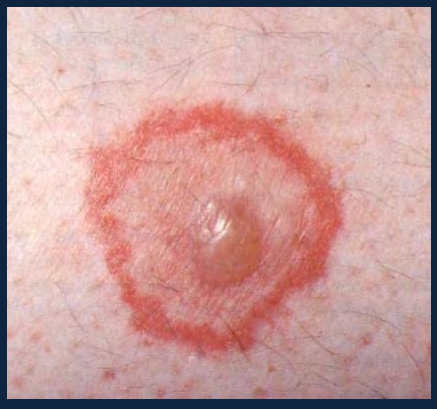
Drug-induced immunobullous disease

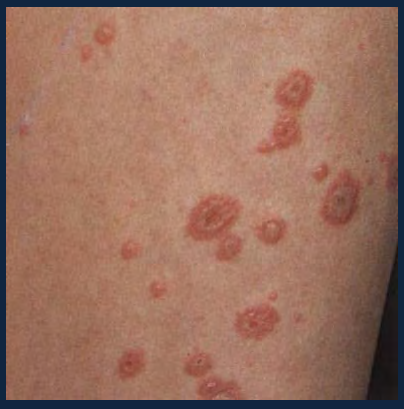
- Histology: dermal-epidermal separation with numerous eosinophils
- Consistent with bullous pemphigoid

Drug-induced immunobullous disease

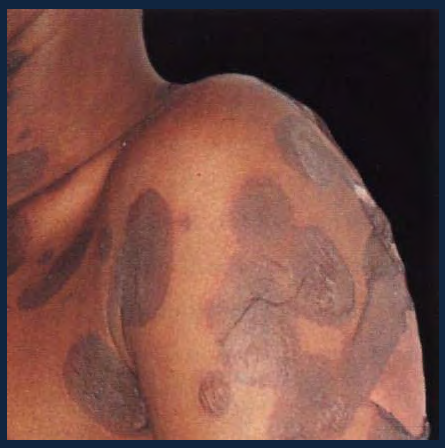
- NOT drug eruption with bullae (erythema multiforme, SJS/TEN, bullous fixed drug eruption)

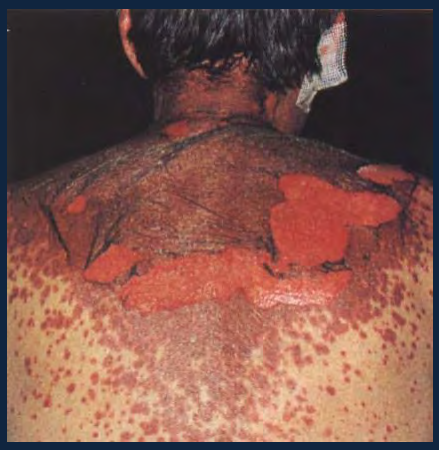
Erythema multiforme



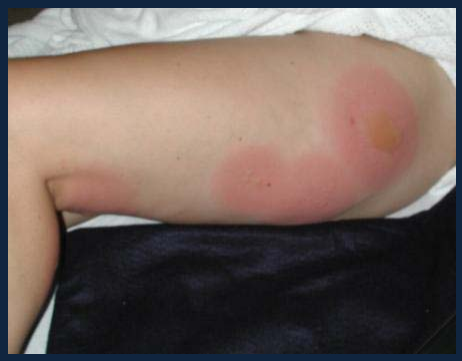


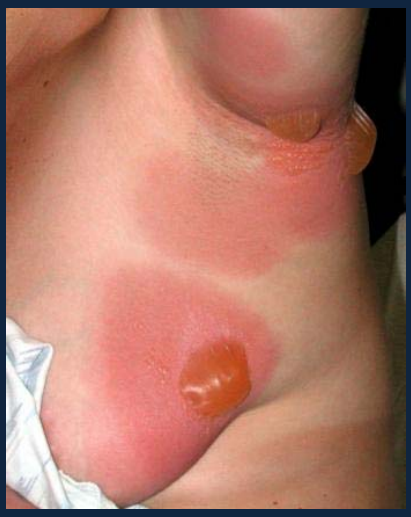
Toxic epidermal necrolysis





Bullous fixed drug eruption: pseudoephredrine in Tylenol Sinus Allergy





Drug-induced immunobullous disease

- NOT drug eruption with bullae (erythema multiforme, SJS/TEN, bullous fixed drug eruption)
- Drug-induced bullous pemphigoid
  - Furosemide, PCN, sulfasalazine
- Drug-induced pemphigus vulgaris (thiol moiety)
  - Penicillamine, ACE inhibitors, gold
- Drug-induced linear IgA disease
  - Vancomycin
- DDx: Paraneoplastic pemphigus
  - Painful, progressive stomatitis

Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial

Kei Muro, Hyun Cheol Chung, Veena Shankaran, Ravit Geva, Daniel Catenacci, Shilpa Gupta, Joseph Paul Eder, Talia Golan, Dung T Le, Barbara Burtness, Autumn J McRee, Chia-Chi Lin, Kumudu Pathiraja, Jared Lunceford, Kenneth Emancipator, Jonathan Juco, Minori Koshiji, Yung-Jue Bang**

Lancet Oncol 2016; 17: 717–26

Summary

Background Expression of PD-L1 has been shown to be upregulated in some patients with gastric cancer. As part of the phase 1b KEYNOTE-012 study, we aimed to assess the safety and activity of the anti-PD-1 antibody pembrolizumab in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Methods This study was a multicentre, open-label, phase 1b trial done at 13 cancer research centres in the USA, Israel, Japan, South Korea, and Taiwan. We enrolled patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. Patients received intravenous pembrolizumab at 10 mg/kg once every 2 weeks for 24 months or until progression or unacceptable toxic effects occurred. Response was assessed every 8 weeks in accordance with Response Evaluation Criteria in Solid Tumors version 1.1. The primary objectives were safety in patients who received at least one dose of pembrolizumab and the proportion of patients achieving overall responses in patients who received at least one pembrolizumab dose and who either had a post-baseline scan or who discontinued therapy because of clinical disease progression or a treatment-related adverse event before the first post-baseline scan. The study is registered with ClinicalTrials.gov, number NCT01848834, and is ongoing but no longer enrolling patients.

Findings From Oct 23, 2013, to May 5, 2014, 39 patients were enrolled. 36 were evaluable for response by central assessment. Eight (22%, 95% CI 10–39) patients were judged to have had an overall response at central review; all responses were partial. All 39 patients were included in the safety analyses. Five (13%) patients had a total of six grade 3 or 4 treatment-related adverse events, consisting of two cases of grade 3 fatigue, one case each of grade 3 pemphigoid, grade 3 hypothyroidism, and grade 3 peripheral sensory neuropathy, and one case of grade 4 pneumonitis. No treatment-related deaths occurred.

