VERONA
Hotel Leon D'Oro

SESSIONE (NON ECM)
PER PAZIENTI, ASSOCIAZIONI PAZIENTI E CITTADINI

Responsabile Scientifico
STEFANIA GORI

Pazienti, associazioni e caregiver domandano...
Gli esperti rispondono...

Ospedale Isola Tiberina
GEMELLI ISOLA

Pietro Sollena MD

DERMATOLOGIA E VENEREOLOGIA

Fondazione Policliclinico «A. Gemelli» IRCCS, Roma
Ospedale Gemelli Isola Tiberina, Roma

CONFLICT OF INTEREST

Ospedale Isola Tiberina
GEMELLI ISOLA

Advisory board for:

- LA ROCHE POSAY – L'OREAL
- AVENE – PIERRE FABRE

I NUMERI DEL CANCRO IN ITALIA 2023

In Italia, nel **2023**, stimate **395.000** nuove diagnosi di tumore:

208.000 uomini

187.000 nelle donne

- carcinoma della mammella (55.900 casi)
- colon-retto (50.500)
- **polmone (44.000)**
- prostata (41.100)
- vescica (29.700)

LUNG CANCER RESEARCH FOUNDATION

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Types of cancer treatment 2024

https://www.lungcancerresearchfoundation.org/for-patients/living-with-lung-cancer/types-of-cancer-treatment/

Chemotherapy

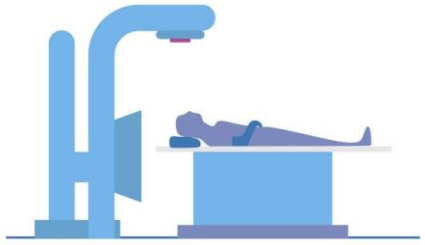
- CISPLATIN
- CARBOPLATIN
- DOCETAXEL
- ETOPOSIDE
- GEMCITABINE
- NAB PACLITAXEL
- PACLITAXEL
- PEMETREXED
- TOPOTECAN
- VINORELBINE
- LURBINECTEDIN
- IRINOTECAN

Combo

Immunotherapy

- NIVOLUMAB
- PEMBROLIZUMAB
- ATEZOLIZUMAB
- DURVALUMAB
- CEMIPLIMAB-RWLC
- TREMELIMUMAB
- IPILIMUMAB

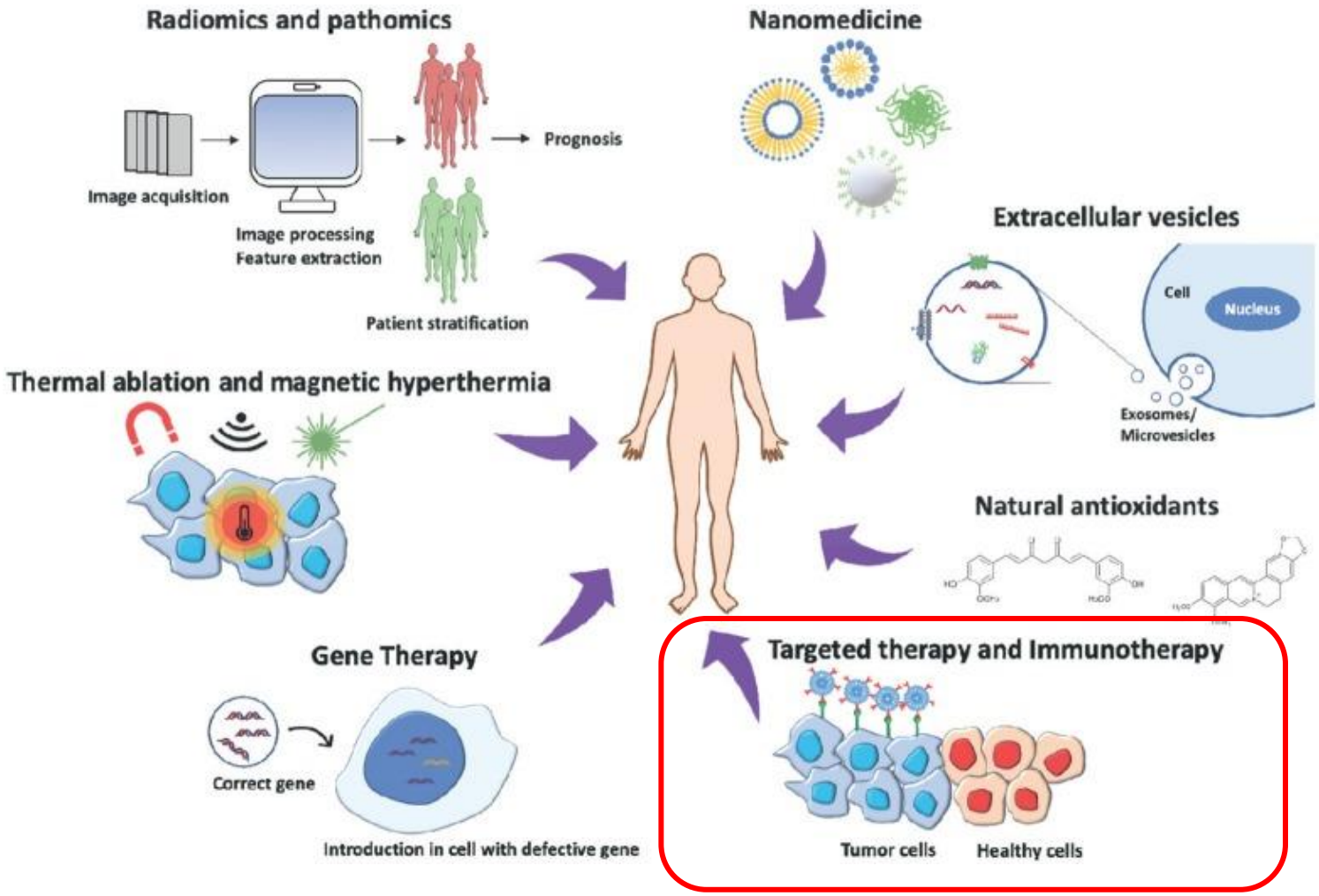
Radiationtherapy



Target therapy

Mutation	Generic Name
ALK	CERITINIB
	CRIZOTINIB
	LORLATINIB
	ALECTINIB
	BRIGATINIB
BRAF	DABRAFENIB
	TRAMETINIB
	VEMURAFENIB
EGFR	ERLOTINIB
	AFATINIB
	GEFITINIB
	OSIMERTINIB
	DACOMITINIB
EGFR EXON 20	MOBOCERTINIB
	AMIVANTAMAB
HER2	TRASTUZUMAB DERUXTECAN
KRAS G12C	SOTORASIB
	ADAGRASIB
MET	CAPMATINIB
	TEPOTINIB
NTRK	ENTRECTINIB
	LAROTRECTINIB
RET	SELPERCATINIB
	PRALSETINIB
ROS1	CERITINIB
	CRIZOTINIB
	LORLATINIB
	ENTRECTINIB

Innovative approaches for cancer treatment

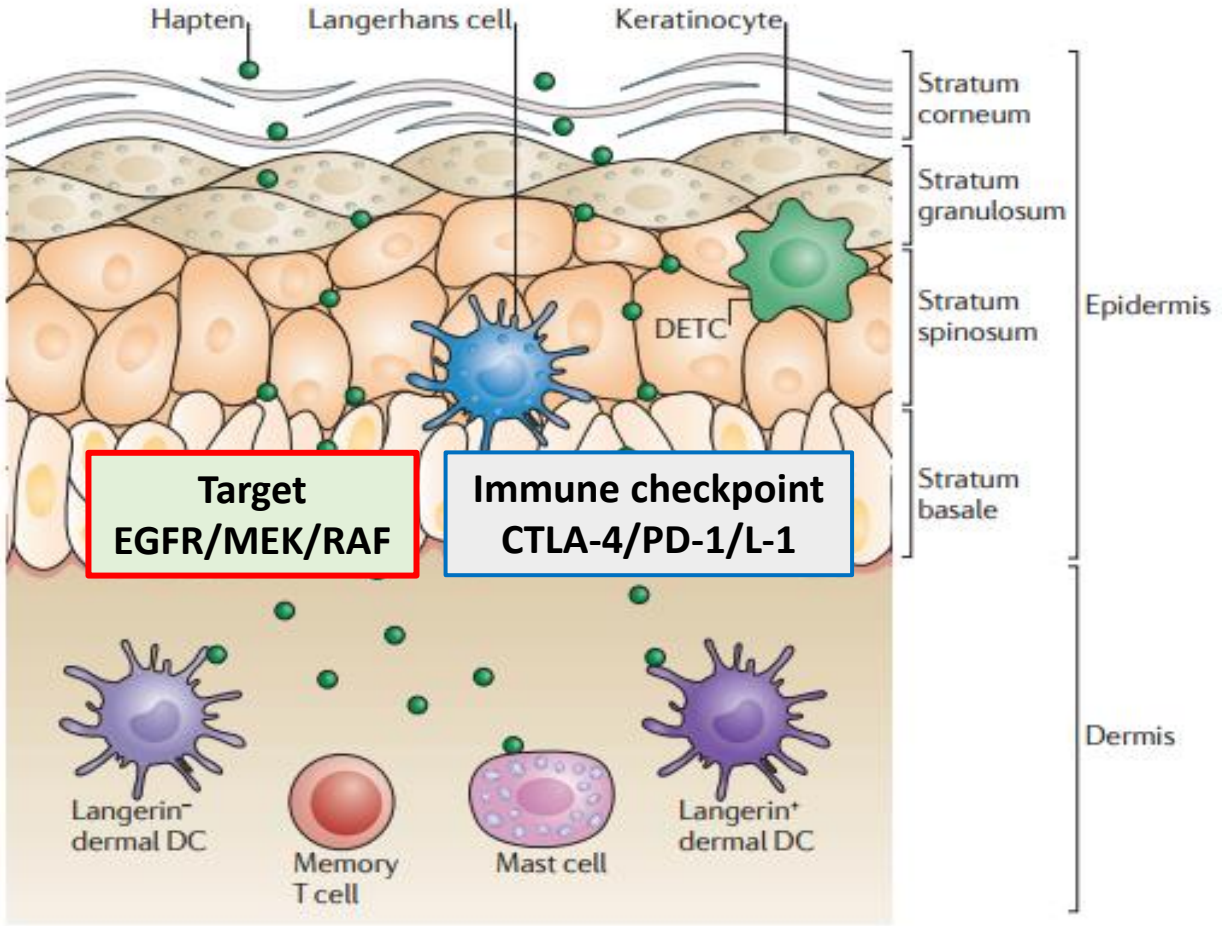


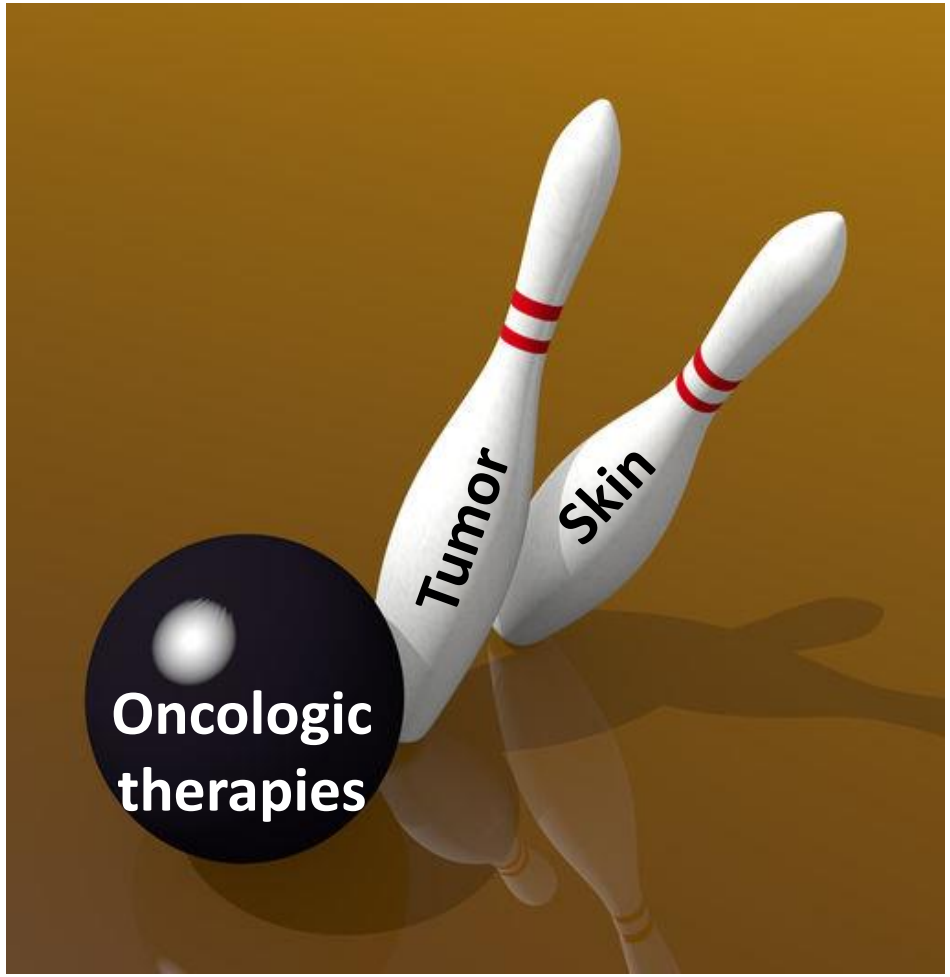
Pucci C, Martinelli C, Ciofani G. *cancermedicalscience*. 2019;13:961

New cutaneous AEs

- **Class specific**
  - Targeted therapies: the target molecule is found in tumour cells but also acts physiological functions in non-tumour cells
  - Checkpoint inhibitors: immune-mediated side effects
- **Drug specific**
  - Vemurafenib: photosensitivity
  - Dabrafenib: hemolytic anemia in patients with G6PD deficiency
- **Tumor specific**
  - Different frequency of side effects due to the same drug prescribed in different tumors and tissues

Why cutaneous toxicities?