Cancer Immunology Miniatures

Cancer Immunology Research

Autoimmune Bullous Skin Disorders with Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1

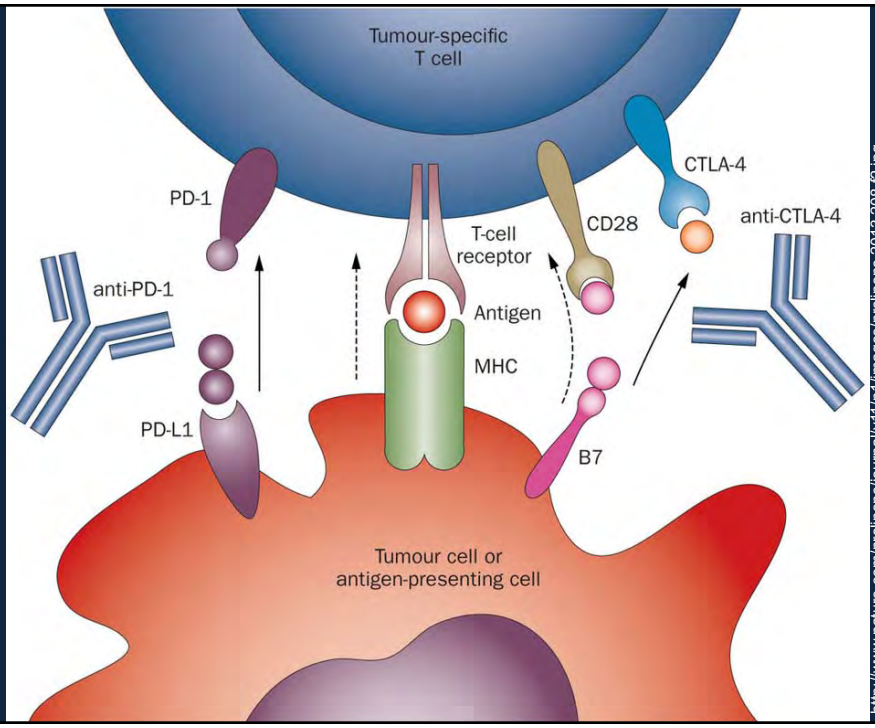
Jarushka Naidoo[1], Katja Schindler[2], Christiane Querfeld[3], Klaus Busam[4], Jane Cunningham[5], David B. Page[6], Michael A. Postow[7,8], Alyona Weinstein[9], Anna Skripnik Lucas[9], Kathryn T. Ciccolini[9], Elizabeth A. Quigley[7,8,10], Alexander M. Lesokhin[7,8], Paul K. Paik[7,8], Jamie E. Chaft[7,8], Neil H. Segal[7,8], Sandra P. D'Angelo[7,8], Mark A. Dickson[7,8], Jedd D. Wolchok[7,8,11], and Mario E. Lacouture[7,8,10]

Cancer Immunol Res 2016; 4(5); 383–9.

Table 1. Patient demographics and diagnostic workup

Age (y)	Sex	Tumor type	Current therapy	Prior therapies	DIF	IIF	Salt-split skin analysis	Time of rash onset (from start of therapy)	BP ELISA titers (from time taken since start of therapy)
80	Male	Melanoma	Nivolumab	Ipilimumab	+	+	+	24 weeks	At 33.9 weeks: BP180: 13.8* BP230: 10.0* At 47.0 weeks BP180: 25.6* BP230: 12.2*
78	Female	Melanoma	Durvalumab	Ipilimumab	+	+	+	17.9 weeks	At 44.1 weeks: BP180: 72* BP230: 21.7*
85	Male	Non-small cell lung cancer	Nivolumab	Carboplatin + paclitaxel	+	NA	NA	6.1 weeks	At 55.1 weeks: BP180: 1.1* BP230: 0.9*

Abbreviations: DIF, direct immunofluroresecence; IIF, immunofixation; NA, not applicable (not completed).
*BP ELISA taken during steroid therapy.



http://www.nature.com/nrclinonc/journal/v11/n1/images/nrclinonc.2013.208-f2.jpg

CTLA-4 inhibitors/PD-1, -L1 inhibitors

- **Anti-CTLA-4**: *ipilimumab* ('11, melanoma)
- **Anti-PD-1**:
  - *nivolumab* ('14, melanoma, '15 NSCLC, RCC, '16 HL)
  - *pembrolizumab* ('14 melanoma, '15 NSCLC)
- **Anti-PD-L1**: *atezolizumab* (May '16, urothelial CA)
- "Immune-mediated reactions"
  - Vitiligo, alopecia areata, dermatitis
  - Colitis, pneumonitis, hepatitis, encephalitis, uveitis, nephritis, hypophysitis

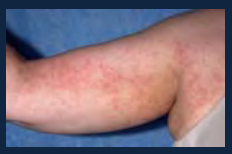
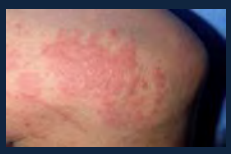




Table IV. Anti-PD-1 and PD-L1 blockade agents currently* in clinical trials.

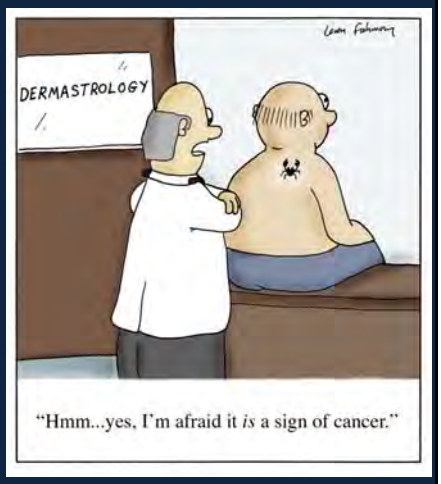
Target/Treatment	Fc Domain
PD-1 (blocks interaction between PD-L1 and PD-L2)	
Nivolumab, BMS-936558, MDX-1106, ONO-4538[1]	Human IgG4, stabilizing mutation *S228P*
Pembrolizumab[3]	Humanized IgG4, *S228P*
Pidilizumab, CT-011[50]	Humanized IgG1
AMP-224 (PD-1 targeting therapy)	PD-L2-Fc fusion protein (blocking)
AMP-514, MEDI-0680	IgG, details unpublished
PD-L1 (inhibits binding to PD-1 and CD80)	
BMS-936559[2]	Human IgG4, *S228P*
MEDI-4736	Engineered human IgG1
MPDL-3280A[58]	Engineered human IgG1
MSB-0010718C	IgG1, details unpublished

Fc = fragment, crystallizable; Ig = immunoglobulin; PD = programmed cell death protein.
*Registered on clinicaltrials.gov as of July 7, 2014.

Clinical Therapeutics/Volume 37, Number 4, 2015

Skin Reactions from New Anti-Cancer Therapies

- Classes
  - CTLA-4, PD-1/L1 inhibitors
  - **EGFR inhibitors**
  - Multikinase inhibitors
  - BRAF inhibitors
  - MEK inhibitors
- Dermato-oncology 'supportive care'



Epidermal Growth Factor Receptor Inhibitors

- Small molecule TKI
  - **Gefitinib** (Iressa®)
  - **Erlotinib** (Tarceva®)
- Monoclonal Ab
  - **Cetuximab** (Erbitux®)
  - **Panitumumab** (Vectibix™)
- EGFR/Her2
  - **Lapatinib (**Tykerb®)
  - **Afatinib** (Gilotrif®)
- Multikinase (EGFR/VEGFR/RET)
  - **Vandetanib** (Caprelsa®)

FDA indications: EGFR+ non-small cell lung CA, colorectal CA, head and neck CA, HER2+ breast CA, medullary thyroid CA

TABLE 1.
Dermatologic Toxicity With Anti-EGFR Therapies*

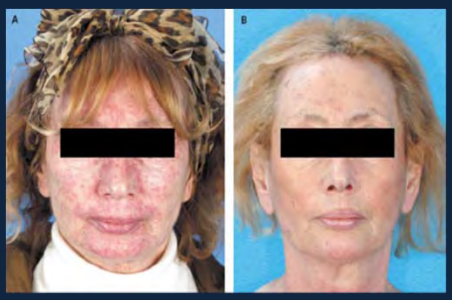
	Any Grade (%)	Grade 3/4 (%)
Cetuximab[6,7]	80-86	5-18
Gefitinib[8]	62-75	up to 4
Erlotinib[9,10]	75-79	5-10

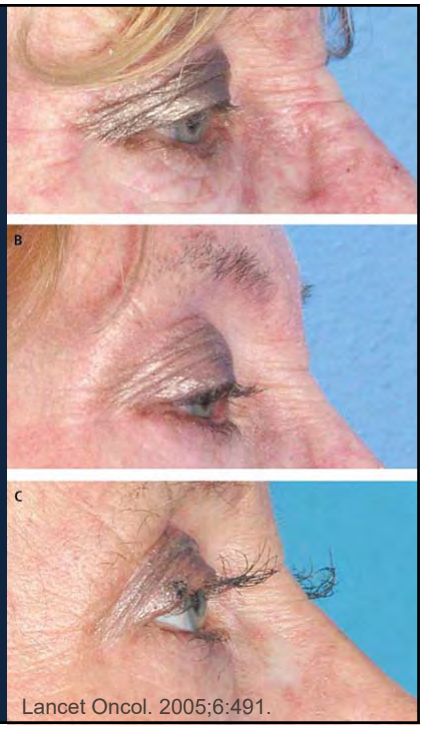
Abbreviation: EGFR, epidermal growth factor receptor.
*Reported with single-agent therapy.