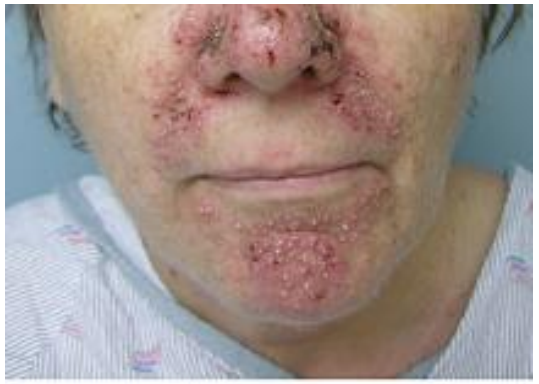




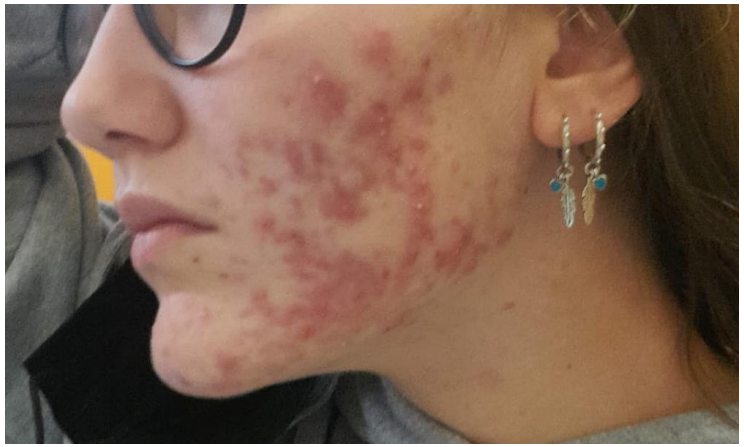
Kaplan *et al. Nat Rev Immunol. 2012*

Clinical cases

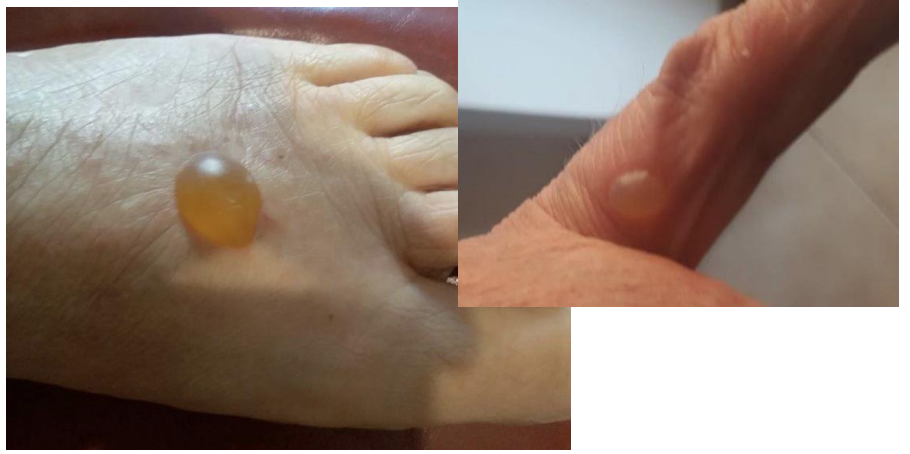
F - 44 yo

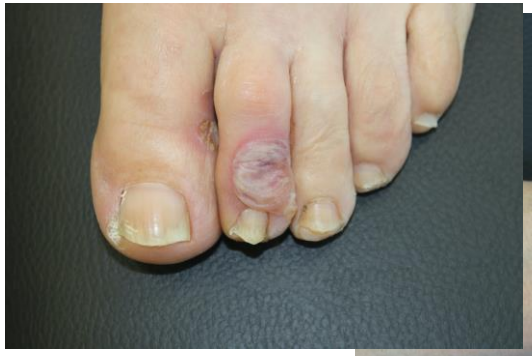


F - 38 yo

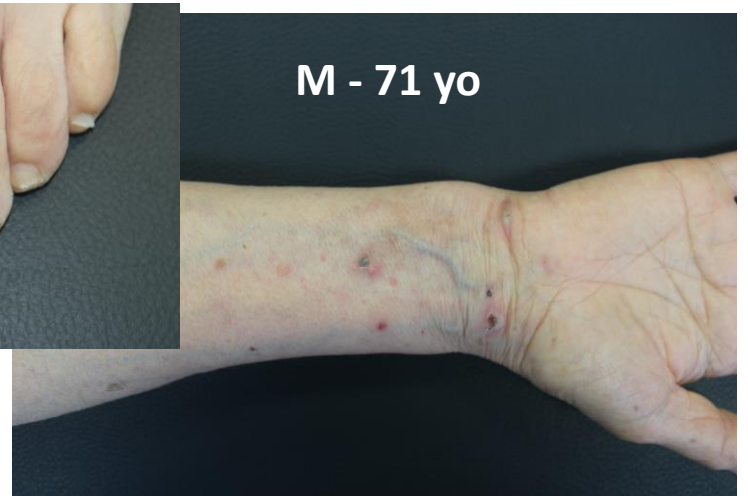


F - 63 yo



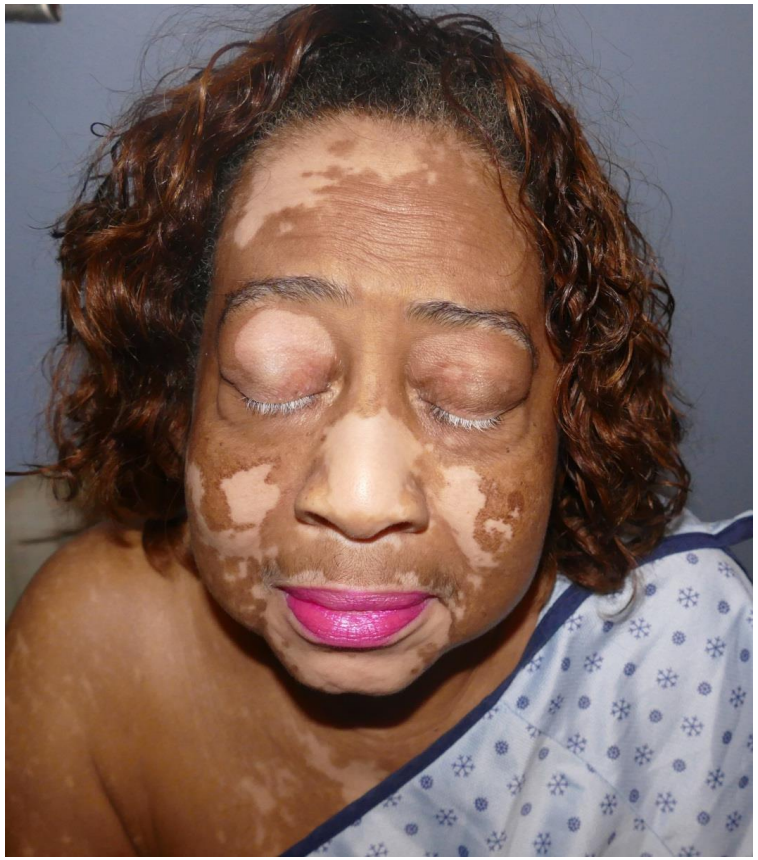


M - 71 yo

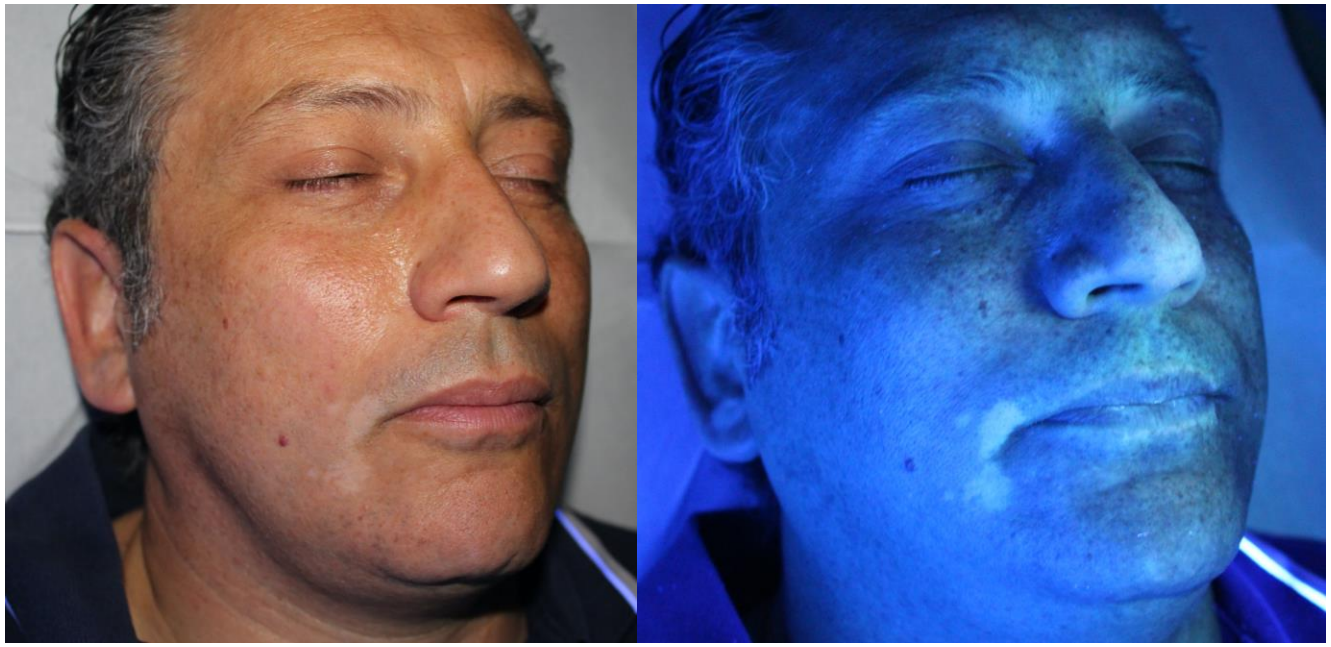


Clinical cases

F - 58 yo



M - 54 yo



SIDeMaST

1885

Società Italiana di Dermatologia
e Malattie Sessualmente Trasmesse

Task force Italiana per la diagnosi e CUra
delle Reazioni cutanee ai farmaci Oncologici

Pazienti, associazioni e caregiver domandano...

Gli esperti rispondono...

20 centri dermatologici universitari

Task force Italiana per la diagnosi e CUra
delle Reazioni cutanee ai farmaci Oncologici

MAPPA CENTRI «TICURO»

- Policlinico Gemelli, Roma
- San Camillo Forlanini, Roma
- TorVergata, Roma
- IFO, Roma
- IDI, Roma

- Sant'Orsola Malpighi, Bologna
- AOU policlinico di Modena
- Ospedale Infermi, Rimini

- Ospedale Piero Palagi, Firenze
- Policlinico «Le scotte», Siena

- Ospedale SS Annunziata, Chieti
- Azienda Ospedaliera Universitaria Policlinico - Paolo Giaccone, L'Aquila

- S. Raffaele, Milano
- ASST Spedali Civili, Brescia

- Federico II, Napoli
- Vanvitelli, Napoli

- Az. Ospedaliera S. Maria della Misericordia, Perugia

- Ospedale San Lazzaro, Torino

- AOU-Policlinico Vittorio Emanuele Rodolico, Catania

- Azienda ospedaliera Padova

Sito web SIDeMaST

SIDeMaST
Società Italiana di Dermatologia
e Malattie Sessualmente Trasmesse

HOME ASSOCIAZIONE SOCI EVENTI DERMATOLOGIA CONTATTI

Pietro Sollena

Coordinatore

Maria Carmela Annunziata

Leonardo Bianchi

Filippo Biondi

Stefano Caccavale

Paola De Simone

Davide Fattore

Vincenzo Maione

Maria Mannino

Alessia Pacifico

Giovanni Paolino

Elia Rosi

Mariateresa Rossi

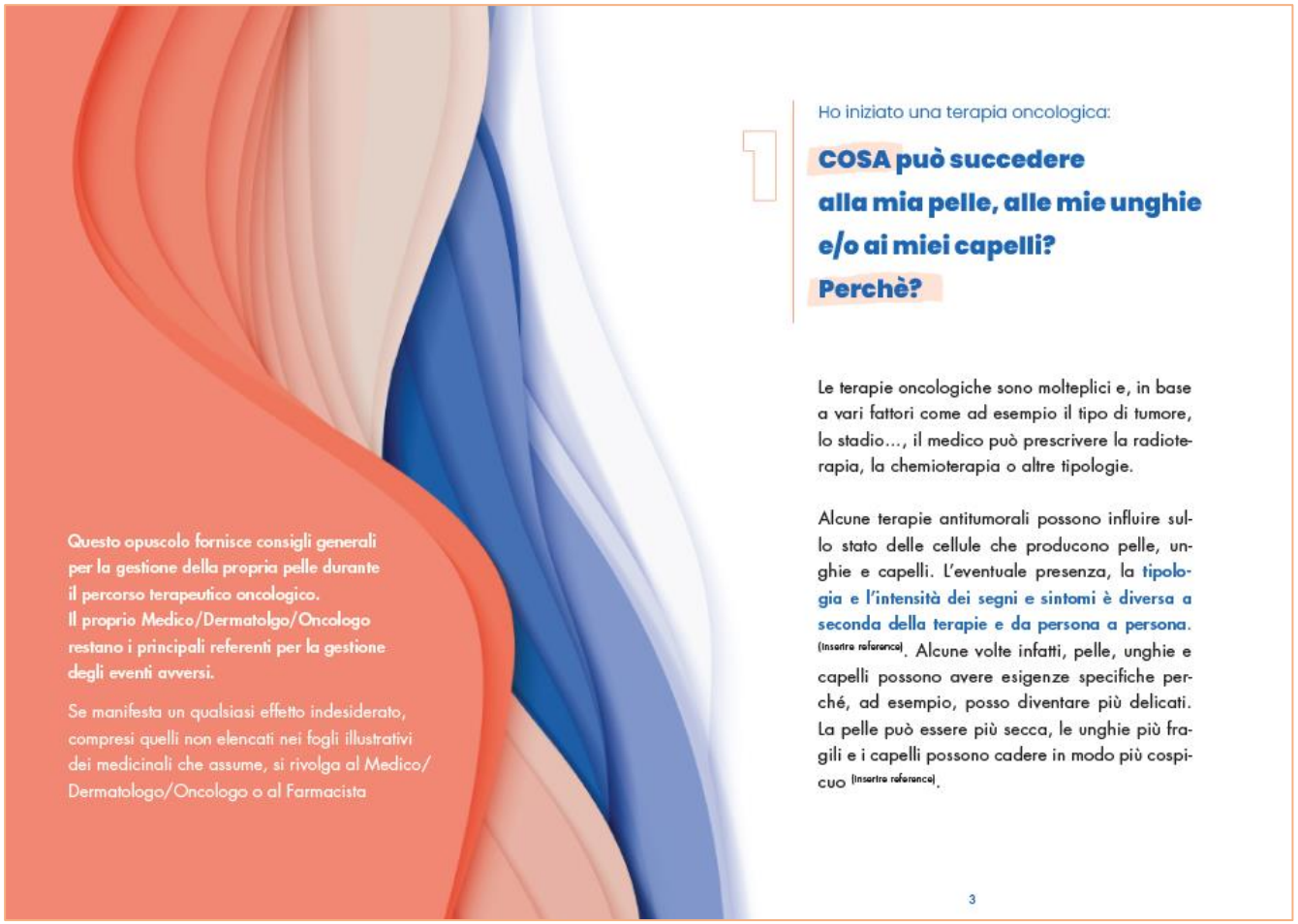
Filomena Russo

Giorgio Stabile

Michela Starace

Silvia Vichi

LEAFLET PAZIENTI



OBIETTIVO: Informare i pazienti che iniziano una terapia oncologica (in particolare se associata al rischio di sviluppare problematiche cutanea) su come gestire la propria pelle, capelli e unghie quotidianamente; dare dei punti di riferimento chiari al paziente (referral al dermatologo e associazione pazienti)

GRUPPO DI LAVORO: Medical Writer + 2 Referenti scientifici + 5 Associazioni pazienti

***TASK FORCE SIDEMAST TICURO > REFERRAL**

DESTINATARIO:

Pazienti e caregiver

DIFFUSIONE E AMPLIFICAZIONE:

Oncologi, dermatologi, associazioni pazienti e farmacie selezionate.

https://pierrefabreformed.com/sites/default/files/2024-02/Leaflet%20pazienti_SKIN%26CANCER.pdf

LEAFLET PAZIENTI

Sono in/sto per iniziare una terapia oncologica

2

QUANDO può succedere qualcosa alla mia pelle, alle mie unghie e/o ai miei capelli?

Possono esserci tempistiche varie, non uguali per tutte le terapie. In linea generale, a livello dermatologico alcuni segni o sintomi possono comparire precocemente dopo l'inizio della terapia (anche pochi giorni),[3] mentre a **mani e piedi** dopo settimane o anche a 6 mesi dall'inizio del trattamento.[4]

Per i **capelli**, la caduta associata alla chemioterapia classica può presentarsi dopo circa 2-3 settimane dall'inizio della terapia e raggiunge la massima estensione entro poche settimane.[5] C'è da sottolineare che in corso di molte delle terapie di ultima generazione non è più riportato questo effetto collaterale avendo meccanismi d'azione che non danneggiano i capelli (terapie a bersaglio molecolare e immunoterapia).

Le **unghie** possono apparire più fragili e infiammarsi circa 4-8 settimane dopo l'inizio della terapia.[6] Va ricordato che i tempi di una reazione possono variare notevolmente da paziente a paziente e in base al tipo di terapia praticata.

Sto facendo un percorso terapeutico oncologico

3

e ho notato CAMBIAMENTI su pelle, capelli e le unghie: COSA devo fare ?

Se durante la terapia oncologica noti cambiamenti su pelle, unghie e/o capelli, è sempre opportuno informare il tuo Medico/Oncologo/Dermatologo.

! **Imparare a descrivere i possibili cambiamenti della pelle può essere di aiuto.**

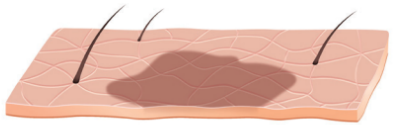


Fig. 1

MACCHIE IPERPIGMENTATE: cambiamento del colore della pelle che diventa **PIÙ SCURA** rispetto alla pelle circostante. *(Fig. 1)*

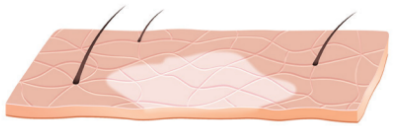


Fig. 2

MACCHIE IPOPIGMENTATE: cambiamento del colore della pelle che diventa **PIÙ CHIARA** rispetto alla pelle circostante. *(Fig. 2)*

Sono in/sto per iniziare una terapia oncologica

posso assumere degli INTEGRATORI alimentari?

18

Gli integratori alimentari sono: "prodotti alimentari destinati ad integrare la comune dieta e che costituiscono una fonte concentrata di sostanze nutritive, quali le vitamine e i minerali, o di altre sostanze aventi un effetto nutritivo o fisiologico, in particolare, ma non in via esclusiva, aminoacidi, acidi grassi essenziali, fibre ed estratti di origine vegetale, sia monocomposti che pluricomposti, in forme predosate".[19]

In assenza di necessità cliniche, non è raccomandato alcun integratore: **rivolgiti al tuo Oncologo per ogni dubbio o necessità e non assumere integratori senza aver prima consultato il tuo Medico/Oncologo.**

Ricorda che l'assunzione di integratori alimentari non deve sostituire una dieta variata ed equilibrata e uno stile di vita sano e prima di assumere qualsiasi tipo di prodotto chiedi il parere al tuo Medico.

Indirizzi utili

ASSOCIAZIONI PAZIENTI

AIMAME - Associazione Italiana Malati di Melanoma e tumori della pelle.
Piazza Barberini 47, 00187 Roma
Tel: 06 49776088 E-mail: info@aimame.it Sito: www.aimame.it

APAIM - Associazione Pazienti Italia Melanoma
Via Amalfi n 7 Ladispoli, Roma
Tel. 3393519071 E-mail: info@apaim.it Sito: www.apaim.it

EUROPA DONNA ITALIA
Tel 02 36709790 E-mail: segreteria@europadonna.it.

FONDAZIONE INCONTRADONNA
E-mail: segreteria@incontradonna.it Sito: www.incontradonna.it

MIO – Melanoma Italia Onlus
E-mail: claudia.cidonio@aimatmelanoma.org
Sito: http://www.melanomaitalia.org
Tel. +39335293911

SIDeMaST TICURO: Task-force Italiana Per Lo Studio Delle Reazioni Cutanee In Corso Di Terapia Oncologica
La task force di TICURO è composta da Dermatologi specialisti con esperienza nel campo della Dermatologia Oncologica.

Conosci gli esperti della task force su Task Force - associazione e area soci – SIDeMaST

SIDeMaST

ticuro

Task-force Italiana per lo studio delle reazioni cutanee in corso di terapia oncologica

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LEAFLET PAZIENTE

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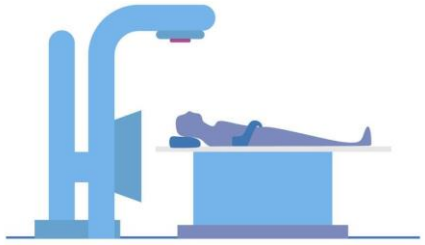
Radiationtherapy



Target therapy

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	LAROTRECTINIB
RET	SELPERCATINIB
	PRALSETINIB
ROS1	CERITINIB
	CRIZOTINIB
	LORLATINIB
	ENTRECTINIB

TARGETED THERAPIES

EGFR inhibitors	Monoclonal antibodies against EGFR: cetuximab, necitumumab, and panitumumab EGFR-specific TKIs: erlotinib, gefitinib, and osimertinib Dual EGFR and HER-2 kinase inhibitors: lapatinib, afatinib Less specific multi-kinase inhibitors: vandetanib
KIT and BCR-ABL inhibitors	Imatinib, dasatinib, ponatinib, nilotinib, and bosutinib
Antiangiogenic agents	Monoclonal antibodies against VEGFR: bevacizumab, ramucirumab, and aflibercept Non-selective antiangiogenic agents: sorafenib, sunitinib, pazopanib, regorafenib, axitinib, lenvatinib, cabozantinib, and nintedanib
RAS-RAF-MEK-ERK pathway inhibitors	BRAF inhibitors: vemurafenib and dabrafenib MEK inhibitors: cobimetinib, selumetinib, and trametinib mTOR inhibitors: sirolimus, everolimus, and temsirolimus
Hedgehog pathway inhibitors	Vismodegib

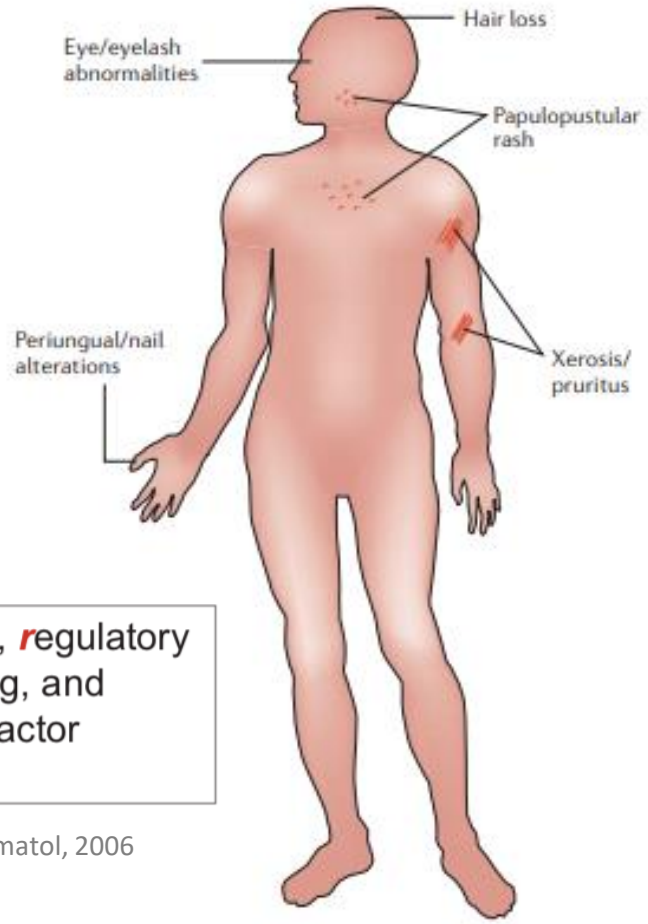
- more specific action than conventional chemotherapy, with **greater efficacy and less toxicity**

Grávalos C, Sanmartín O, Gúrpide A, et al. *Clin Transl Oncol*. 2019;21(5):556-571.