- Acneiform eruption
- Xerosis
- Dermatitis
- Nail abnormalities
  - Paronychia
  - PG-like lesions
  - Brittle nails
- Photosensitivity
- Telangiectasia
- Follicular abnormalities
  - Alopecia (scarring/non-scarring)
  - Trichomegaly
  - Hirsutism
  - Textural changes

EGFRi follicular abnormalities

- Onset: 2-3 months after drug initiation
- Alopecia (5-21%)
- Decreased frontal hairline growth
- Hair texture changes: fine/brittle
- Hirsutism: upper lip
- Trichomegaly
  - EGFR-mediated disruption of hair cycle (anagen → catagen)

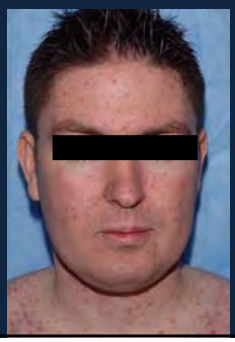


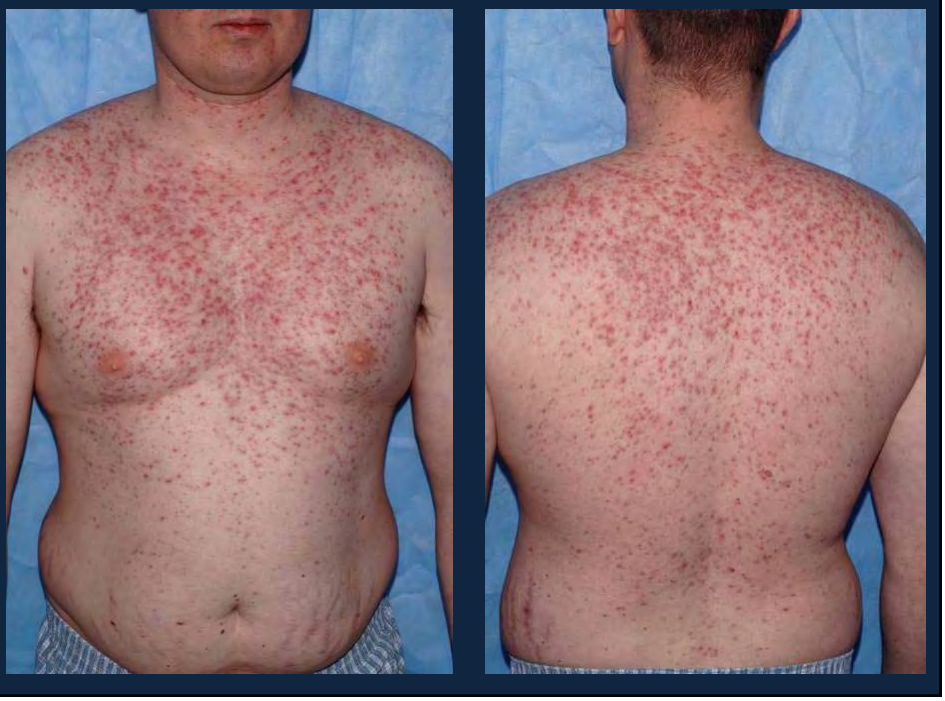


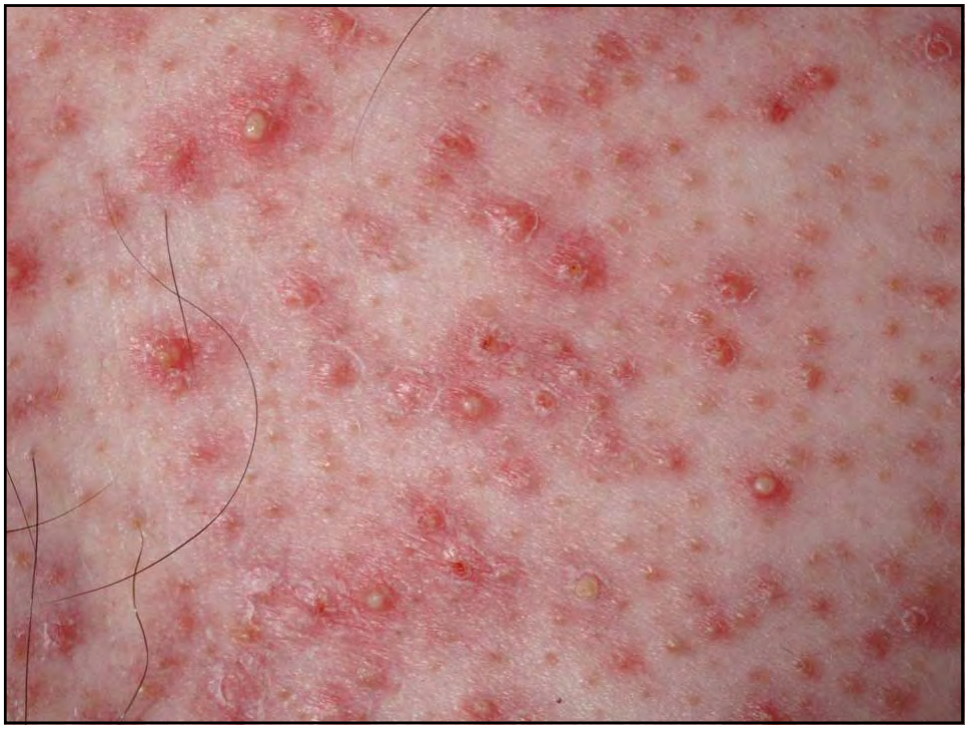
Lancet Oncol. 2005;6:491.