EGFR inhibitor-associated dermatological toxicity

Organ site	Clinical manifestation
Skin	Acneiform rash (papulopustular rash) 75-90%
	Xerosis
	Erythema
	Photosensitivity
	Fissures and crack
	Hyperpigmentation
	Telangiectasia
	Pruritus
Nail 12-16%	Paronychia
	Onyxis
Hair 21%	Trichomegaly in eyelash
	Hypertrichosis in eyelash, eyebrow and mustache
	Alopecia in scalp hair
Eye	Conjunctivitis
	Blepharitis
	Xerotic
	Keratitis
	Lacrimation

Cutaneous toxicities are prominent, affecting 45-100% of patients under EGFR-I therapy

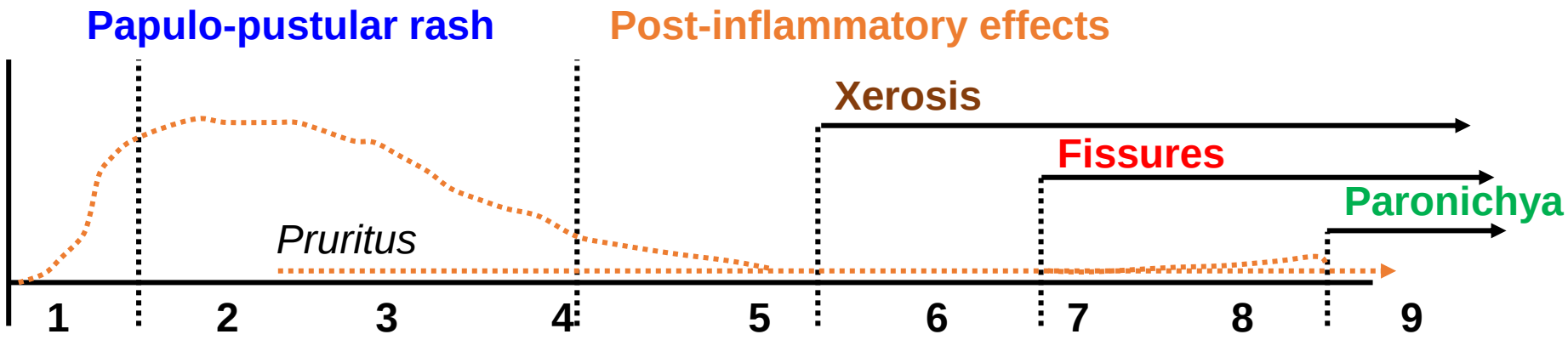


Papulopustules and/or ***p***aronychia, ***r***egulatory abnormalities of hair growth, ***i***tching, and ***d***ryness due to ***e***pidermal growth factor receptor inhibitors

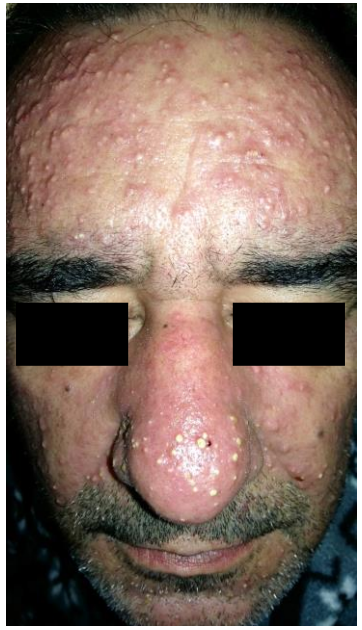
Lacouture ME. The PRIDE syndrome. Br J Dermatol, 2006

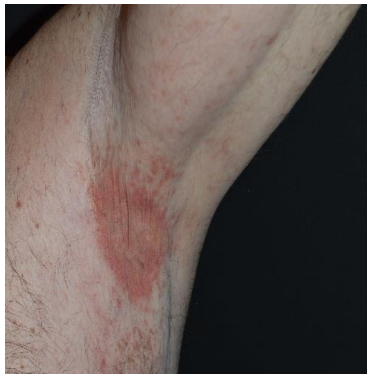
Lacouture, ME Nature Reviews Cancer 2006.; *Chen AP et al.* JAAD 2012; *Clubbers JMK et al.* Support Care Cancer 2016

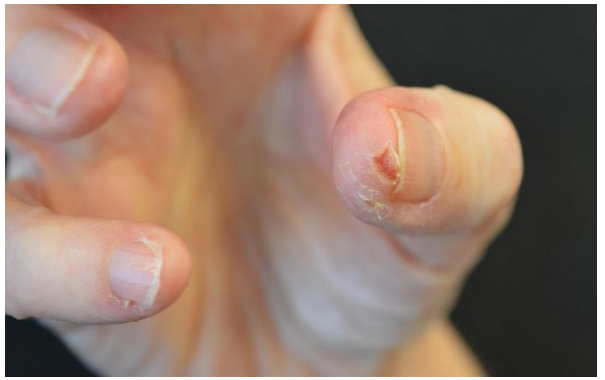
Timing cutaneous AE of EGFRi

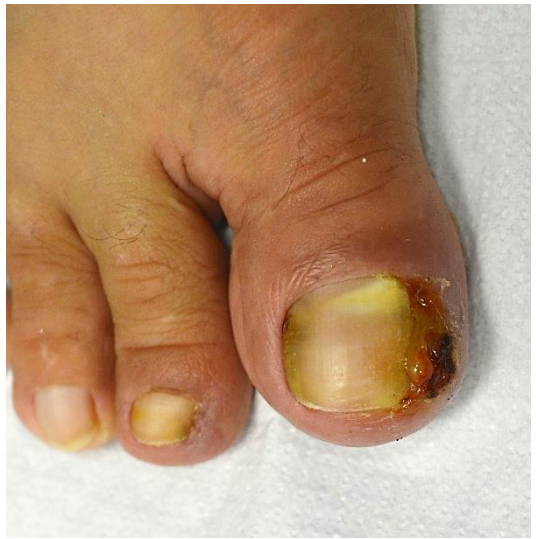


This skin reaction has an **early-onset**, but the **severity** of EGFR-inhibitor induced papulopustular eruptions often **decreases** with continued use of the drug









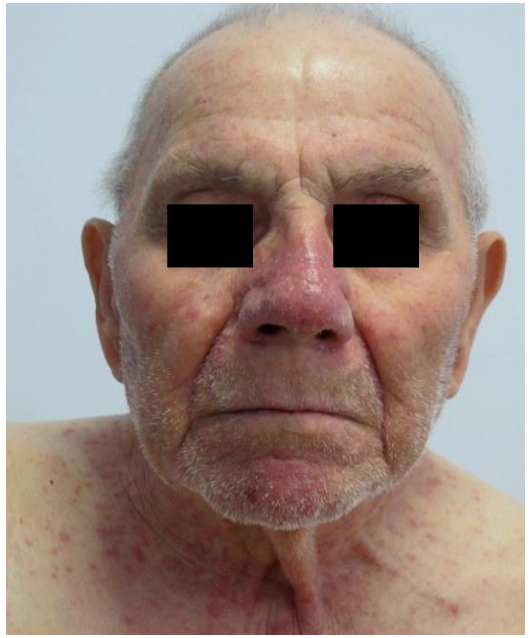
Van Cutsem E. Oncologist. 2006;11:1010-1017. Lacouture ME, et al. J Clin Oncol. 2010;28:1351-1357. Scope A, et al. J Clin Oncol. 2007;25:5390-5396.

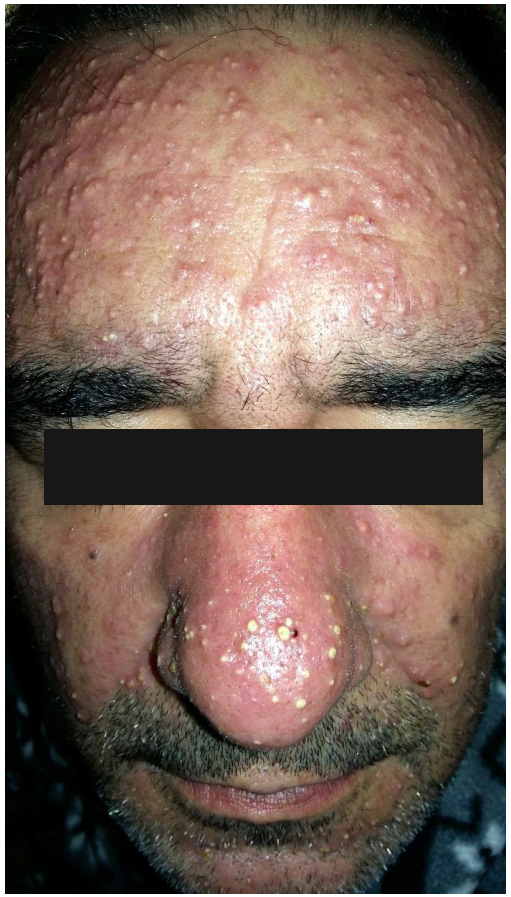
Cutaneous rash by EGFRi

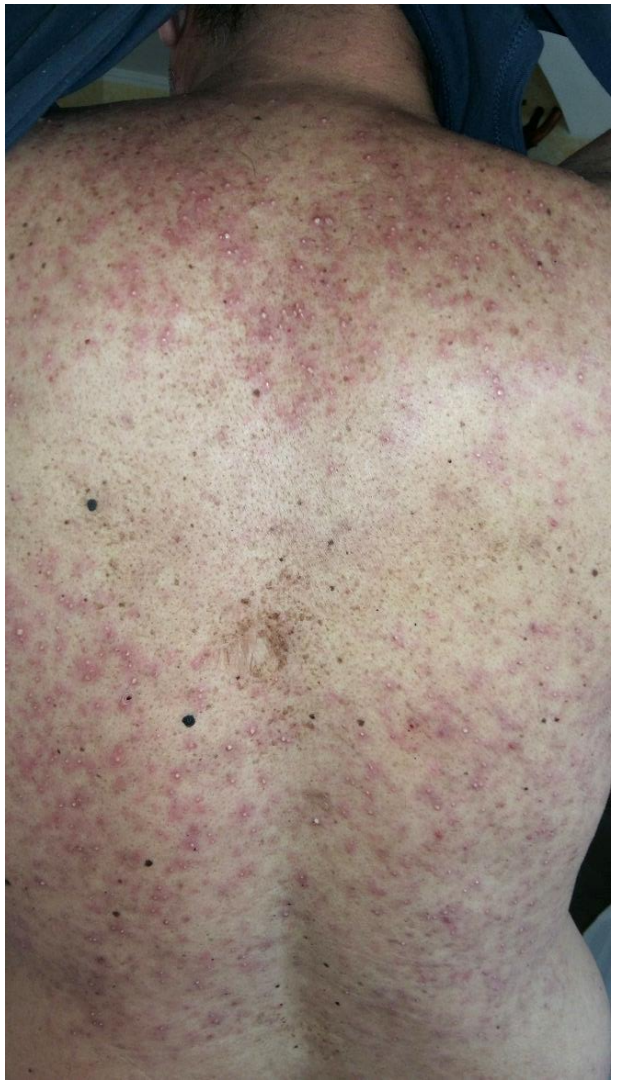
Follicular and perifollicular papules and pustules

Pruritus and/or burning sensation in 62%

- Erlotinib 150 mg QD[2]
  - All grade: 75%
  - **Grade 3: 9%**
- Cetuximab[3]
  - All grade: 85%
  - **Grade 3: 10%**
- Panitumumab[4]
  - All grade: 90%
  - **Grade 3: 16%**
- Lapatinib[5]
  - All grade: 27%
  - **Grade 3: 1%**

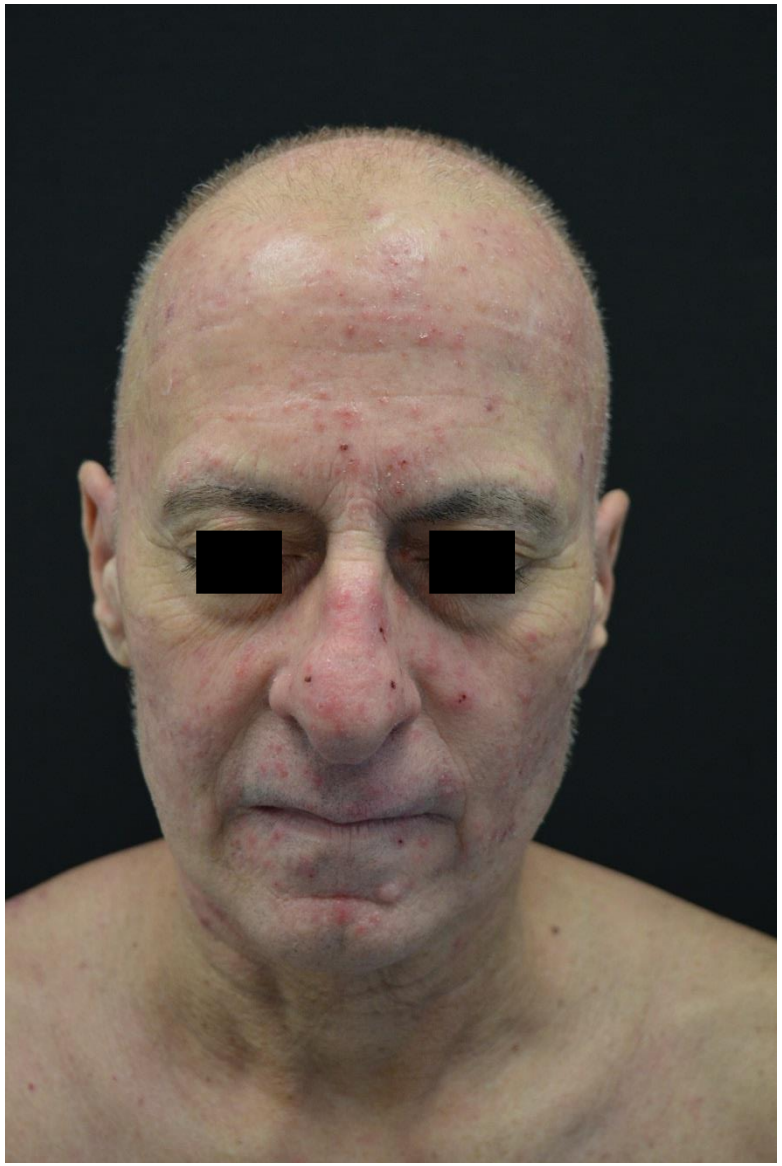


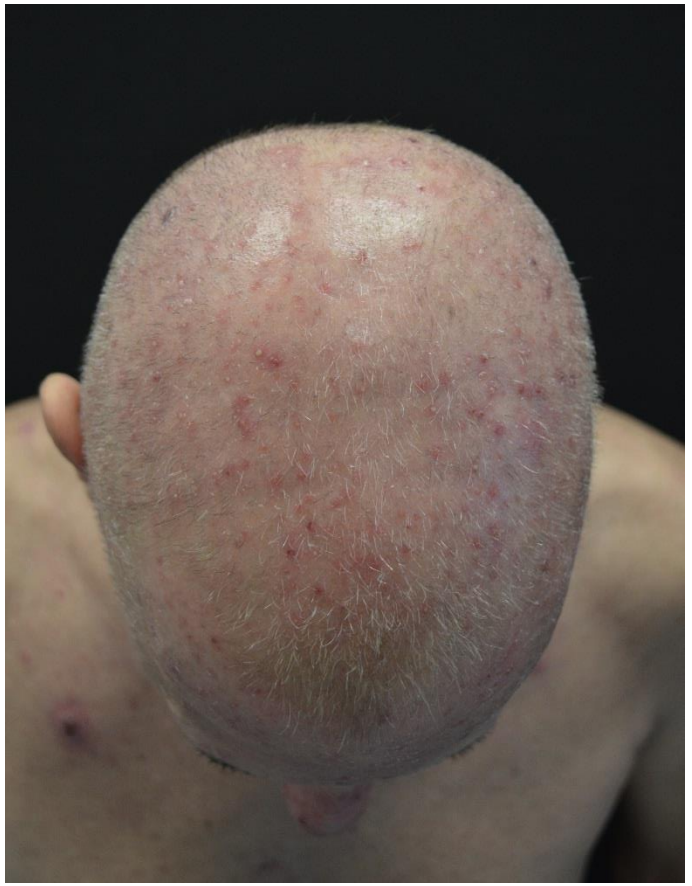




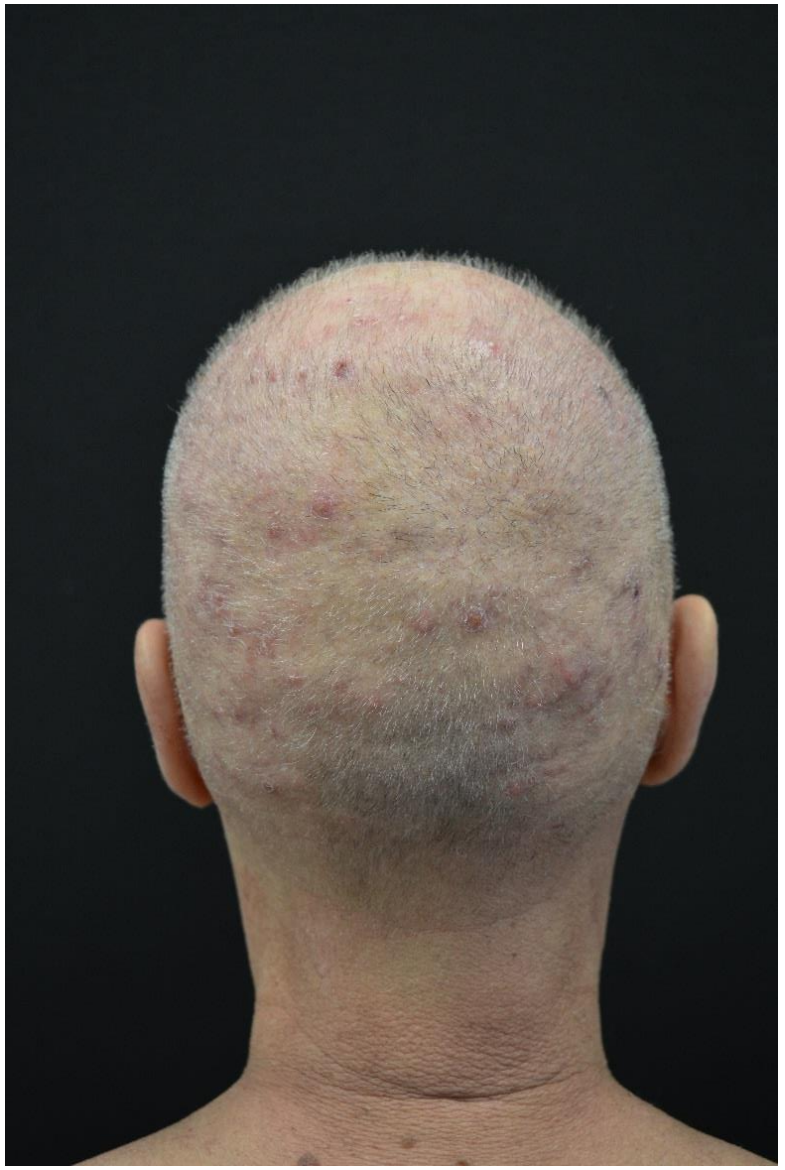
1. Lacouture ME, et al. Br J Dermatol. 2006;155:852-854.
2. Shepherd FA, et al. N Engl J Med. 2005; 353:123-132.
3. Rosell R, et al. Ann Oncol. 2008;19:362-369.
4. Van Cutsem E, et al. J Clin Oncol. 2007;25:1658-1664.
5. Geyer CE, et al. N Engl J Med. 2006;355:2733-2743.

Cutaneous toxicities of EGFRi: Papulo-pustolar rash





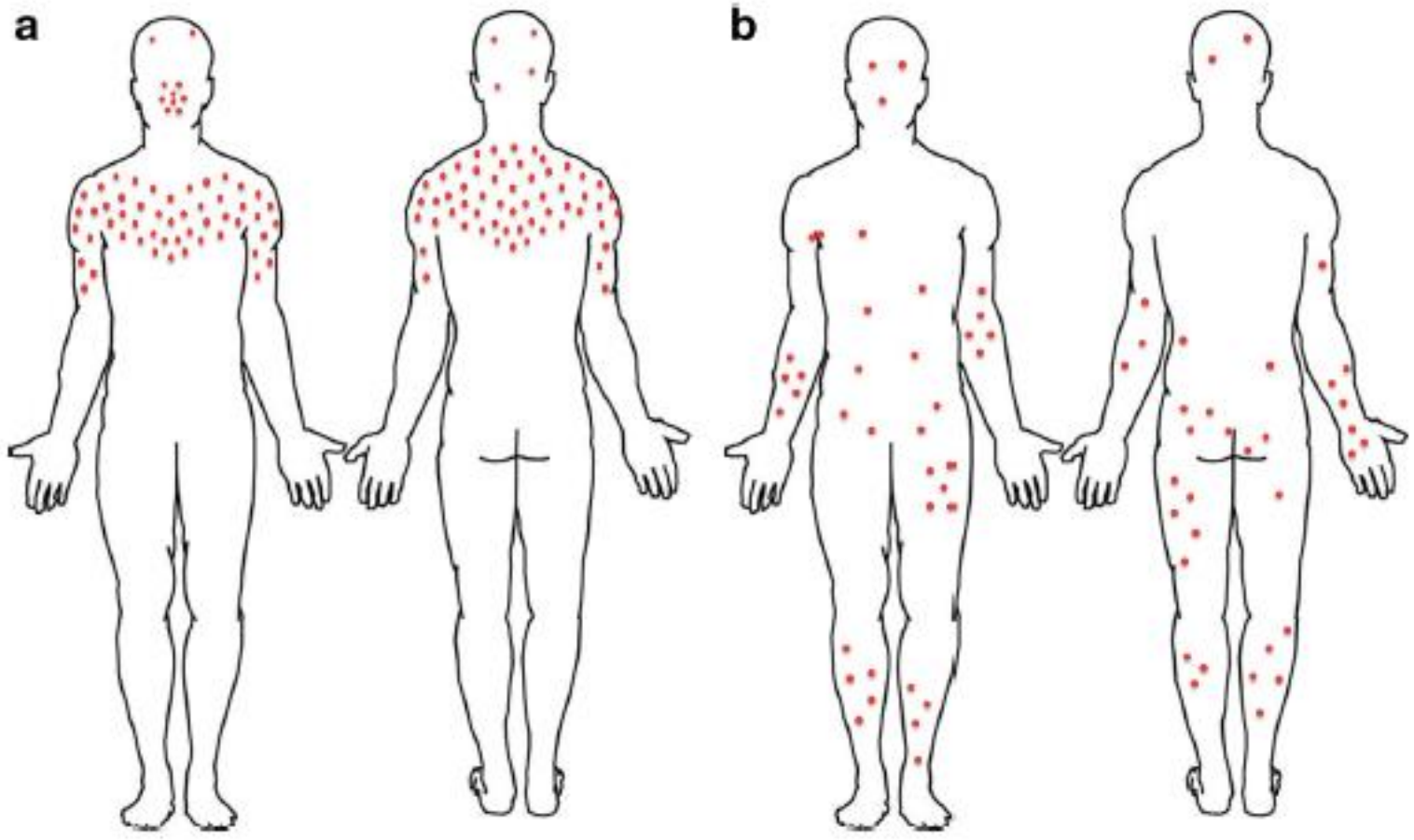
typically occurs in a seborrheic distribution, primarily on the face, scalp, neck, and upper torso



Papulo-pustolar rash and bacteria

Differentiating from superimposed bacterial infection

Fig. 3 Geographic distribution of papulopustular eruption versus bacterial superinfection. The relative locations of the papulopustular eruptions (a) and bacterial superinfections (b) observed in this study



Braden RL et al. *Support Care Cancer* 2016

Skin papulopustular rash as useful marker of efficacy

184 patients harboring the wild-type EGFR and wild-type KRAS genes were analysed

92 patients with cutaneous toxicity

92 patients without CT

Occurrence of rash within the treatment (ERLOTINIB) was strongly associated with longer PFS (3.0 vs. 1.2 months, p<0.001, n=184), longer OS (13.9 vs. 5.8 months, p<0.001, n=184) and higher ORR (17.4% vs. 3.3%, p=0.001, n=172)

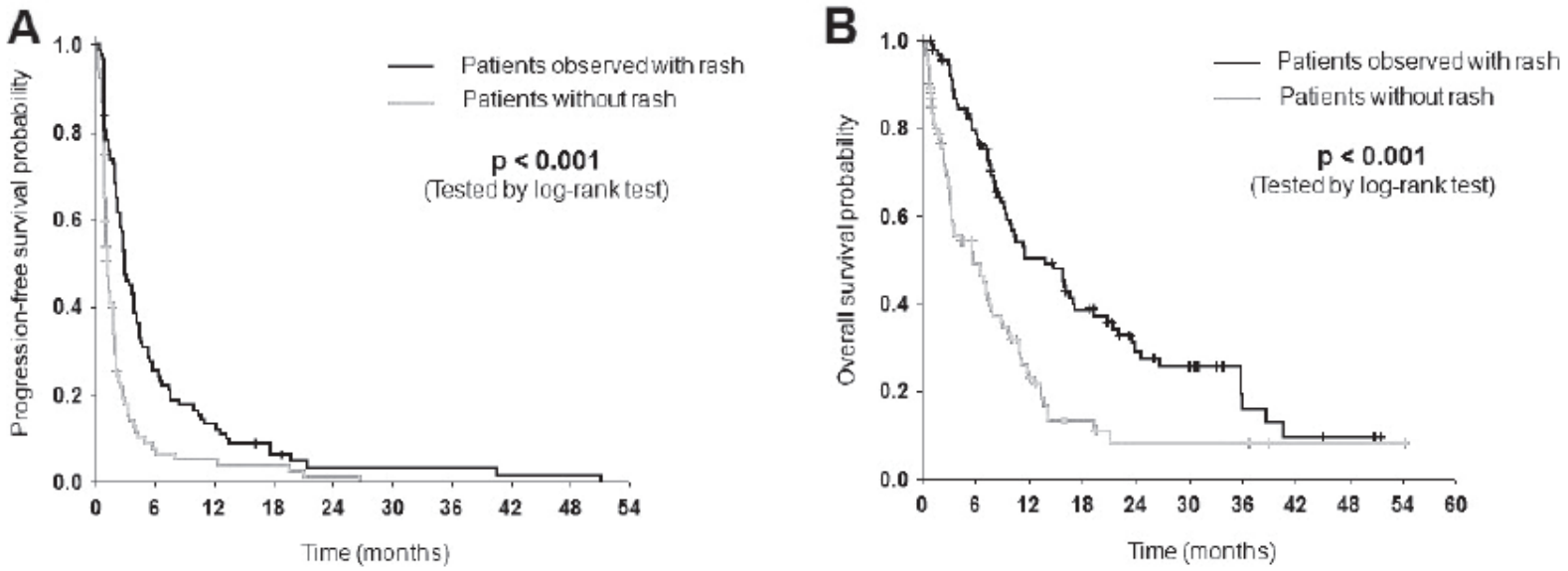
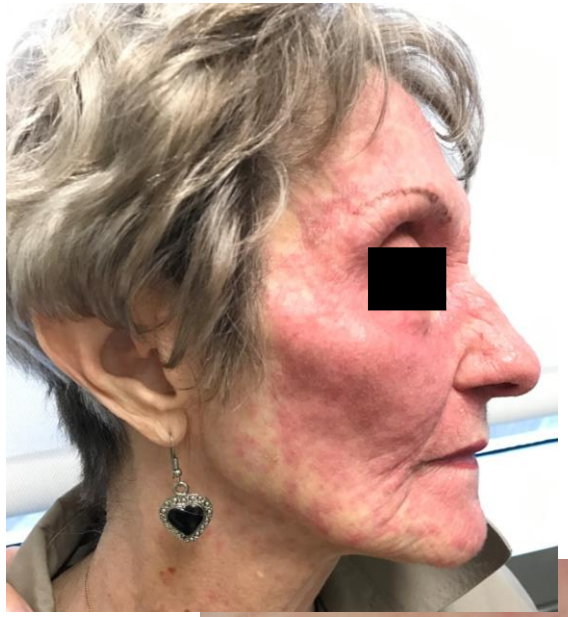


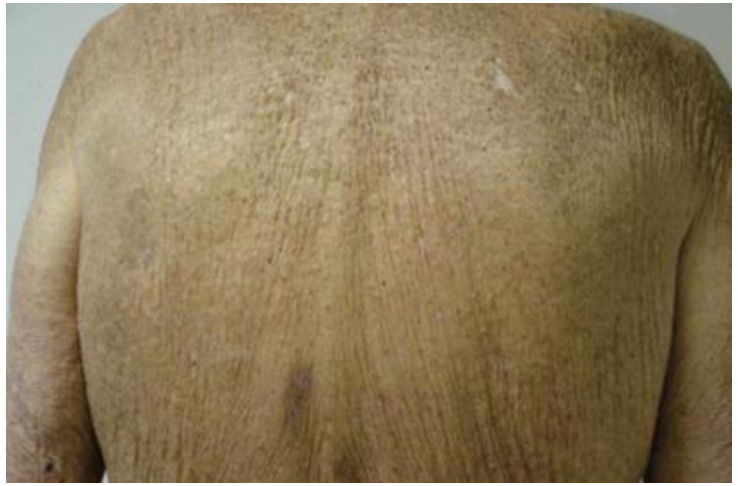
Figure 1. Comparison of PFS (A) and OS (B) between patients who observed with rash and patients without rash.

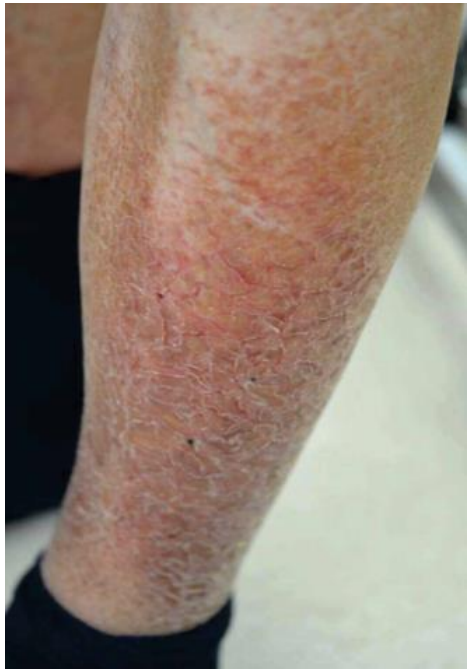
Fiala O. et al. Neoplasma 60,1,2013;
Perez-Soler R. Clinical Lung Cancer, Vol. 8, Suppl. 1, S7-S14, 2006

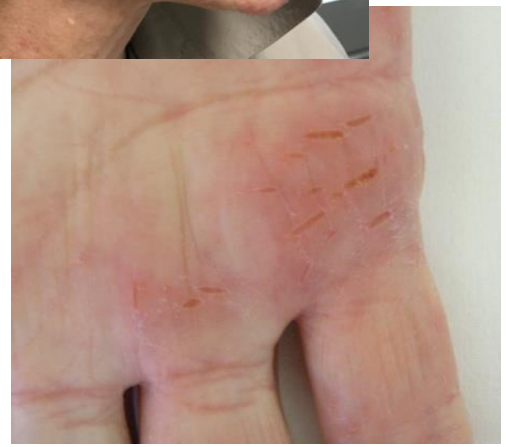
Cutaneous toxicities of EGFRi: xerosis and pruritus

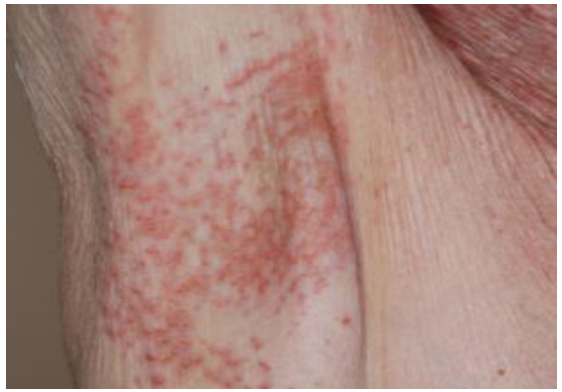
Xerosis and pruritus have a major negative impact on HRQoL during the first 6 weeks of EGFRI treatment

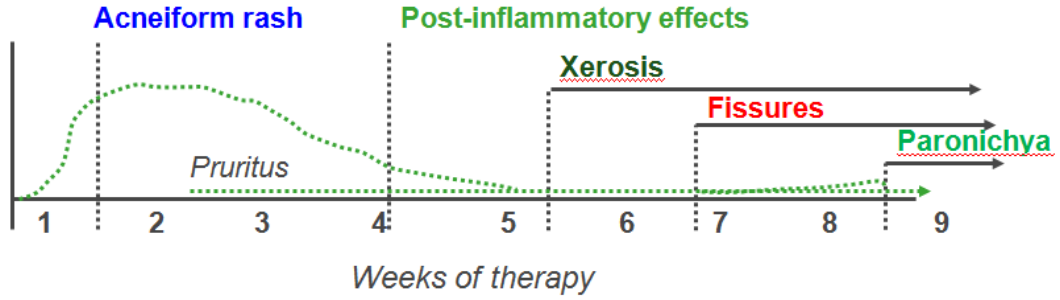






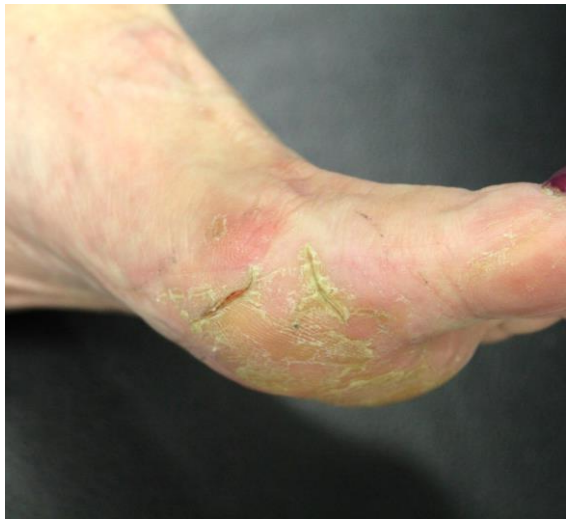
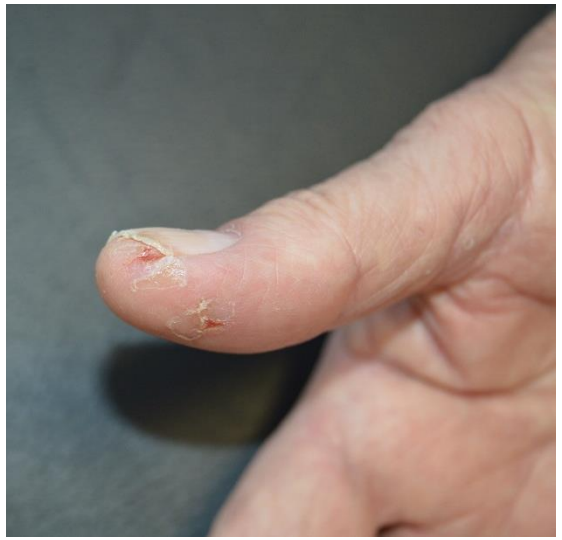
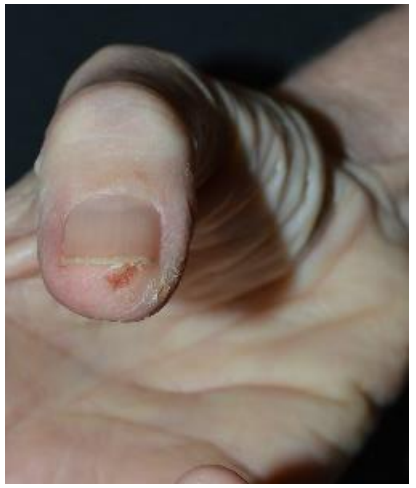
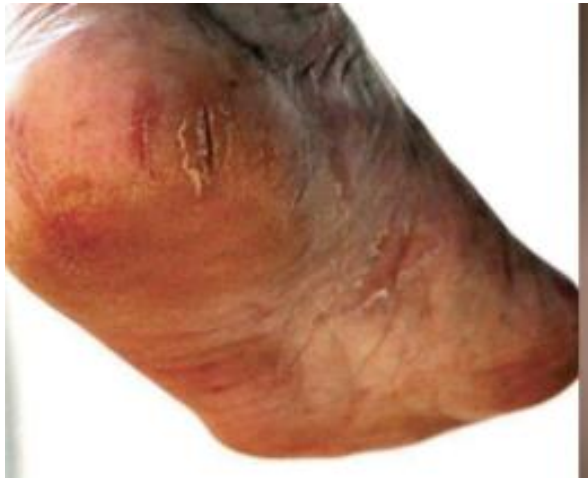
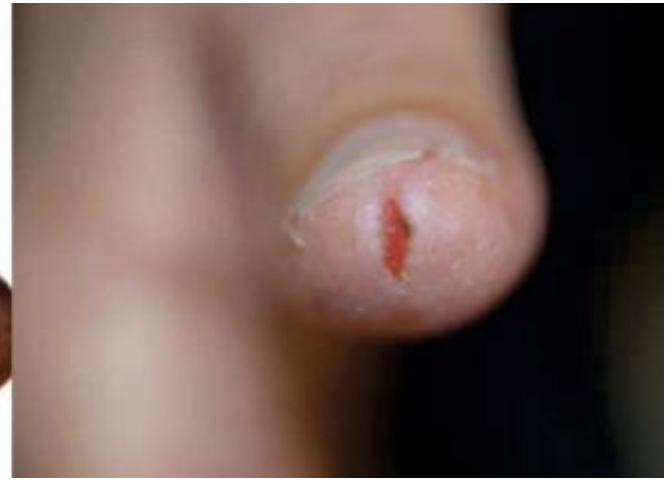
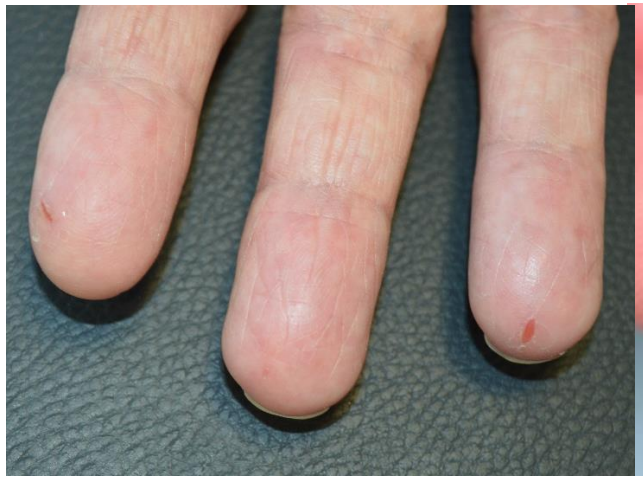






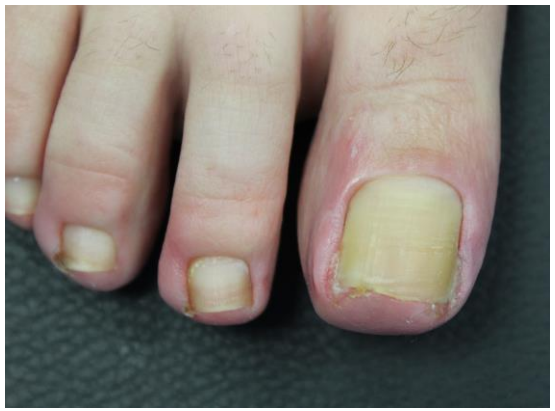
Clabbers JMK et al. *Support Care Cancer.* 2016; Heidary N *J Am Acad Dermatol,* 2008

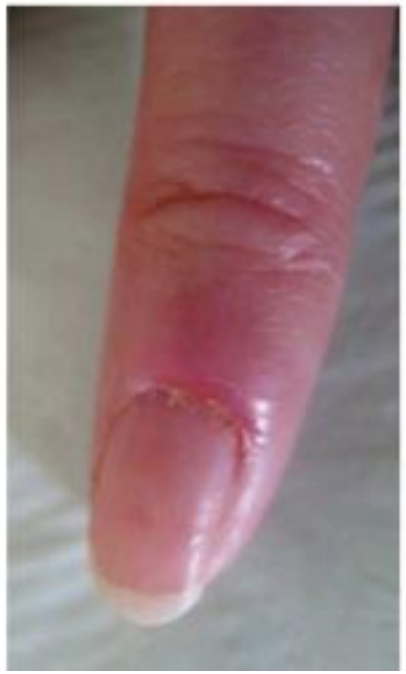
Cutaneous toxicities of EGFRi: fissures

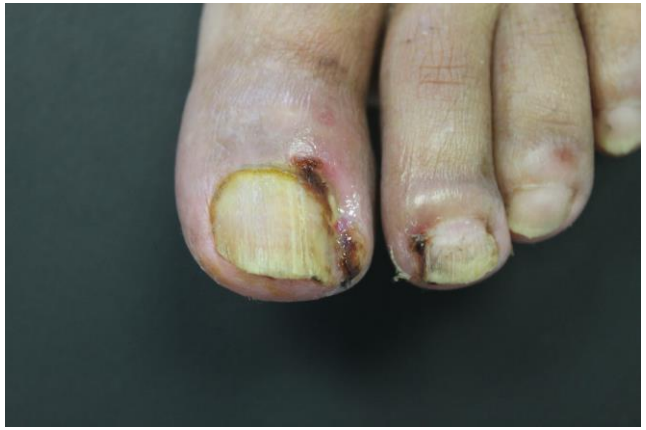








Lacouture ME, et al. *Br J Dermatol.* 2006; Mitchell EP, et al. *Oncology (Williston Park).* 2007; Osio A, et al. *Br J Dermatol.* 2009; Lacouture ME. *Support Care Cancer* 2011

Cutaneous AE – paronychia







Paronychia is a disorder characterised by an **inflammatory process** involving the soft tissues around the nail