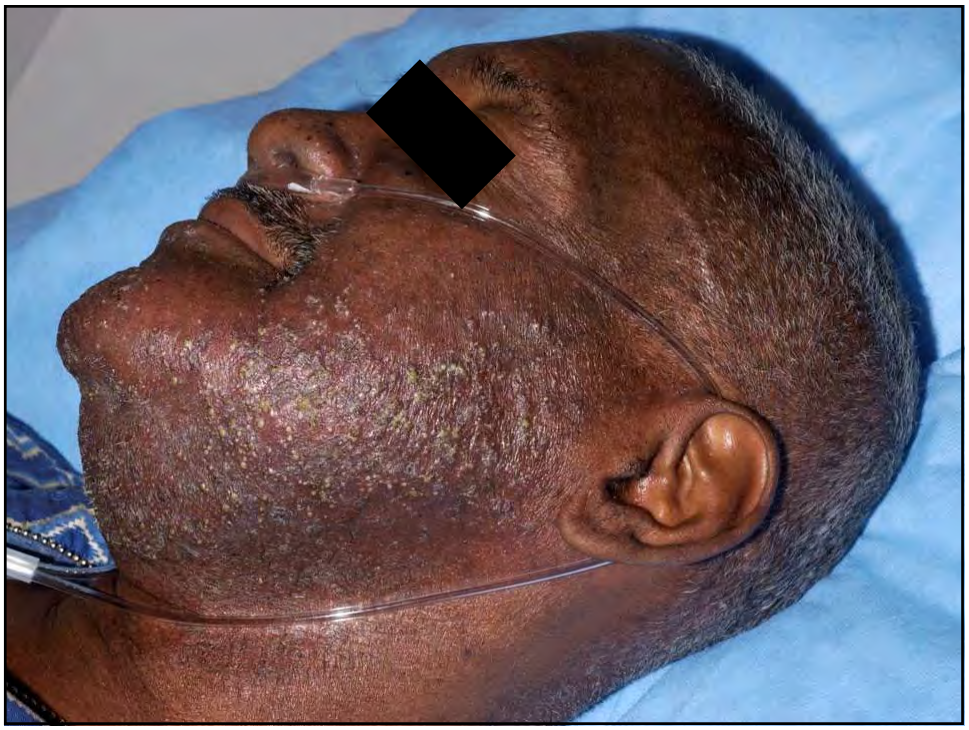
EGFRI acneiform eruption

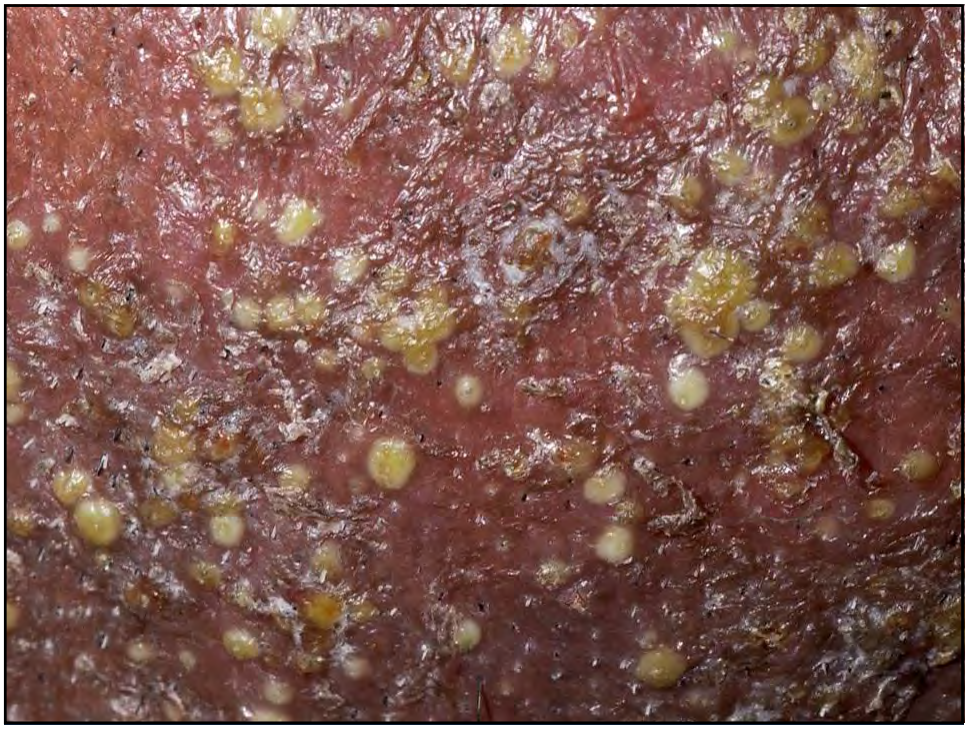
- Most common skin reaction
  - 43–85% of patients (Severe: 10%)
  - Cetuximab, panitimumab > erlotinib > gefitinib
  - Median onset: 7-10 days after drug initiation (> 3wks)
  - Radiation sites often spared









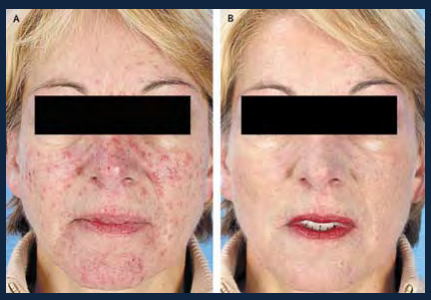


EGFRI eruption:natural history

- Spontaneous improvement
- Waxing and waning course
- Dose dependent (correlates with CA response)
- Cessation of therapy
  - Improvement in 1-2 weeks
  - Cetuximab: 50% persistent rash >30 days after exposure to drug
- S. aureus abscess/sepsis

EGFRI eruption: treatment

- Sun protection/avoidance
- Camouflage cosmetics
- Benzoyl peroxide
- Oral antihistamines
- Topical antibiotics
  - Metronidazole
  - Clindamycin
  - Erythromycin
- Systemic antibiotics
  - Doxycycline 100mg/day
- No standardized treatment
  - Controlled trials of interventions needed



EGFRI camouflage: Lancet Oncol. 2005;6:491.

Annals of Oncology. 2005;16:1425.

EGFRI rash: Therapeutic ladder

Thick emollients/sun protection Oral antihistamines Topical clindamycin Topical hydrocortisone 1%-2.5% Topical pimecrolimus 1% cream	**Grade I**
Doxycycline 100mg BID Minocycline 100mg BID	**Grade II/III**
Delay EGFRI infusion interval (EGFRI antibodies) Reduce dose of EGFRI Systemic steroids (short course)?	**Grade III/IV**

T. Lynch *et al.* Oncologist 2007;12:610-21.

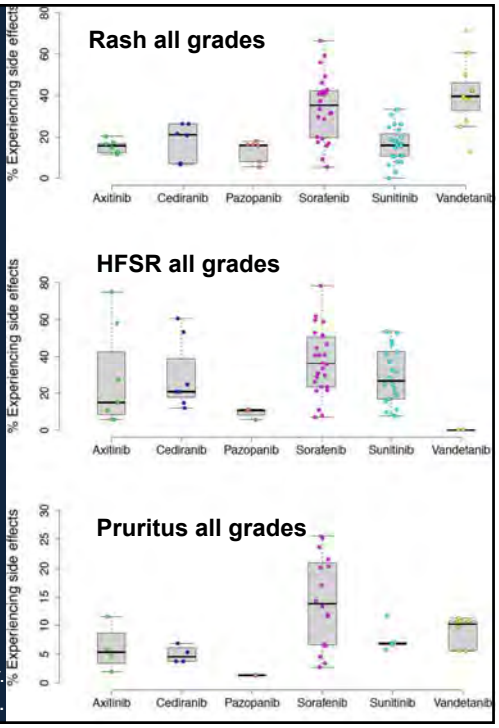
Skin reactions to VEGF inhibitors

- Selective
  - Bevacizumab
  - Ranibizumab
- Non-selective (MKI)
  - **Sorafenib**
  - **Sunitinib**
  - **Axitinib**
  - **Cabozantinib**
  - **Pazopanib**
  - **Cediranib**
  - **Vandetanib**

Non-selective VEGF inhibitors

- Non-selective (MKI)
  - Sunitinib
  - Sorafenib
  - Vandetanib
  - Cabozantinib
  - Axitinib
  - Pazopanib
  - Cediranib

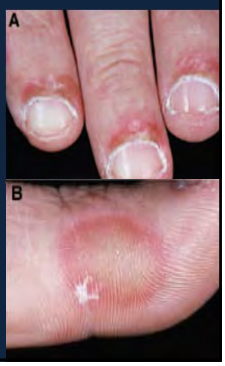
Support Care Cancer. 2015;23:1827.