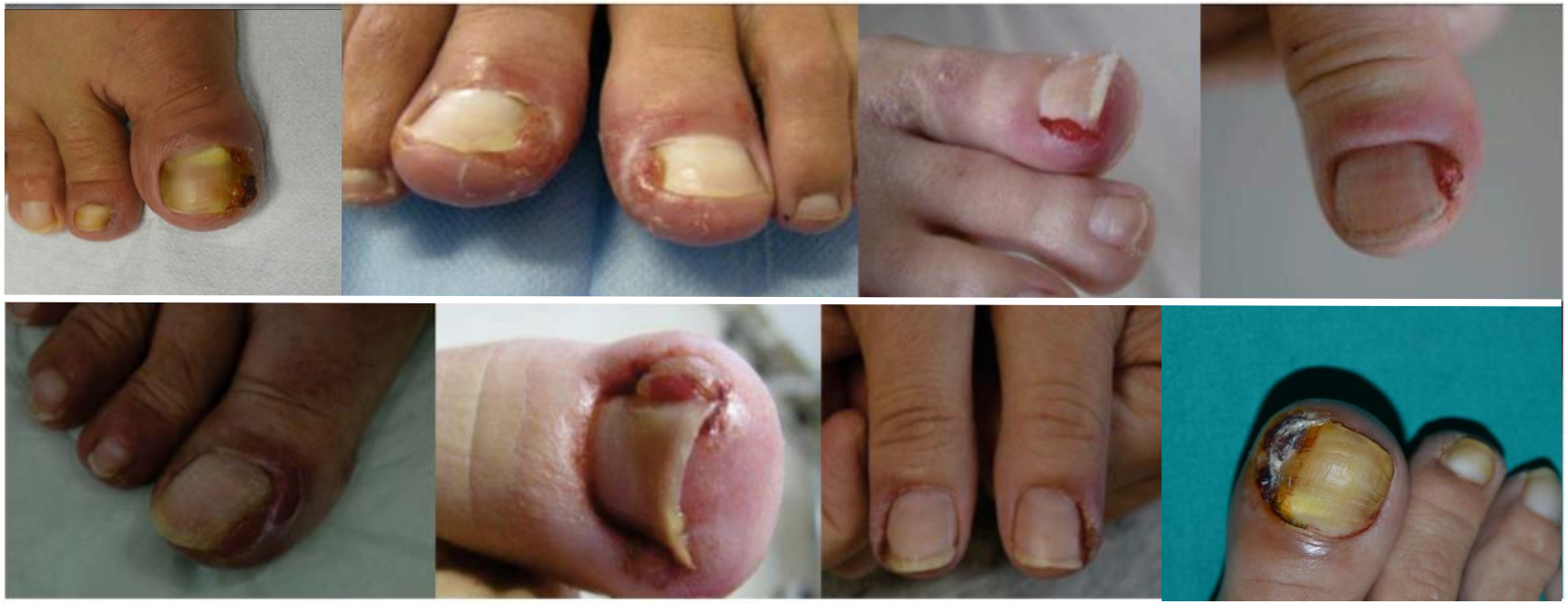
It can lead to **infection**, and the consequent swelling and tenderness often **affect activities of daily living**

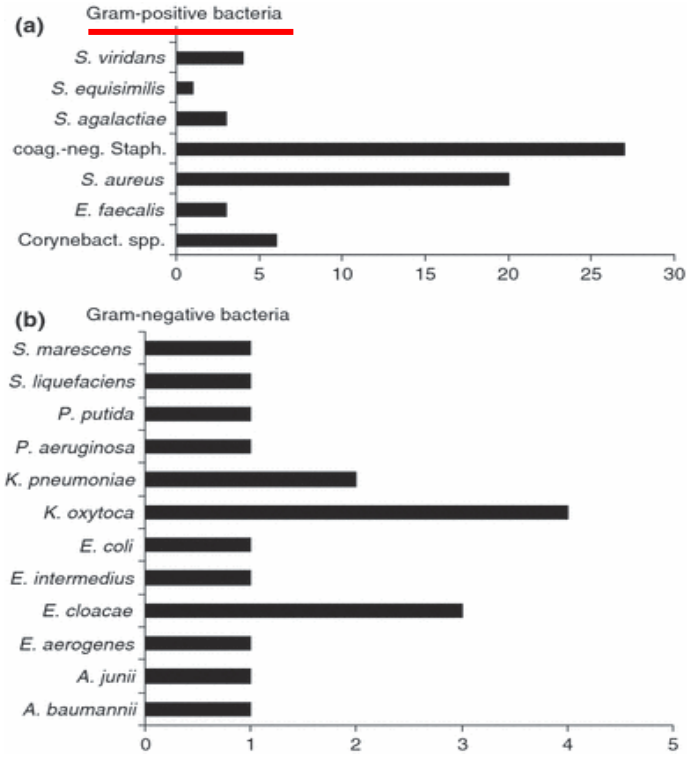
It is important to **avoid skin irritants**, to avoid soaking of hands and feet for prolonged time period in soapy water, and to make sure that feet is **dry** before putting on shoes

Lacouture ME, et al. *Br J Dermatol.* 2006; Mitchell EP, et al. *Oncology (Williston Park).* 2007; Osio A, et al. *Br J Dermatol.* 2009

Cutaneous AE – Pyogenic granuloma

Overgrowing of friable **granulation tissue** on lateral and/or proximal nail folds, **mimicking ingrown nails**. **Secondary infections** (Staph.aureus ...) are frequent





Garden et al, *JAAD* 2012; Eames T *J Eur Acad Dermatol* 2010; Van Cutsem E. *Oncologist* 2006

Cutaneous AE – Ocular toxicities

The EGFR is also expressed on the eye surfaces as well as in the tear and sebaceous glands..

Up to 15% of patients receiving anti-EGFR therapy can experience ocular toxicity

corneal erosions and blepharitis

blepharitis

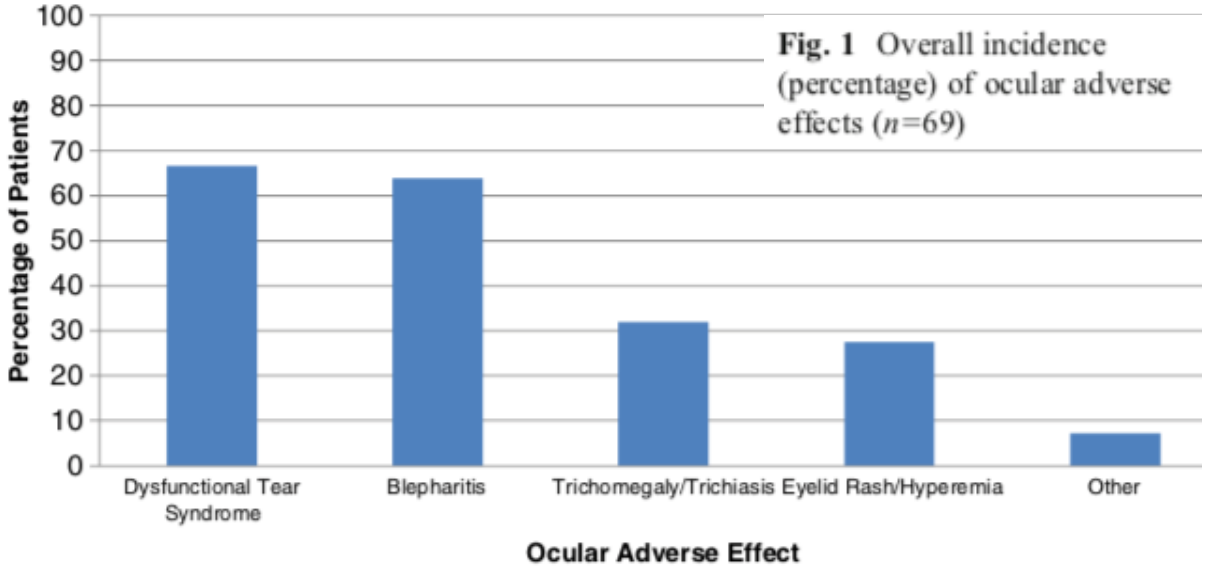


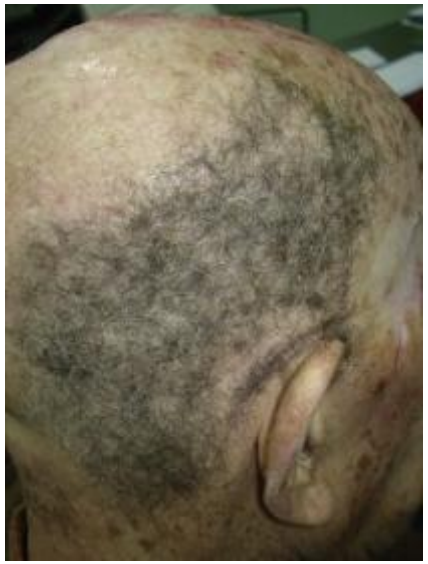
Fig. 1 Overall incidence (percentage) of ocular adverse effects (n=69)

Lacouture ME, et al. Br J Dermatol. 2006;155:852-854. Mitchell EP, et al. Oncology (Williston Park). 2007;21 Osio A, et al. Br J Dermatol. 2009;161:515-521. Borkar DS et al. Support Care Cancer 2013; 21(4):1167-74

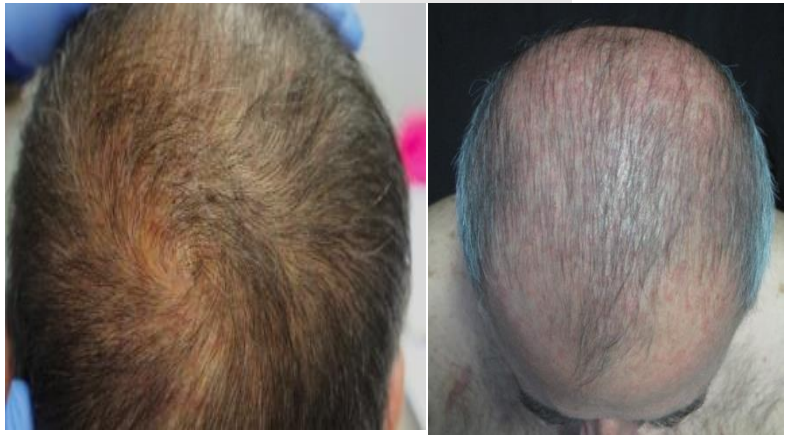
Cutaneous AE – Hair alterations

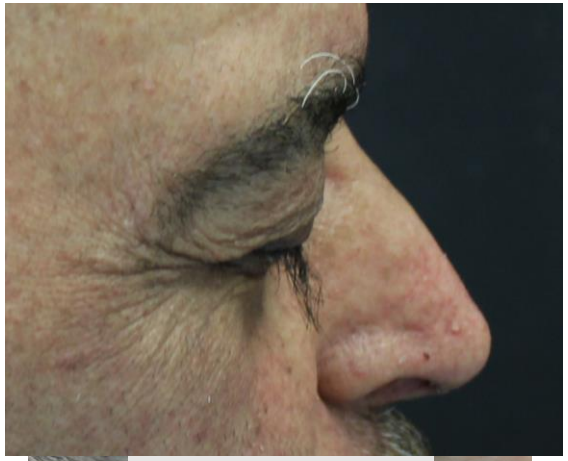
EGFR is expressed in both the keratinocytes of the epidermis and at the root of hair follicles

- **↑ third month of treatment**
  - Alopecia and curly hair
  - Hirsutism
  - Trichomegaly (eyelashes)

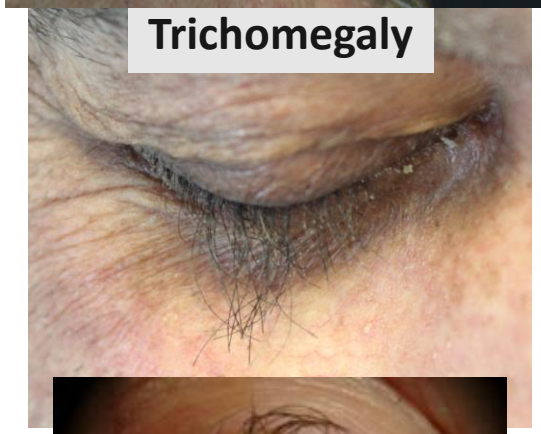


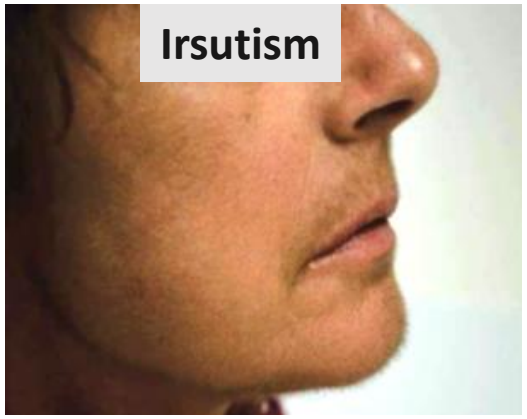
Alopecia





Trichomegaly





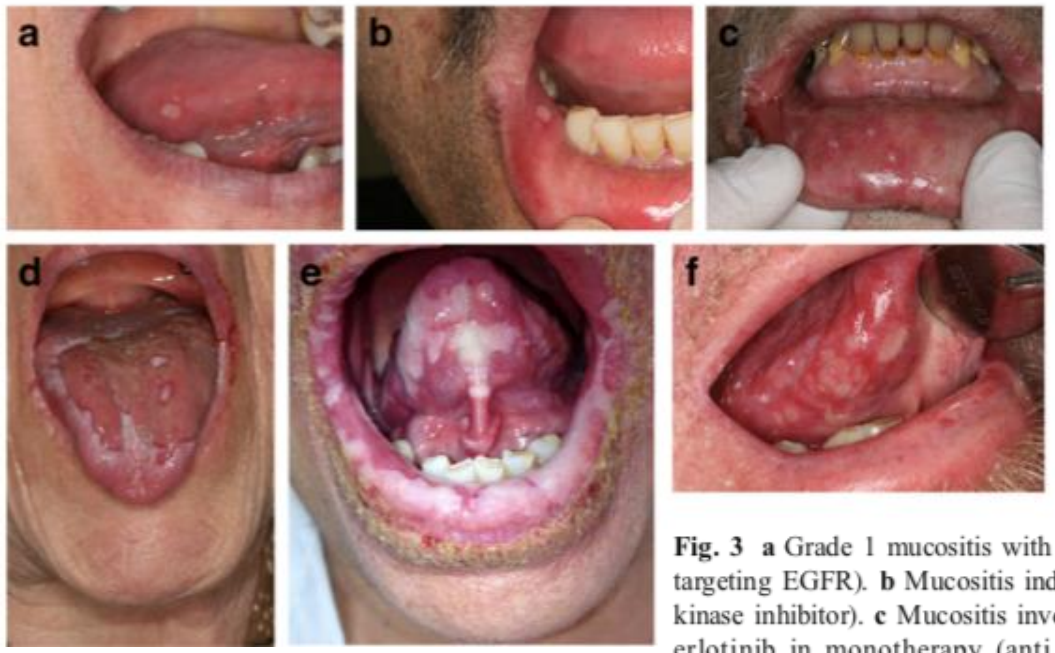
Irsutism

Lacouture ME, et al. Br J Dermatol. 2006;155:852-854.
Roe E, et al. J Am Acad Dermatol. 2006;55:429-437.
Vano-Galvan S, et al. J Am Acad Dermatol. 2010;62:531-533.
Kerob D, et al. Arch Dermatol. 2006;142:1656-1657.
Robert C. Lancet Oncol 2005; 6: 491-500.

Cutaneous AE – stomatitis and mucositis

Oral changes induced by targeted therapies are less well described and have been only sporadically characterized mainly reported using nonspecific terminology (stomatitis, mucositis)

The incidence of mucositis with EGFRi varies between 7 and 24%, but the incidence rate of high-grade (≥3) mucositis has never been reported to exceed 1%



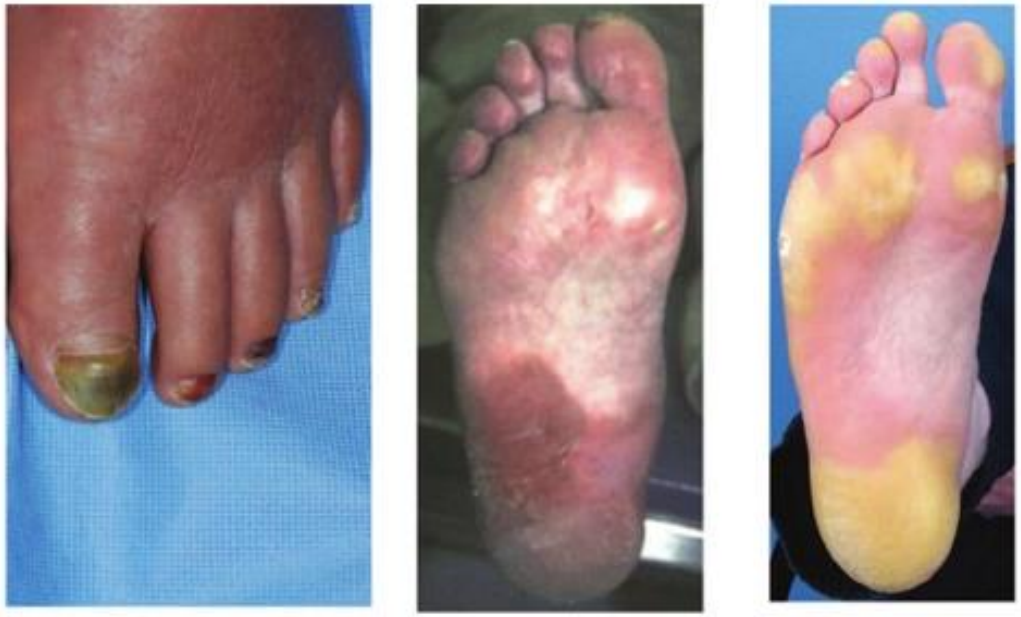
Vigarios E et al. *Support Care Cancer* 2017

Fig. 3 **a** Grade 1 mucositis with panitumumab (monoclonal antibody targeting EGFR). **b** Mucositis induced by afatinib (pan-HER tyrosine kinase inhibitor). **c** Mucositis involving the labial mucosa induced by erlotinib in monotherapy (anti EGFR). **d** Diffuse radio-induced mucositis affecting the keratinized mucosa (dorsum of the tongue). **e** High-grade ≥3 mucositis induced by the association of head and neck radiotherapy and cetuximab. **f** Mucositis induced by cetuximab and chemotherapy (carboplatin and 5FU) in combination

Hand and foot skin reaction

- **painful, edematous, erythematous, and keratotic symmetric lesions** on acral surfaces, particularly weight- bearing sites
- **1 to 6 weeks after** therapy is initiated
- Acral dysesthesia and paresthesia commonly precede the lesions. In severe cases, blisters and extensive shedding can be observed

HFSR is distinct from the hand –foot syndrome (HFS) that develops with conventional cytotoxic agents such as fluorouracil (5-FU).