Sunitinib maleate (SU11248/Sutent®)

- Multi-kinase inhibitor
  - VEGFR1, 2, 3, PDGFR, c-KIT, FLT3, CSF-1R, RET

- Dermatologic adverse reactions
  - Rash 38%
  - **Yellow pigmentation 33%**
  - **Hair depigmentation 17%**
  - Hand-foot syndrome 14%
  - Alopecia 12%



Support Care Cancer 2008;15:557; J Clin Oncol. 2006;24:25.

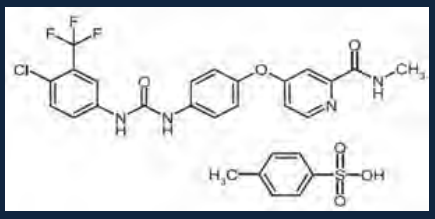
Sunitinib: Skin coloration

- <u>Yellow</u> skin coloration appears after 1 week of treatment in patients (30%)
- Increased in intensity at higher doses
- Associated with a yellow coloration of urine due to the excretion of the drug and metabolites
- May be due to drug itself (yellow in color)

J Clin Oncol 2006;24:25-35.; Sutent® package insert, NY:Pfizer, 2006.

Sorafenib tosylate (BAY 43-9006/Nexavar®)

- Indications
  - 2005: Advanced renal cell cancer
  - 2007: Hepatocellular carcinoma
  - 2013: Metastatic thyroid cancer
- Inhibits
  - Ras/Raf signaling pathway
  - VEGFR1,2,3
  - PDGFR-β
  - FLT3
  - c-KIT
  - RET

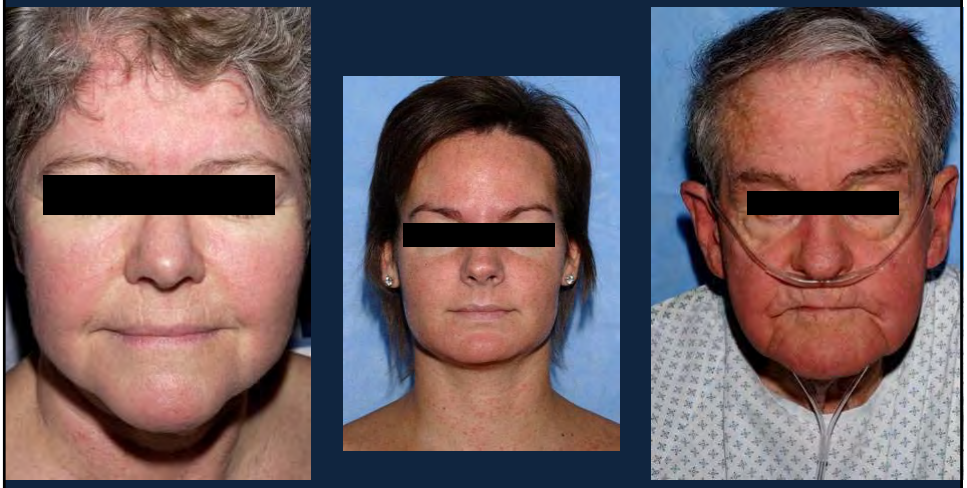


Sorafenib tosylate (BAY 43-9006/Nexavar®)

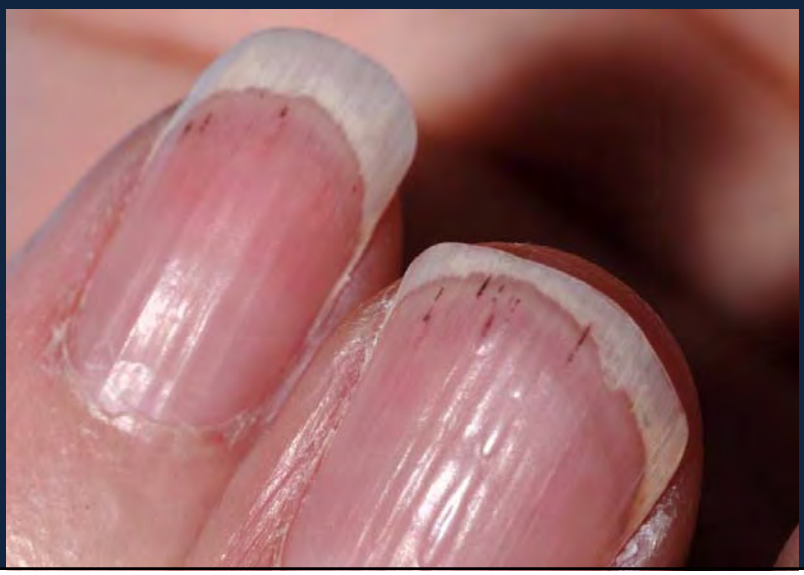
- Hypertension (VEGFR inhibition): 23%
- Dermatologic reactions
  - Facial/Scalp erythema/dysesthesias (~60%)
  - Hand-foot syndrome (37-50%)
  - Alopecia (~30%)
  - Subungual hemorrhages (~30%)
  - Pruritus (19%)
  - Xerosis (11%)
  - Mucositis (10-20%)
  - "Sorafenib dermatitis"
  - Erythema multiforme

Wu *et al.* Lancet Oncol 2007;9:117.

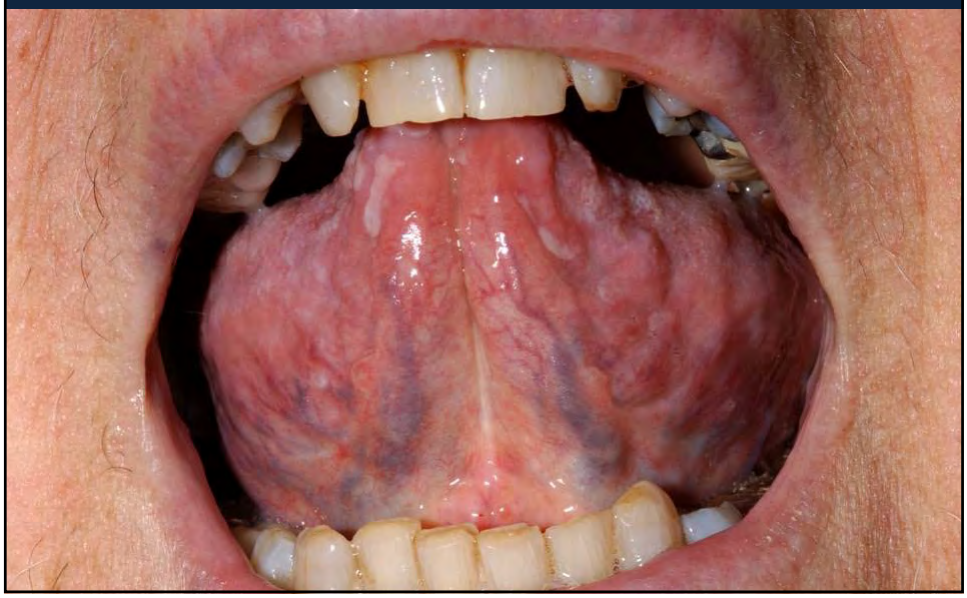
Sorafenib: Facial/Scalp erythema



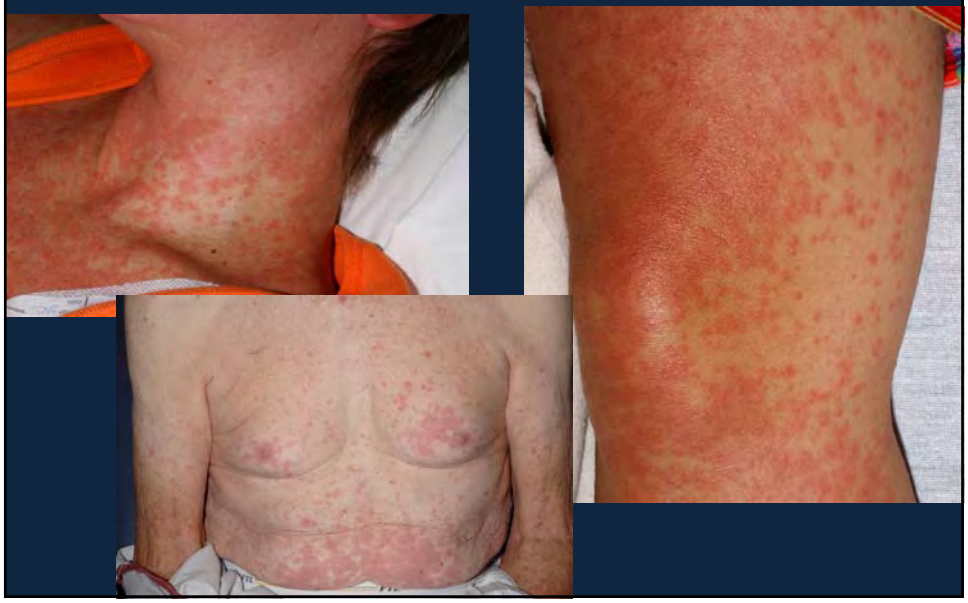
Sorafenib: Subungual hemorrhages



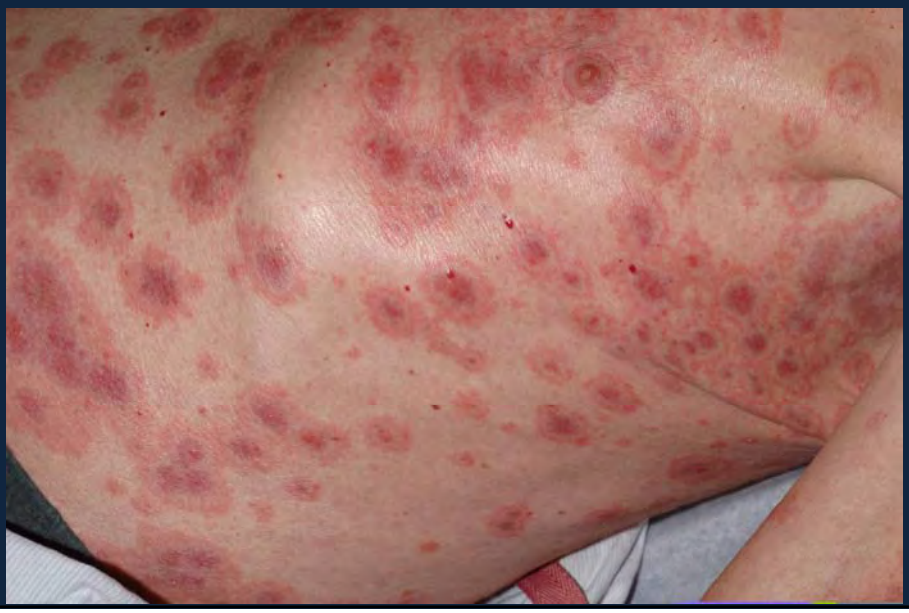
Sorafenib: Mucositis



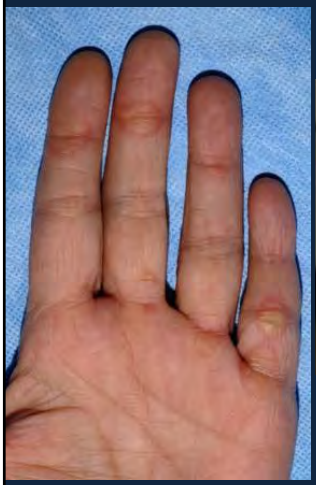
Sorafenib dermatitis

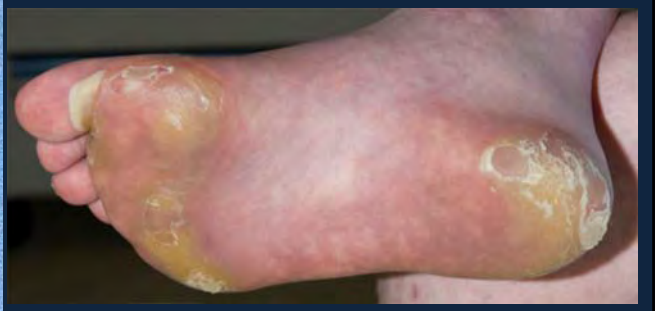


Sorafenib: EM-LIKE ERUPTION



Sorafenib: Acral erythema/hand-foot syndrome

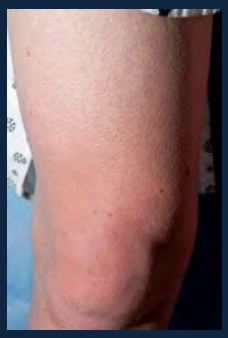




BRAF inhibitors

- **Vemurafenib, Dabrafenib**
  - Photosensitivity (V >> D)
  - Folliculocentric rash (68%)
    - Emollients → Anti-H_2 → top steroids → po steroids
  - Hand/foot syndrome (6-60%)
  - Eruptive nevi, 2nd melanoma
  - Seb derm-like eruption
  - Epidermal neoplasms
    - Verrucous keratoses
    - Squamous cell carcinoma/keratoacanthoma type (20-30%)
      - Associated with older age

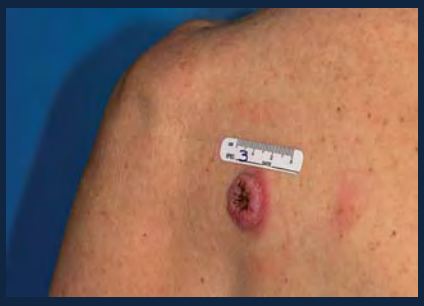
J Am Acad Dermatol 2015;72:221-36.

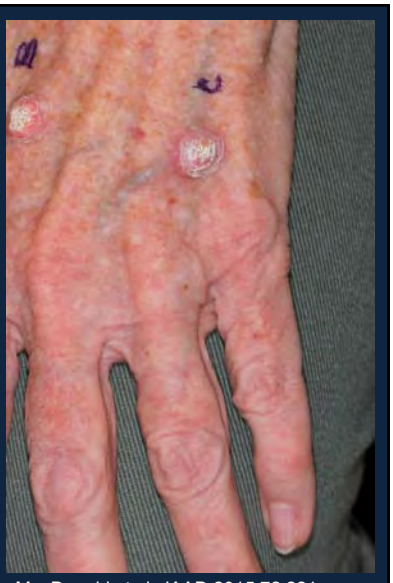


KP-like eruption vemurafenib

Verrucous keratosis

Well–differentiated SCCs during BRAF inhibitor therapy

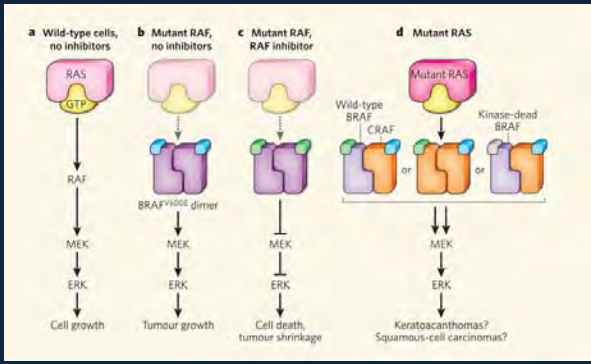




MacDonald et al. JAAD 2015;72:221.