Drug Class	Taxanes	Anthracyclines/ Antimetabolites	Multikinase Inhibitors
Lesion type	Erythematous maculopapules	Edema, erythema and fissuring	Blisters with erythematous halo, followed by hyperkeratosis
Schedule specific	No	Yes	No
Location in hands	Dorsal	Ventral, diffuse palmar	Ventral, digit tips, over IP joints, thenar and hypothenar
Location in feet	Dorsal: Achilles tendon, malleoli	Ventral: diffuse soles	Ventral: heels, forefoot
Nail changes	Onycholysis	Hyperkeratosis	Subungual hemorrhages

Pastore S, et al. *Arch Toxicol.* 2014. Gomez P, Lacouture ME *Oncologist.* 2011. Ishak et al. 2013. Li J, Gu J *Critical Reviews in Oncology / Hematology* 2017

IMMUNOTHERAPIES

Ipilimumab (FDA appr 2011)

Nivolumab (2014)

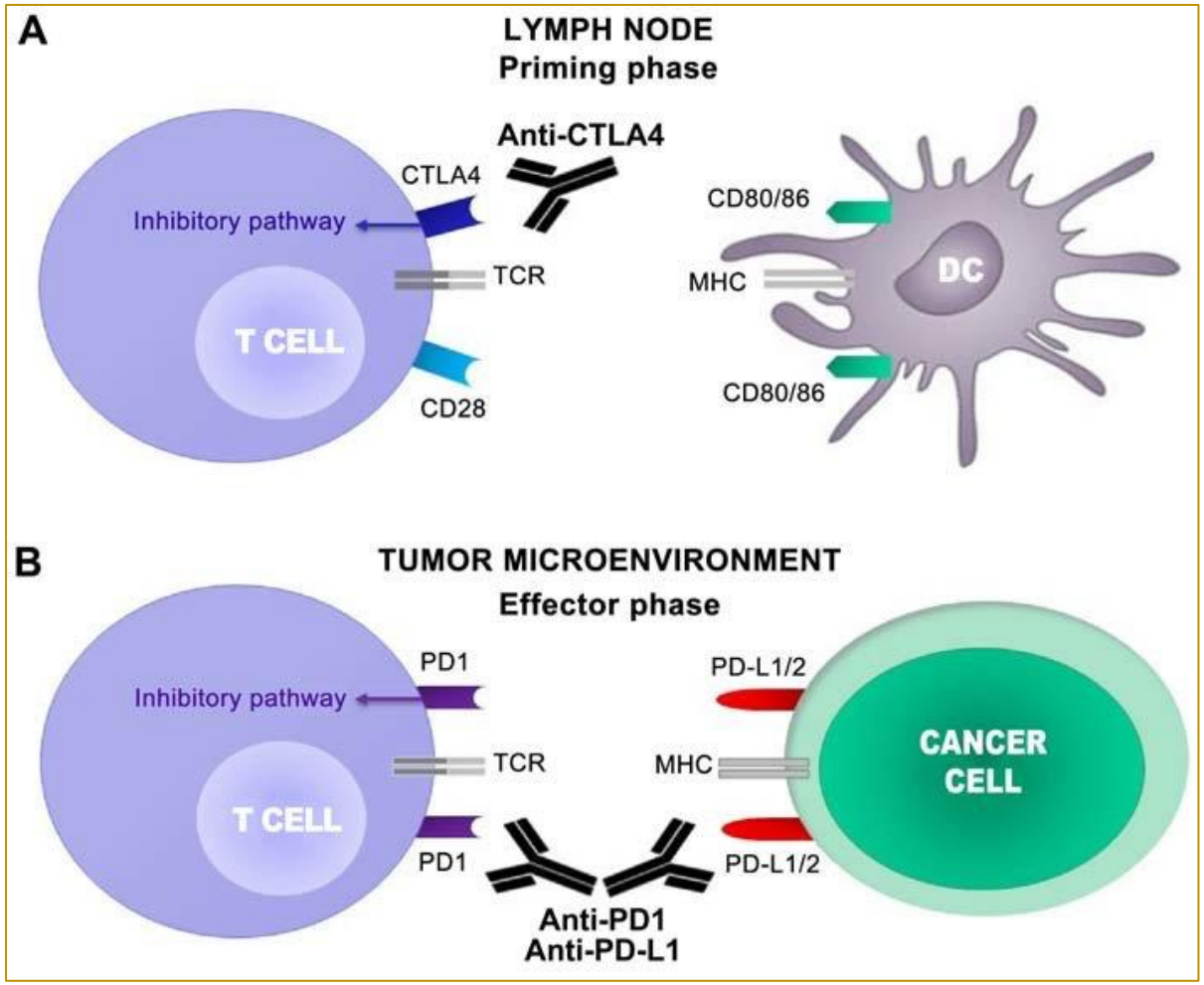
Pembrolizumab (2015)

Atezolizumab (2016)

Durvalumab (2017)

Avelumab (2017)

Cemiplimab (2018)



Stucci S. et al. Oncol Lett. 2017 Nov;14(5):5671-5680

Immune related adverse events

Pulmonary
- Pneumonitis
- Sarcoidosis

Cutaneous 10-45 %
- Pruritus
- Maculopapular eruption
- Vitiligo
- Lichenoid eruption
- Sarcoidosis
- Psoriasiform eruption
- Ulcers Pioderma Gangr.-like
- Photosensibility
- Sweet syndrome

Neurological and ophthalmological
- Autoimmune neruropathy
- Hypophysitis
- Uveitis
- Cranial nerves paresis
- Motor dysfunction
- Guillain-Barrè syndrome
- Miastenic syndrome

Renal
- Nephritis

Endocrinology 1-8%
- Hyperthyroidism/Hypothyroidism
- Hypophysite
- Adrenal insufficiency
- Hypopituitarism
- Insulin-dependent diabetes

GI 6-16 %
- Colitis
- Hepatitis
- Pancreatitis
- Diarrhea

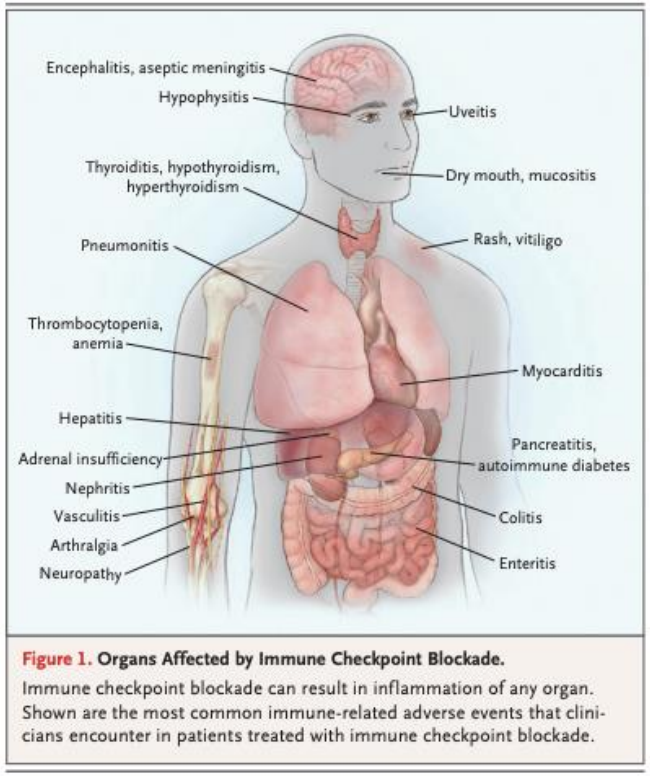


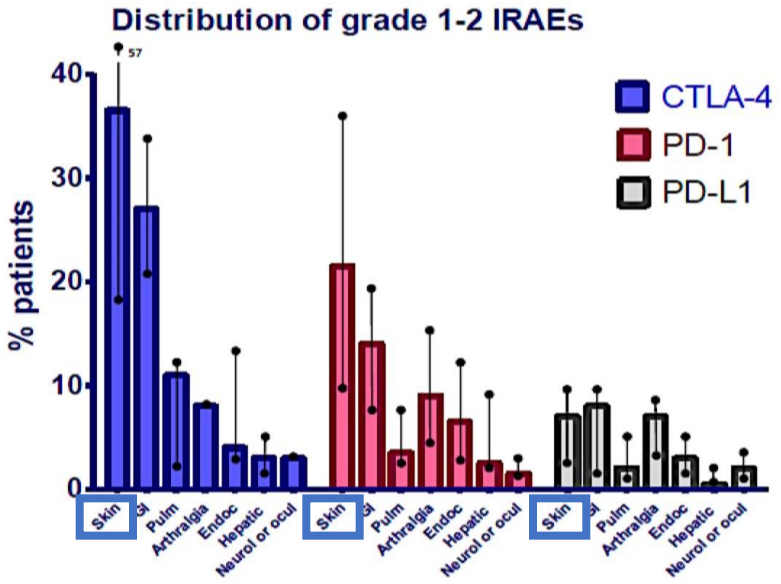
Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

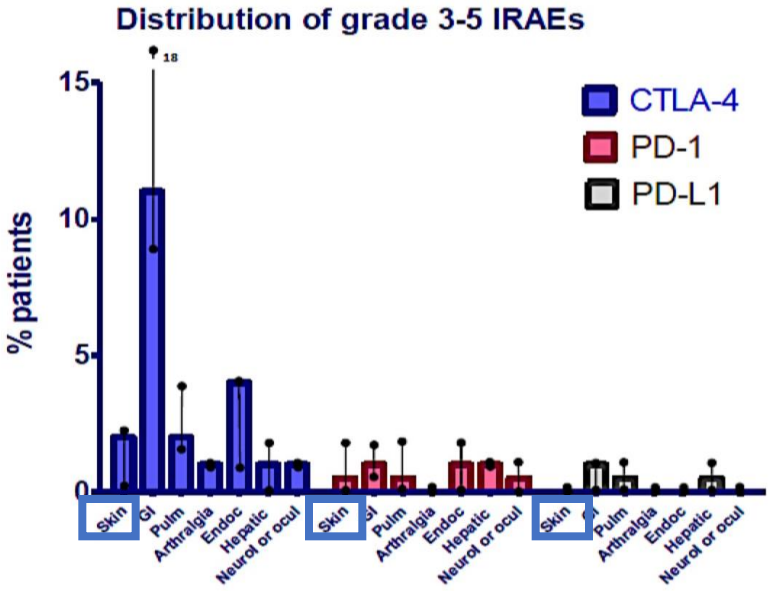
→ **Severe irAEs may lead to death in less than 2% of cases**

Puzanov I et al. Immunother Cancer. 2017;5(1):95
Suozzi KC, et al. JAAD Case Rep. 2016 Jul 14;2(3):264-8
Hofmann L. et al. Euro J Cancer. 60 (2016): 190-209
Belum VR, et al. Eur J Cancer 2016; 60: 12-25

INCIDENCE

- Any grade: 30-40%
- Grade 3-4: 2%
- More reactions with anti-CTLA-4 than with anti-PD1/PDL1
- Typically occurs at least 3 weeks after exposure to the drug



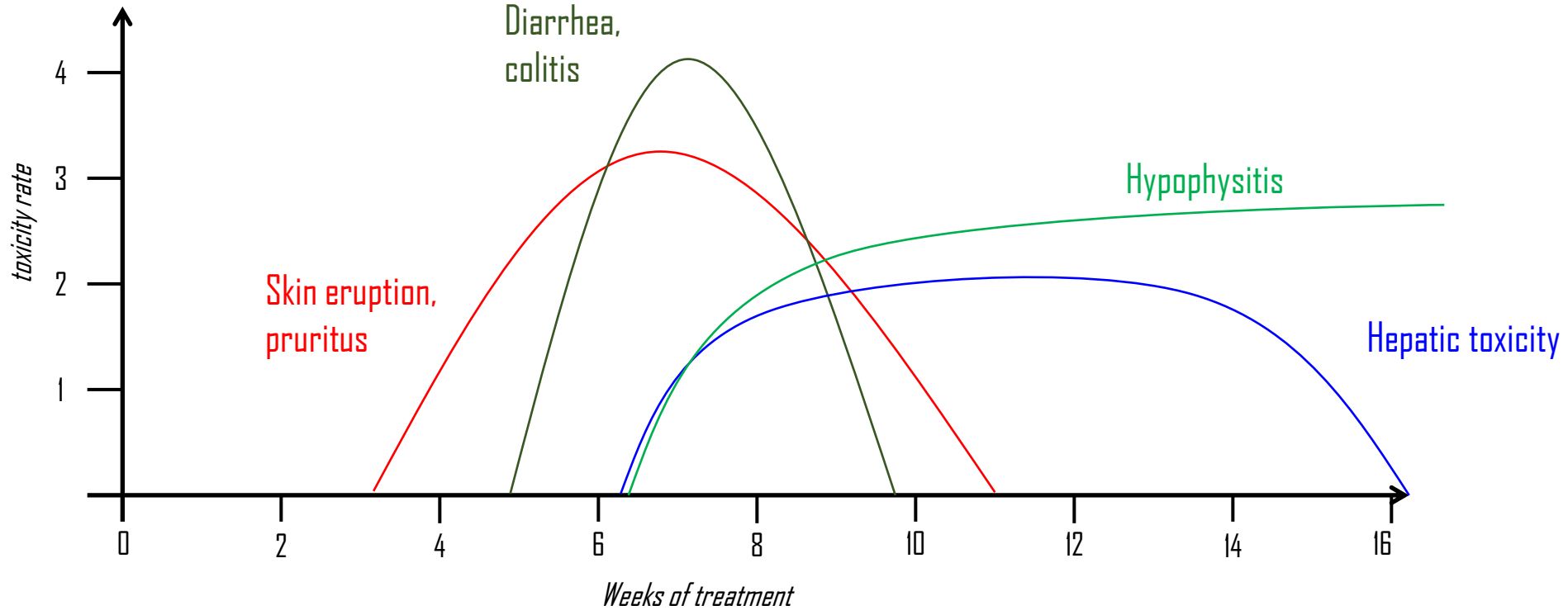


Michot, et al. "Immune-related adverse events…." Eur J Cancer. 2016.

SENTINEL FUNCTION

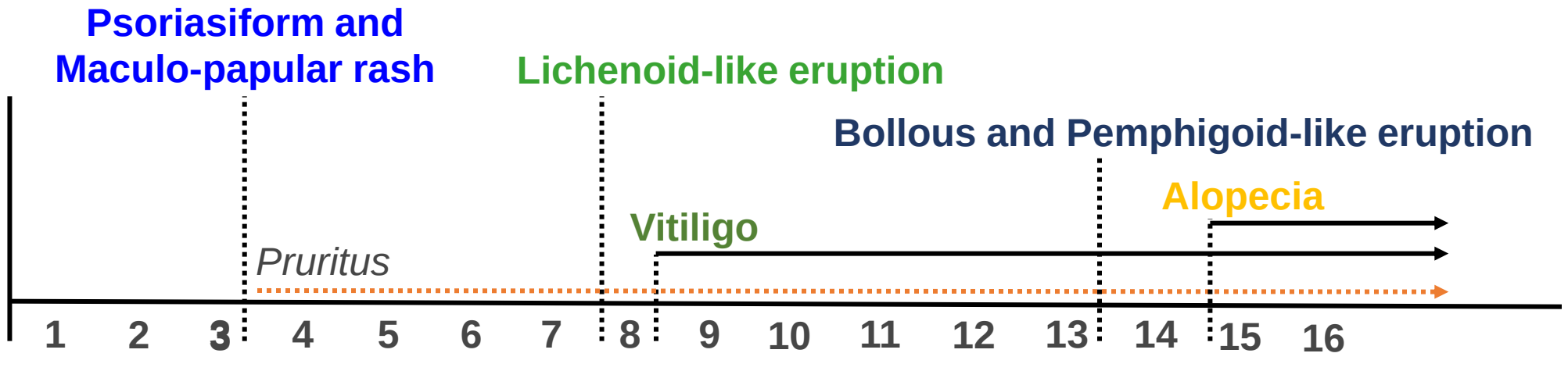
Cutaneous irAE occur earlier than other irAE

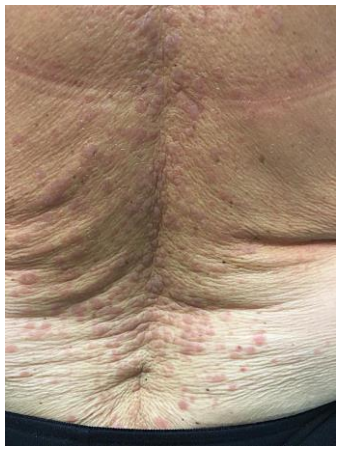
Most of the irAEs occur within 3–6 months from the initiation of ICI treatment

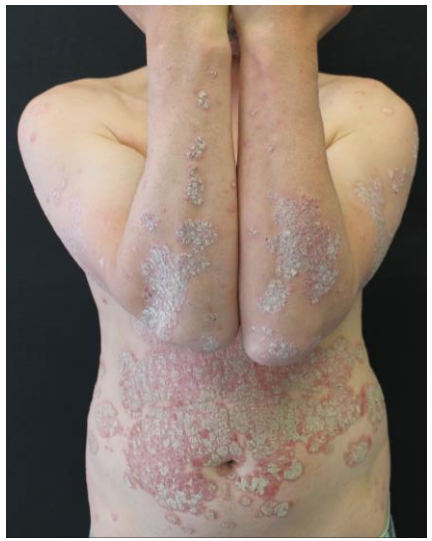


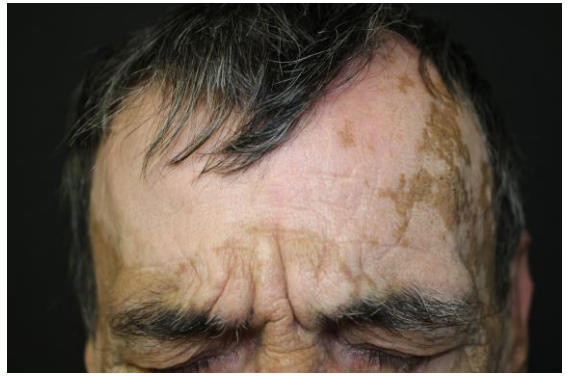
Adapted from Weber at al. 2012

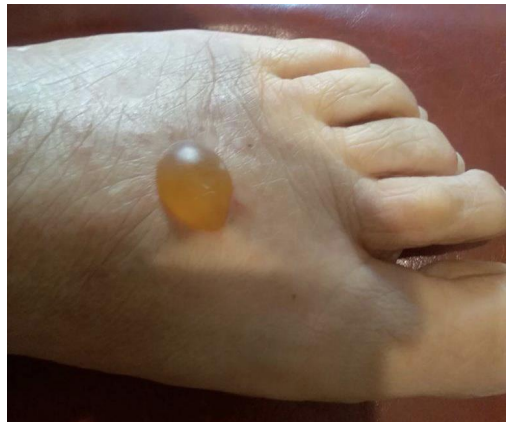
Time to onset of immuno-related cutaneous AE

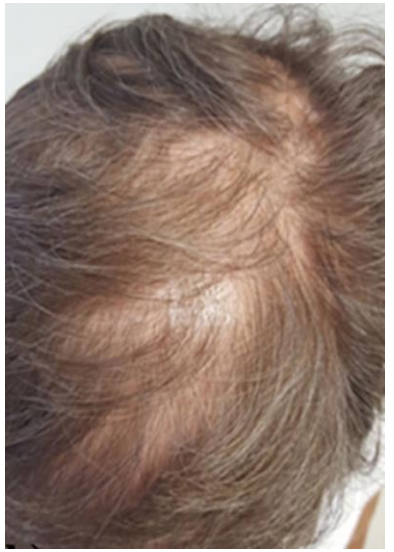












- No relationship between earlier IRAE onset and increased ICI response
- Severe AE (SJS, TEN, DRESS) may occur at any time during ICI treatment

Geisler AN, et al. JAAD 2020;S0190-9622(20)30963-4
Dearden HC, et al. J Clin Oncol. 2018;36(15):S9545
Siegel j, et al. JAAD 2018

COMPLIANCE

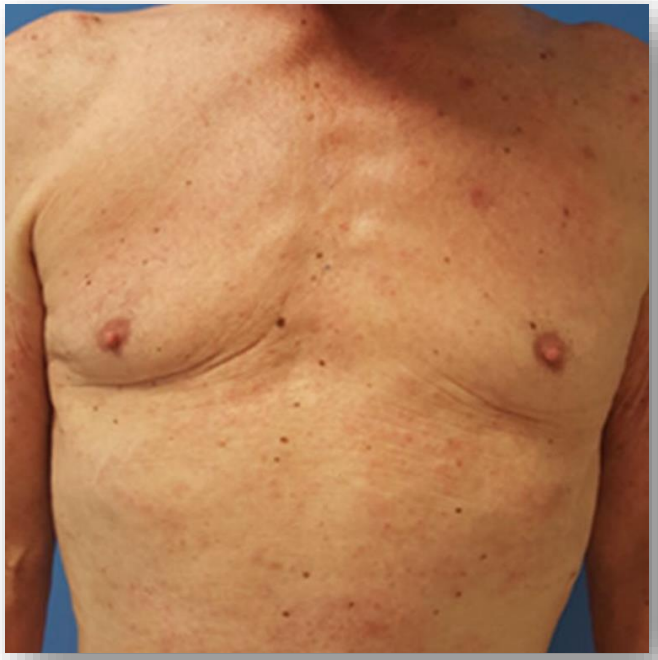
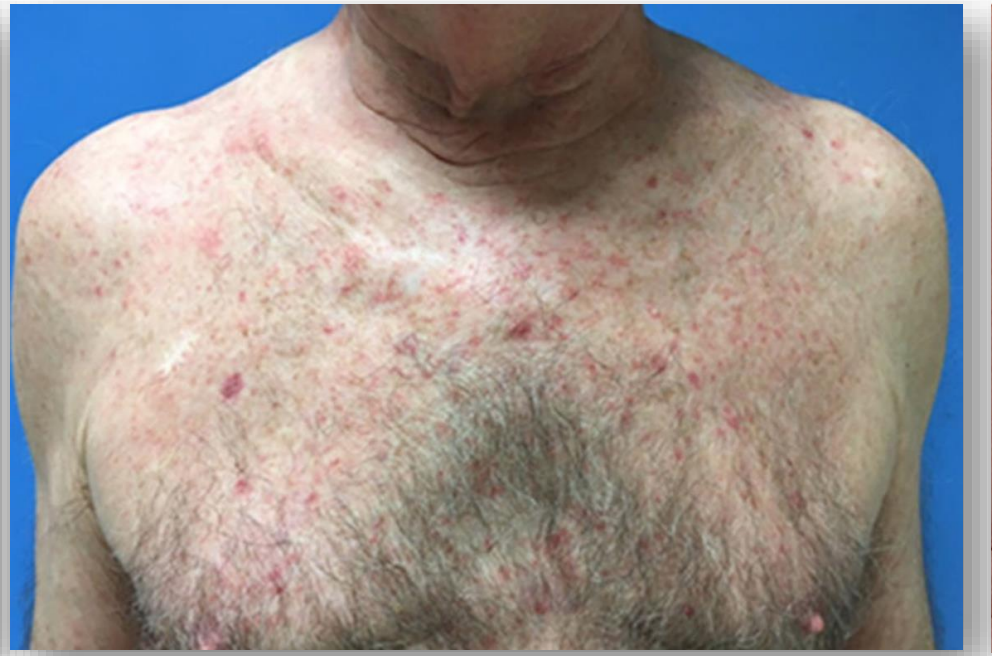
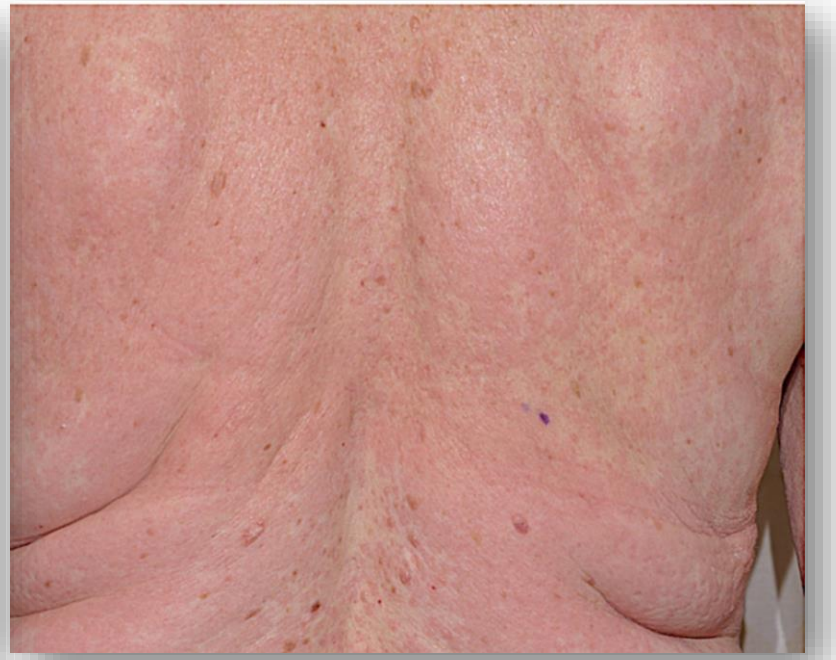
significant impact on adherence to treatment

- 20% of those who show adverse skin events interrupt therapy for the appearance of further toxicity

- Skin irAE usually resolve in a few weeks and are reversible (with the exception of vitiligo-like lesions).