BRAF inhibitor-associated SCC

- Mechanism
  - *RAS* mutations in 60% of vemurafenib pts.
  - Paradoxical increase in MAPK signaling in cells harboring mutated *HRAS*
  - Suggest that MEK inhibition might abrogate this potentiation



N Engl J Med 2012;366:207-15; J Am Acad Dermatol 2015;72:221-36.

MEK/ERK inhibitors

- Cobimetinib (Cotellic™); Trametinib (Mekinist);
- Concurrent use with BRAF inhibitor therapy associated with decreased risk of KA/SCC
- Exanthematous morbilliform eruption
- Cutaneous adverse events similar to EGFRI
  - Acneiform eruption
  - Paronychia
  - Alopecia (mild)
  - Xerosis

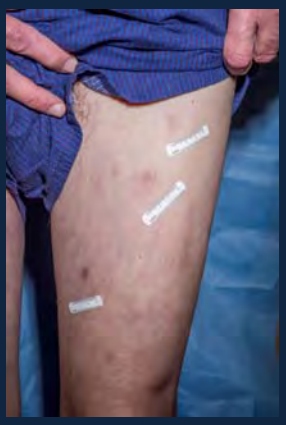
Table 2. Adverse Events Reported in Part C.*

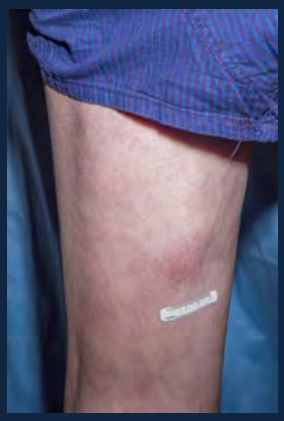
Trametinib

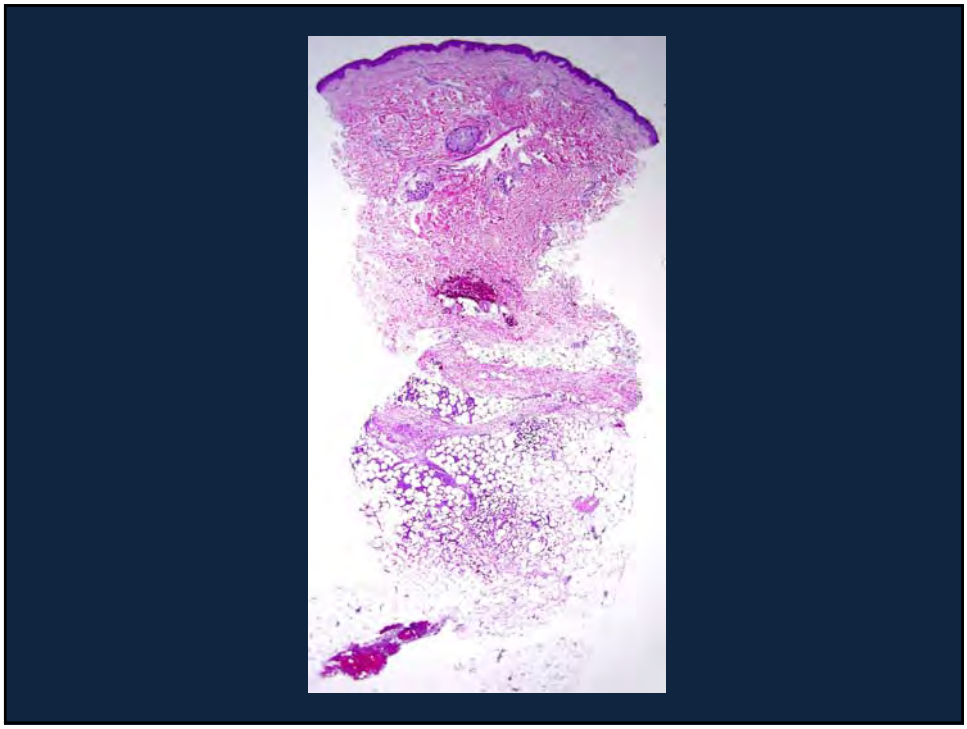
Adverse Event	Dabrafenib Monotherapy (N=53)†		Combination 150/1 (N=54)		Combination 150/2 (N=55)†	
	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades
	number of patients (percent)					
Any event	23 (43)	53 (100)	26 (48)	53 (98)	32 (58)	55 (100)
Pyrexia	0	14 (26)	5 (9)	37 (69)	3 (5)	39 (71)
Chills	0	9 (17)	1 (2)	27 (50)	1 (2)	32 (58)
Fatigue	3 (6)	21 (40)	1 (2)	31 (57)	2 (4)	29 (53)
Nausea	0	11 (21)	3 (6)	25 (46)	1 (2)	24 (44)
Vomiting	0	8 (15)	2 (4)	23 (43)	1 (2)	22 (40)
Diarrhea	0	15 (28)	0	14 (26)	1 (2)	20 (36)
Headache	0	15 (28)	1 (2)	20 (37)	0	16 (29)
Peripheral edema	0	9 (17)	0	13 (24)	0	16 (29)
Cough	0	11 (21)	0	6 (11)	0	16 (29)
Arthralgia	0	18 (34)	0	24 (44)	0	15 (27)
Rash	0	19 (36)	0	11 (20)	0	15 (27)
Night sweats	0	3 (6)	0	8 (15)	0	13 (24)
Decreased appetite	0	10 (19)	0	16 (30)	0	12 (22)
Myalgia	1 (2)	12 (23)	0	13 (24)	1 (2)	12 (22)
Constipation	0	6 (11)	1 (2)	9 (17)	0	12 (22)
Elevated blood alkaline phosphatase	0	1 (2)	3 (6)	12 (22)	0	5 (9)
Hyperkeratosis	0	16 (30)	0	3 (6)	0	5 (9)
Alopecia	0	18 (34)	0	5 (9)	0	3 (5)
	Grade 3‡	All Grades	Grade 3‡	All Grades	Grade 3‡	All Grades
Cutaneous squamous-cell carcinoma§	9 (17)	10 (19)	1 (2)	1 (2)	3 (5)	4 (7)
Skin papilloma	0	8 (15)	0	4 (7)	0	2 (4)
Hyperkeratosis	0	16 (30)	0	3 (6)	0	5 (9)
Decreased ejection fraction	0	0	1 (2)	2 (4)	0	5 (9)
Cardiac failure	0	0	1 (2)	1 (2)	0	0
Hypertension	0	2 (4)	0	2 (4)	1 (2)	5 (9)
Chorioretinopathy	0	0	0	0	1 (2)	1 (2)

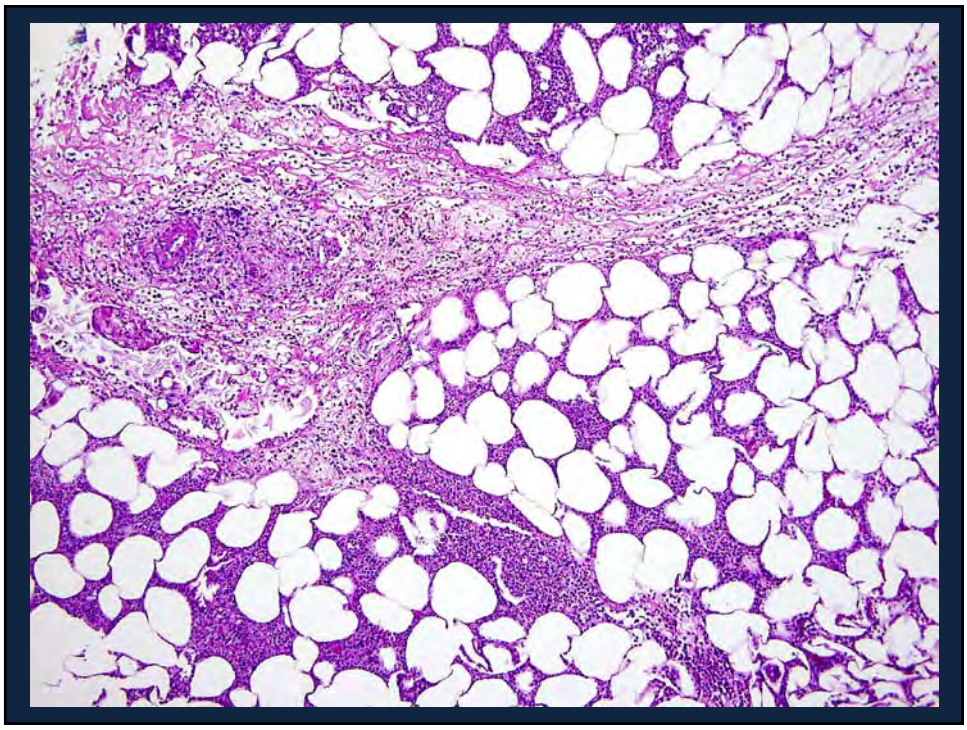
N Engl J Med 2012; 367:1694-1703

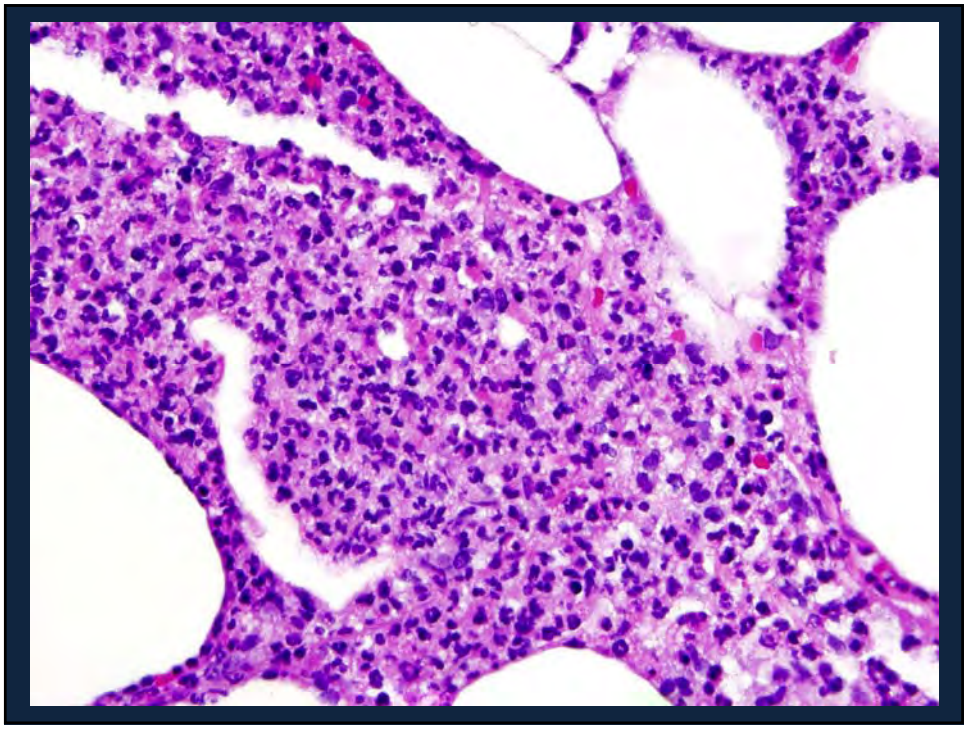
BRAF inhibitor-associated panniculitis











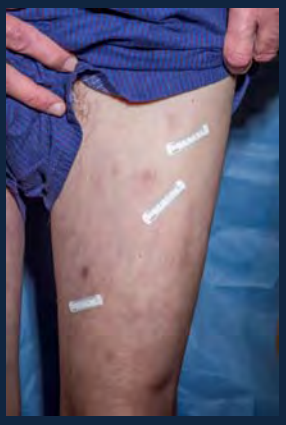
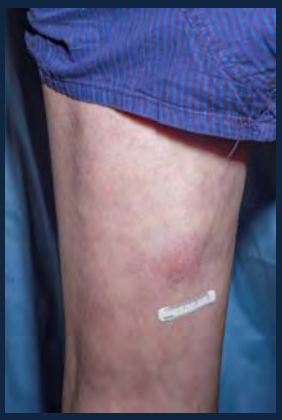
Dabrafenib vs. vemurafenib

Table 1. Dermatologic Adverse Effects of Dabrafenib vs Vemurafenib

Effect	BRAF Inhibitor Therapy, No. (%) of Patients		P Value
	Dabrafenib Mesylate (n = 119)	Vemurafenib (n = 36)	
Acneiform reaction	9 (7.6)	1 (2.8)	.31
Actinic keratosis	32 (26.9)	11 (30.6)	.67
Angioma or hemangiomas	14 (11.8)	2 (5.6)	.28
BCC	18 (15.1)	7 (19.4)	.54
Gray or curly hair	15 (12.6)	6 (16.7)	.53
Cutaneous SCC	31 (26.1)	13 (36.1)	.24
Drug reaction	1 (0.8)	4 (11.1)	.002[a]
Eczema	8 (6.7)	6 (16.7)	.07
Folliculitis	8 (6.7)	5 (13.9)	.17
Granuloma annulare	1 (0.8)	0	.58
Grover disease	51 (42.9)	14 (38.9)	.67
Hair loss	17 (14.3)	7 (19.4)	.45
Hyperkeratosis NOS[b]	12 (10.1)	3 (0.38)	.76
Inflammation NOS[b]	8 (6.7)	4 (11.1)	.39
Keratosis pilaris	2 (1.7)	2 (5.6)	.20
Panniculitis	3 (2.5)	4 (11.1)	.03
Photosensitivity	1 (0.8)	14 (38.9)	.0001[a]
Plantar hyperkeratosis	47 (39.5)	14 (38.9)	.95
Primary melanoma	3 (2.5)	0	.34
Verruca vulgaris	14 (11.8)	8 (22.2)	.12
Verrucal keratosis	79 (66.4)	26 (72.2)	.51
Vitiligo	5 (4.2)	1 (2.8)	.70

Carlos G et al. *JAMA Dermatol*. **151,** 1103–1109 (2015).

BRAF inhibitor-associated panniculitis

- Management: NSAIDS, low dose prednisone

Targeted anti-neoplastic skin AEs

Table 3. Cutaneous Adverse Effects of Targeted Therapies and Associated Kinase Inhibition[a,b]

Adverse Effect	Cabozantinib	Sorafenib	Sunitinib	Imatinib	Erlotinib, Gefitinib, Cetuximab	Vemurafenib, Dabrafenib	Trametinib, Selumetinib
Kinase inhibition	VEGFR2, c-MET, RET, c-KIT, FLT3, Tie-2	VEGFR2/3, PDGFR, RAF (A,B,C), FLT3	VEGFR2, PDGFR, c-KIT, FLT3	Bcr-abl, PDGFR, c-KIT	EGFR	BRAF	MEK
Hand-foot skin reaction	+	+	+			+	
Hair or skin depigmentation	+		+			+	
Xerosis	+	+	+	+	+	+	+
Scrotal erythema or ulceration	+	+	+				
Nail splinter hemorrhage	+	+	+				
Paronychia					+	+	+
Periorbital edema			+	+			
Facial erythema		+			+	+	+

Zuo RC, et al. JAMA Derm Feb 2015.

Conclusion

- New drug 'allergies' are challenging
- Targeted treatments
  - Mechanistic approach to understanding adverse reactions
- New therapeutic options for chronic, difficult diseases
  - Severe psoriasis
  - Fungal infection
  - Melanoma
- Long-term treatment → management dilemma

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