Suozzi KC, et al. JAAD Case Rep. 2016 Jul 14;2(3):264-8
Hofmann L. et al. Euro J Cancer. 60 (2016): 190-209

MACULO-PAPULAR ERUPTION

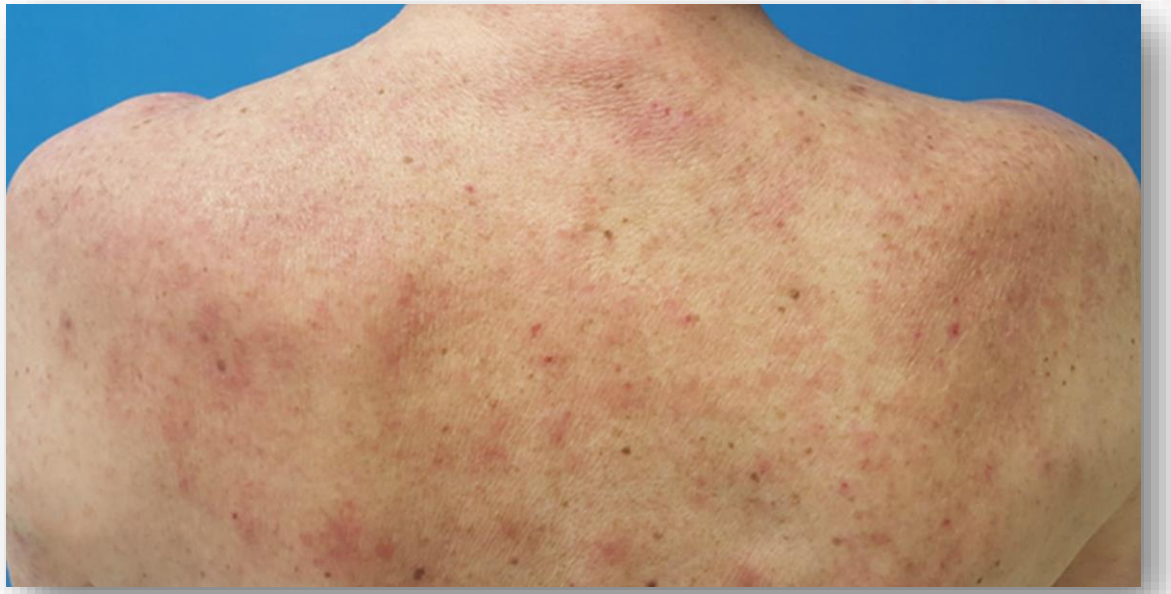




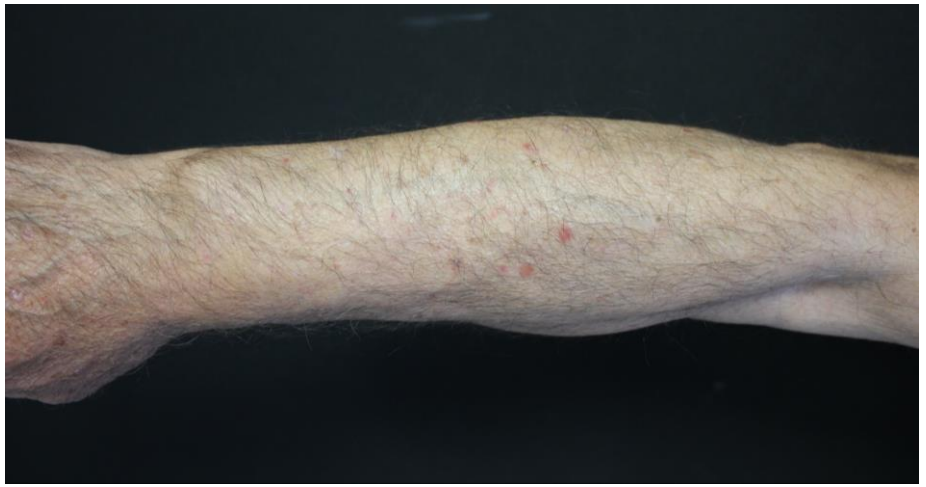
- usually after 3 weeks of therapy; however, cases also occur after 2 years of therapy

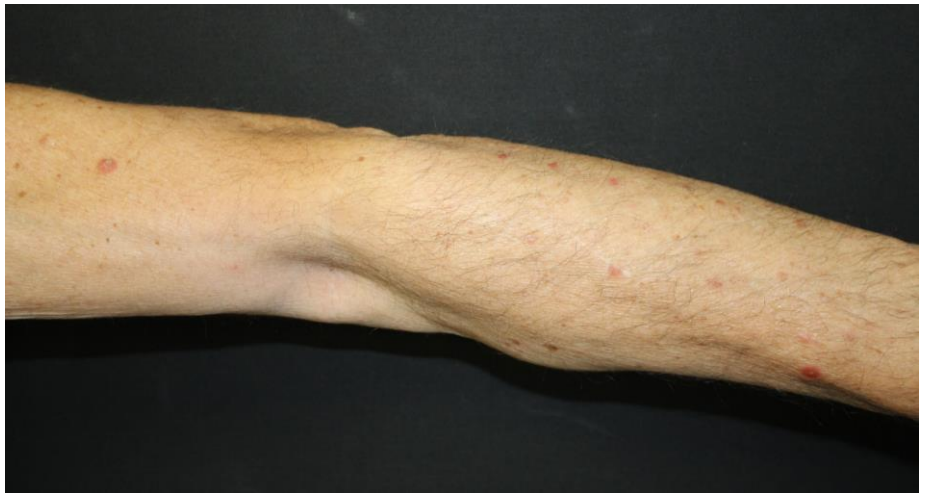
- occur with numerous scattered maculopapular lesions, sometimes associated with desquamation, with or without itching

Shi VJ, et al. JAMA Dermatol 2016;152: 1128–1136.
Suozzi KC, et al. JAAD Case Rep. 2016 Jul 14;2(3):264-8
Hofmann L. et al. Euro J Cancer. 60 (2016): 190-209
Belum VR, et al. Eur J Cancer 2016; 60: 12-25
Vincent Sibaud et al. Am J Clin Dermatol 2018

PRURITUS



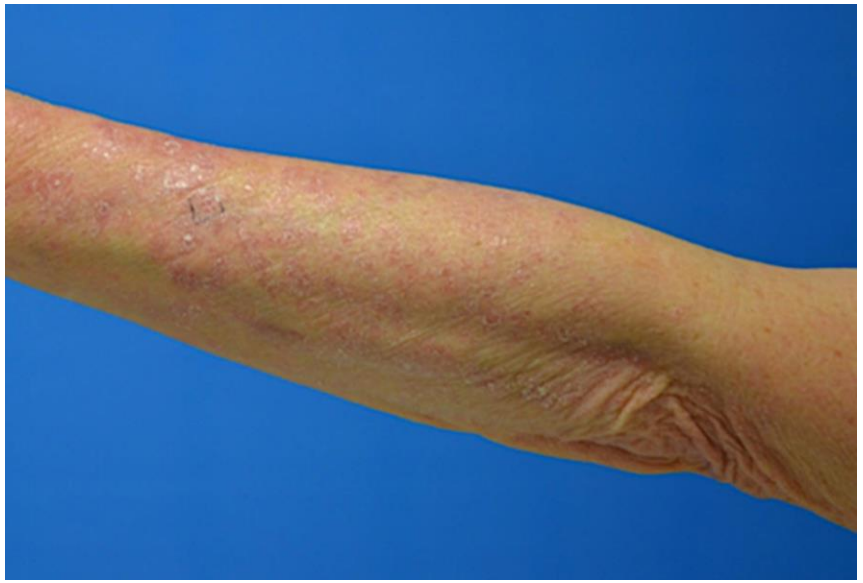


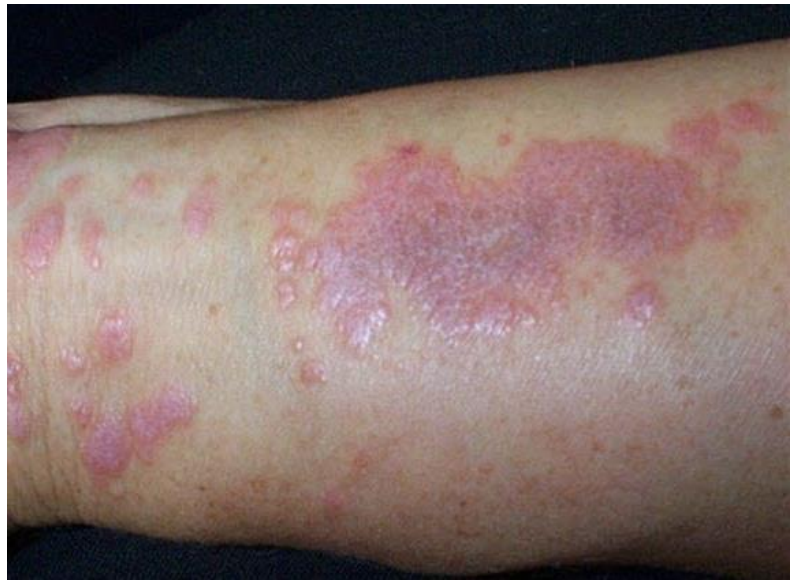


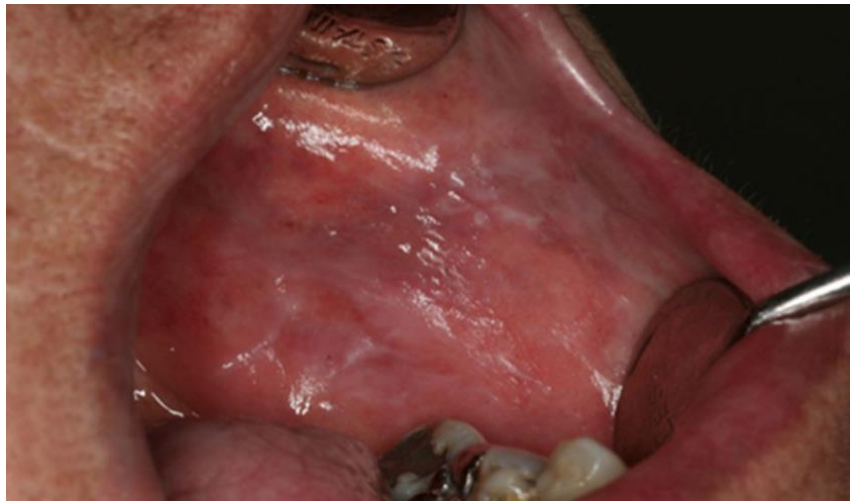
- Pruritus is among the most prevalent irAEs induced by immune checkpoint inhibitors
- By meta-analysis, its all-grade incidence ranges from 13 to 30%
- may occur with and without cutaneous eruption but typically develops concomitantly with maculopapular rash

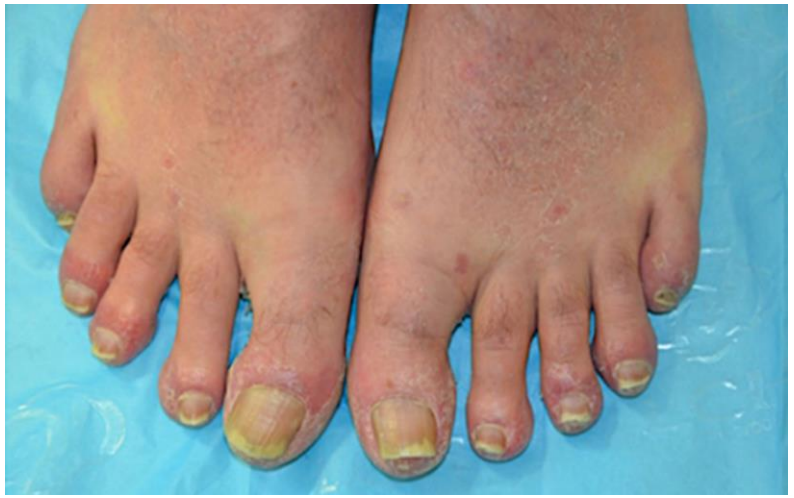
Shi VJ, et al. JAMA Dermatol 2016;152: 1128–1136.
Suozzi KC, et al. JAAD Case Rep. 2016 Jul 14;2(3):264-8
Hofmann L. et al. Euro J Cancer. 60 (2016): 190-209
Belum VR, et al. Eur J Cancer 2016; 60: 12-25

LICHENOID ERUPTION





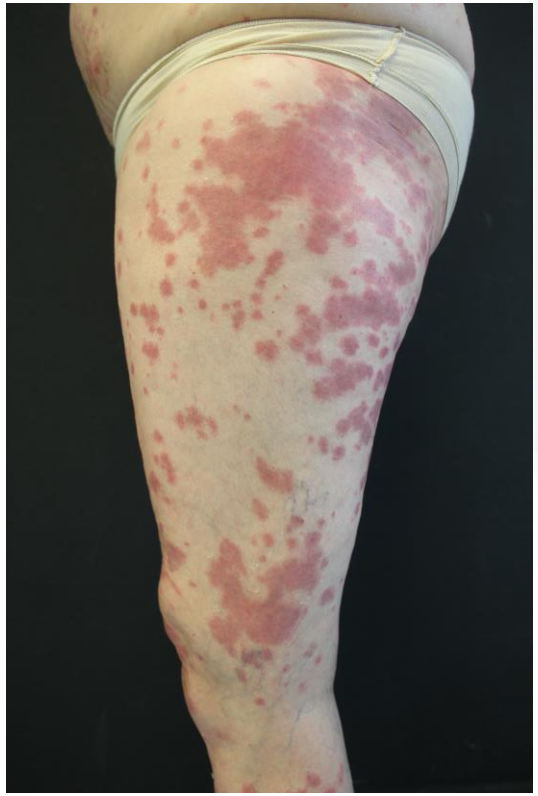


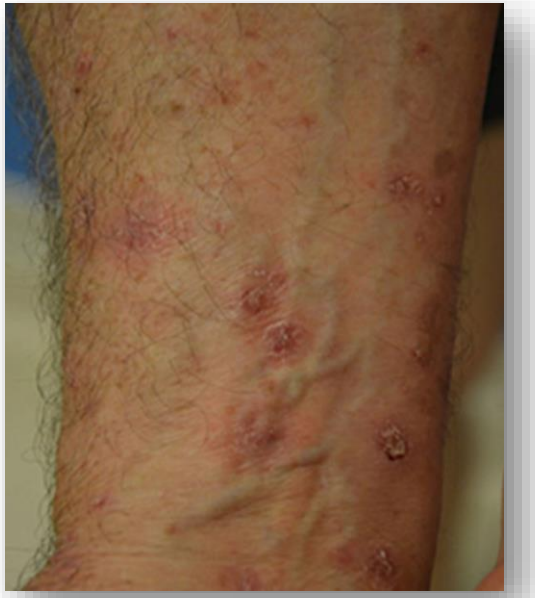


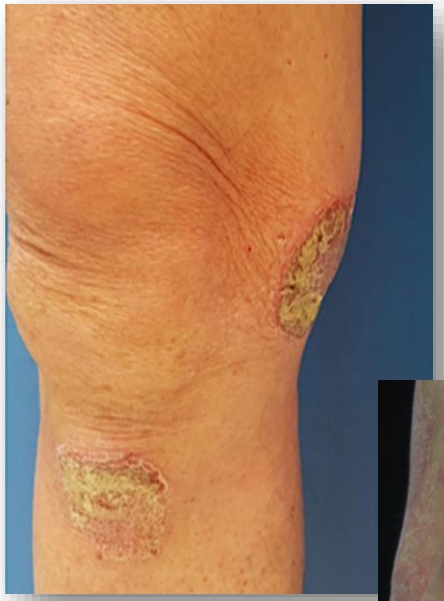
- The diagnosis is generally made after a histologic analysis, and it is likely that the incidence has remained greatly underestimated
- It may represent the most prevalent identified histologic feature in patients treated with anti-PD-1 therapy
- concomitant genital, oral or ungual involvement is possible and needs to be systematically searched

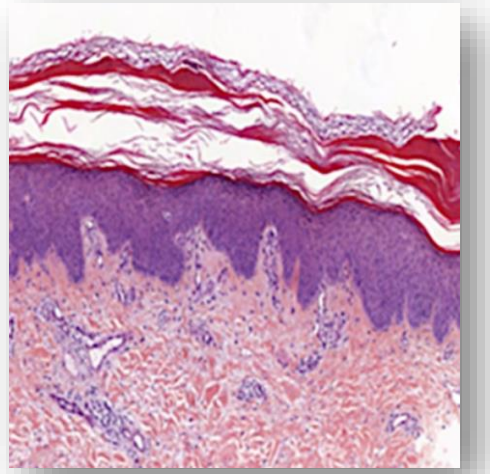
Vincent Sibaud. Am J Clin Dermatol 2018

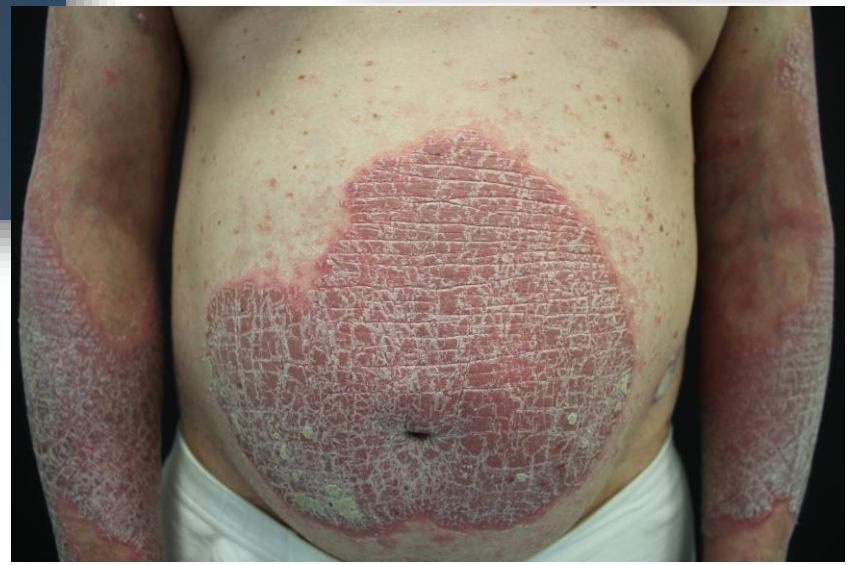
PSORIASIFORM REACTION

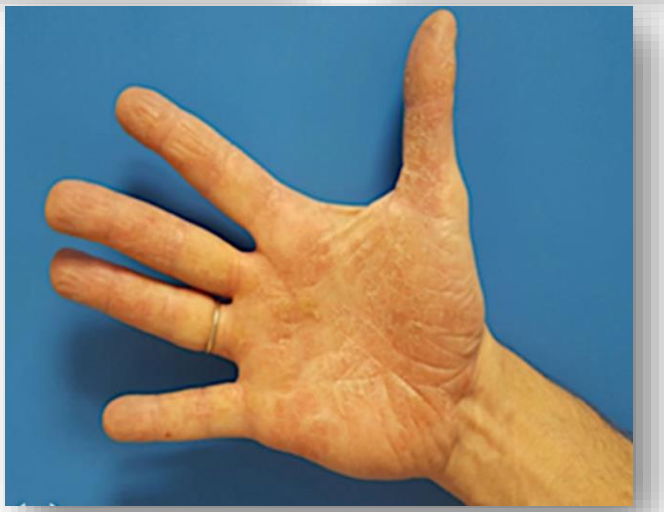






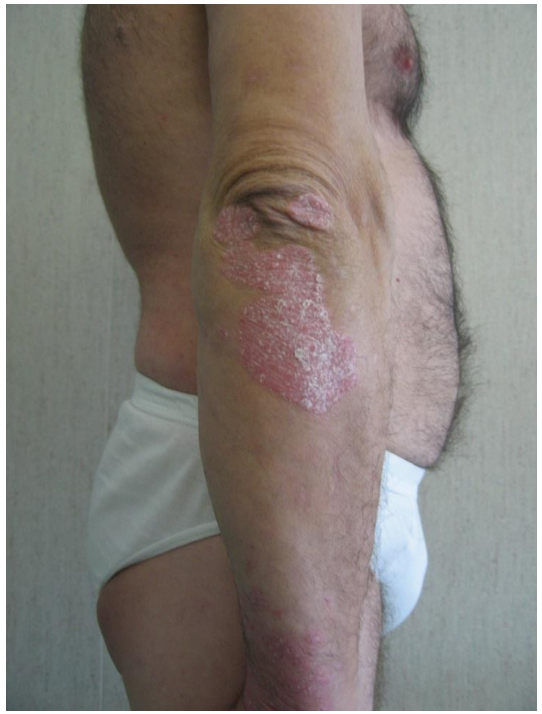


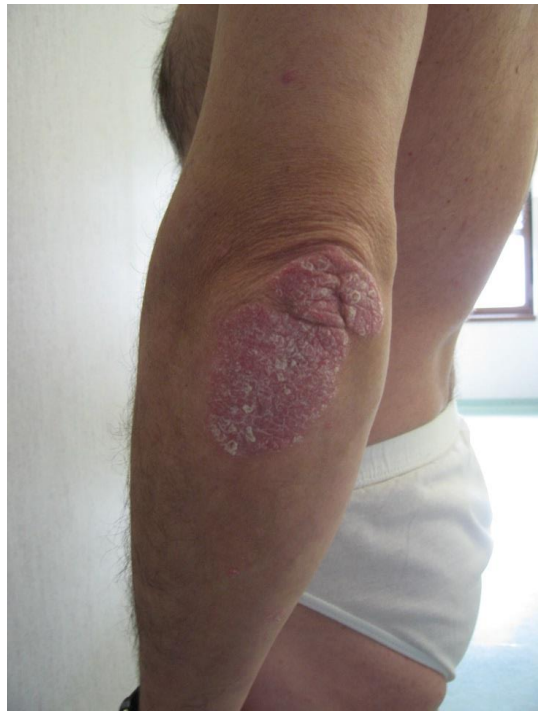




Bonigen et al. JEADV 2017, 31, e224–e272
Vincent Sibaud. Am J Clin Dermatol 2018
Nikolau V., Sollena P, et al. JAAD 2020 article in press

PSORIASIFORM RASH





Patients with personal history of psoriasis were affected by psoriatic rash significantly earlier

Nikolau V., et al. JAAD 2020

JAAD
Journal of the American Academy of Dermatology

Table 2: Number of infusions until psoriasis

	Number of infusions (Mean, SD)	*P- value* ∓
Sex		*0.025*
Male	10.1 (13.7)	
Female	14.9 (18.1)	
Psoriasis type		*0.09*
Plaque psoriasis	10.3 (9.63)	
Pustular psoriasis	17.8 (35.1)	
Palmoplantar psoriasis	10.5 (8.33)	
Guttate psoriasis	16.6 (17.9)	
Nail psoriasis	23.5 (13.4)	
Inverse psoriasis	10	
Erythrodermic psoriasis	14 (17.3)	
> 1 type	8.83 (15.8)	
Personal history of psoriasis		*0.076*
No	11.5 (13.2)	
Yes	9.82 (17.9)	
ICI		*0.615*
Anti-PD1	11.3 (15.4)	
Anti-PDL1	10.9 (12.0)	
Active psoriasis at initiation		*0.019*
No	12.2 (15.8)	
Yes	5.43 (3.87)	
Family history		*0.808*
No	11.3 (13.6)	
Yes	11.9 (18.3)	
Type of cancer		*0.773*
NSCLC	9.87 (10.4)	
Melanoma	20.8 (29.3)	
Head & Neck SCC	6.5 (5.24)	
Renal Cell Carcinoma	7.33 (4.63)	
Urothelial Carcinoma	15.3 (18.3)	
Hodgkin's Lymphoma	6.5 (0.70)	
Merkel Cell Carcinoma	18	
Hepatocellular Carcinoma	7 (5.00)	
Gastric Cancer	5 (4.24)	
Mesothelioma	5	
Ovarian Cancer	9	
Pulmonary Neuroendocrine	4	

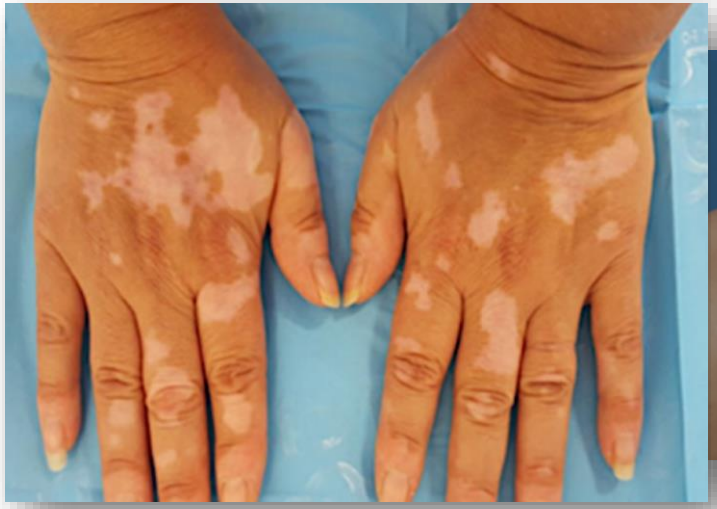
∓: *p-value for dichotomous variables (sex, ICI, etc.) based on Mann – Whitney t – test and for nominal variables (type of psoriasis and cancer) based on ANOVA Kruskal – Wallis.*

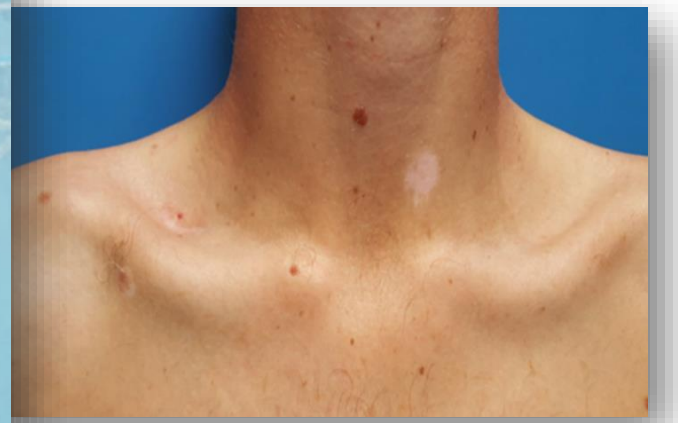
VITILIGO and ICI

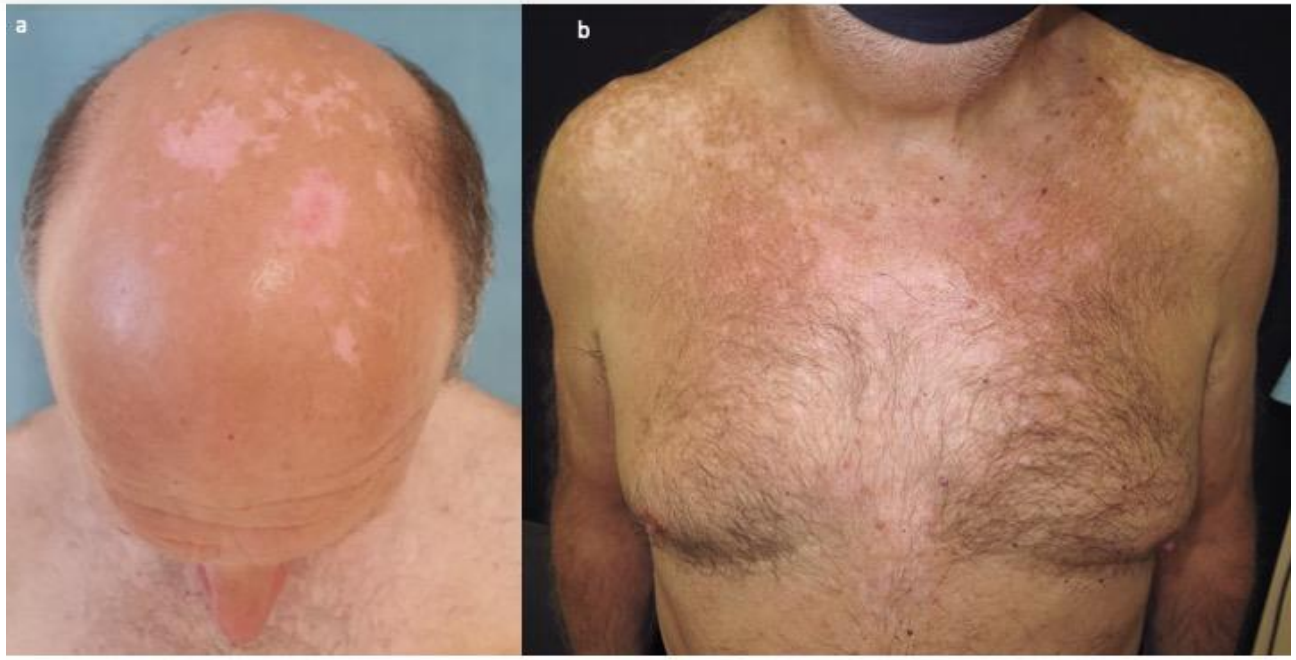
- Start after 4-10 weeks from CPI therapy initiation (it can range from 1 to 36 months)
- The risk of CPI-related skin hypopigmentation/depigmentation among patients with melanoma is 10-fold higher than in the general population (incidence 6-12%)
- In most cases does not resolve after discontinuation or interruption of treatment
- The resolution of ICI-induced vitiligo without treatment could be a marker of disease progression

Sibaud V et al. Am J Clin Dermatol 2018
Hua C et al. JAMA Dermatol 2016; 152: 45-51.
Freeman-Keller M, Clin Cancer Res 2016; 22: 886-94.
Geisler AN et al. J Am Acad Dermatol. 2020 Nov ;83(5):1255-1268.
Babai S et al., Drug Safety (2020) 43:111–117

VITILIGO







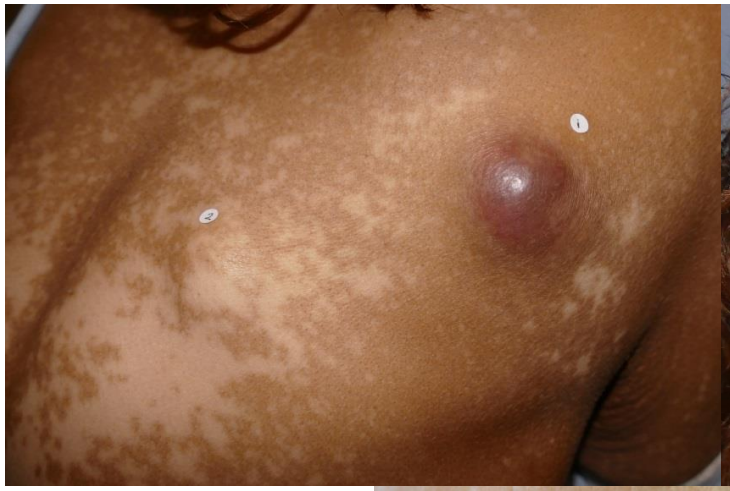
Skin sites

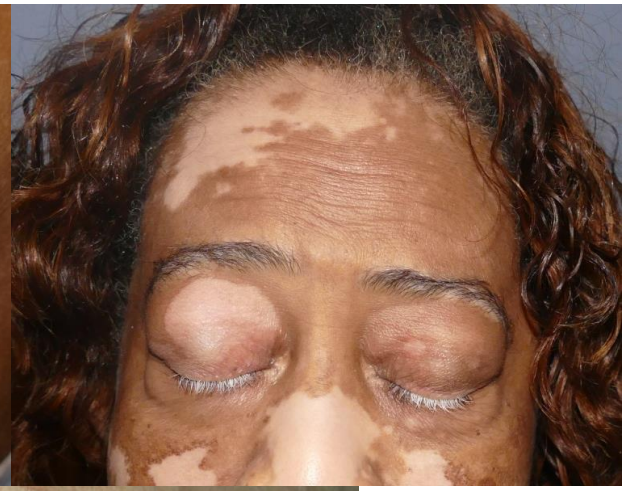
- on the back of the hands
- on single metastatic lesions at a distance
- in the scarring area of previous melanoma
- on multiple metastatic lesions throughout the body
- as white halo surrounding benign melanocytic nevi

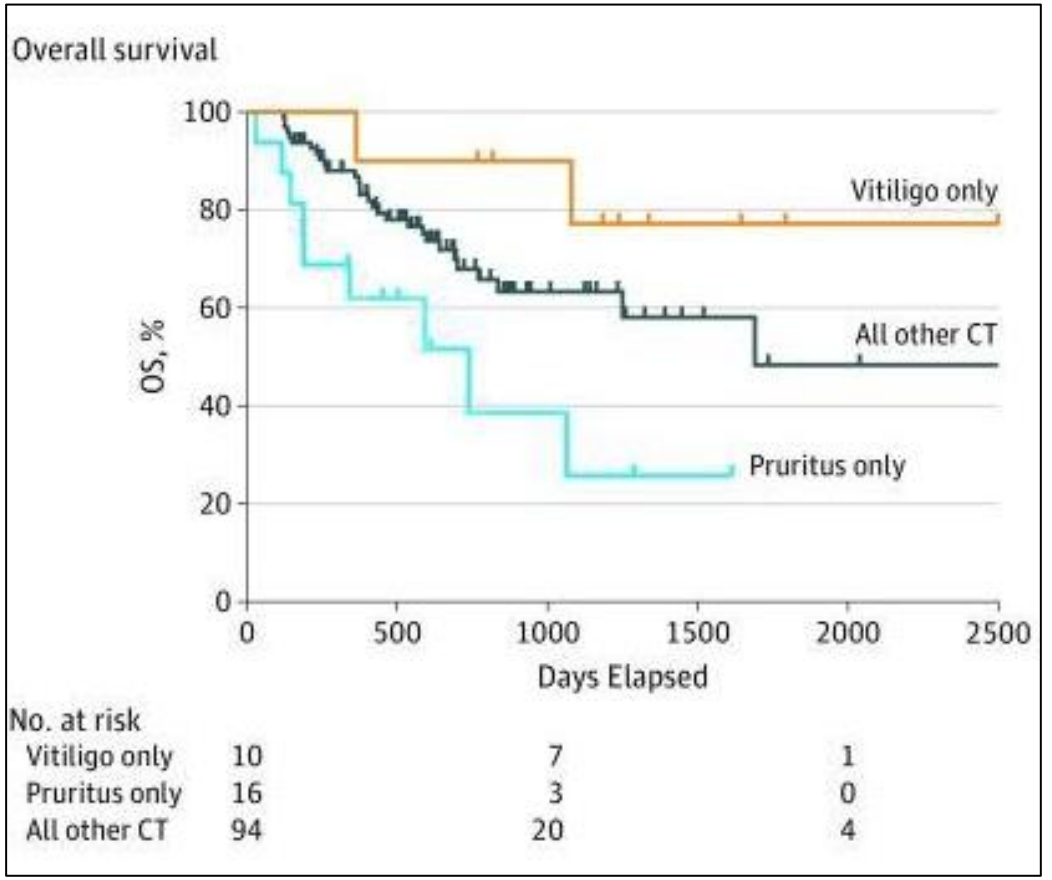
Kamińska-Winciorek G. et al. Advances in Dermatology and Allergology 4, August 2019
Sibaud V et al. Am J Clin Dermatol 2018

VITILIGO - *positive predictive factor*

Vitiligo-like depigmentation has been associated with a favorable response to treatment, especially in metastatic patients with melanoma



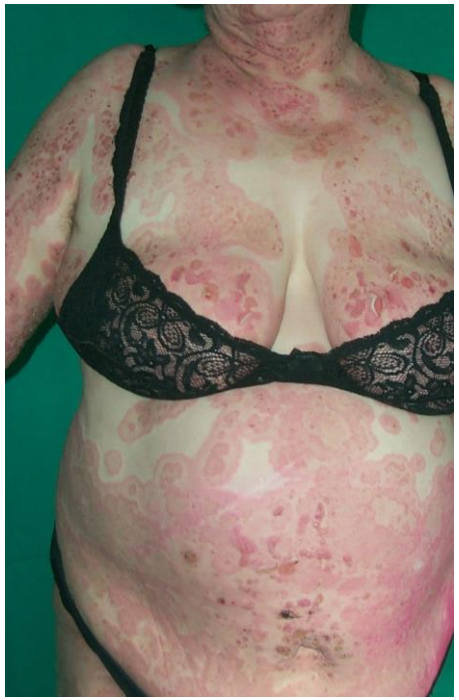


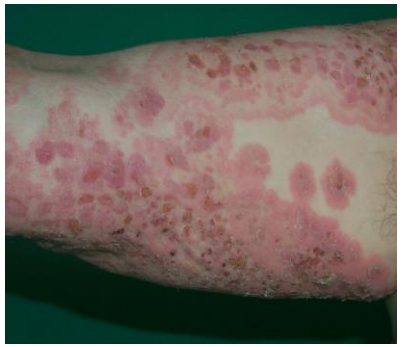


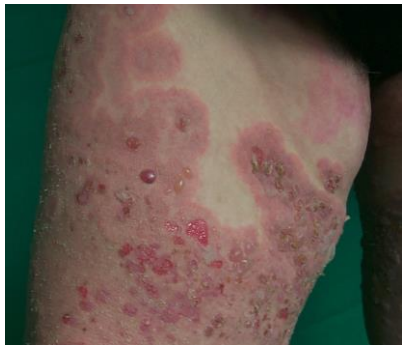
Quach HT, et al. JAMA Oncol. 2019
Emily S. Yin et al. JAAD 2016
Geisler AN et al. JAAD 2020 Nov ;83(5):1255-1268.

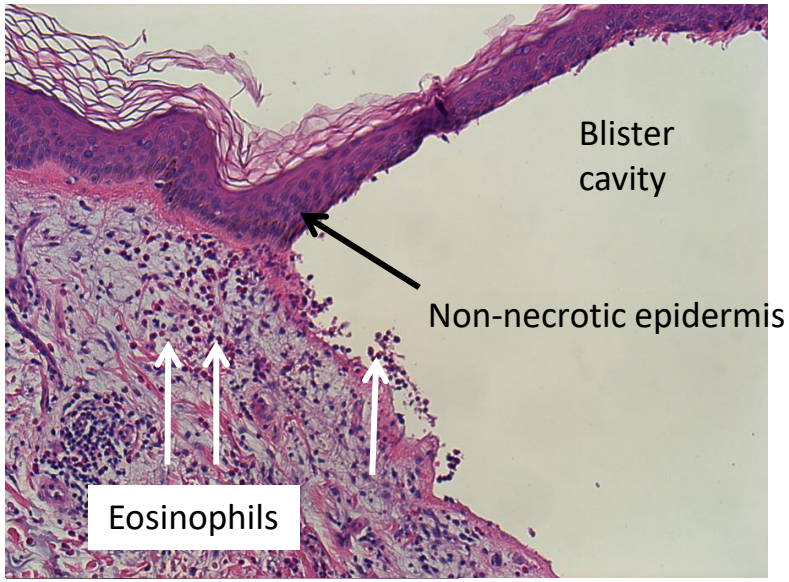
BOLLOUS DISEASES

Sadik CD, et al Frontiers Immunol 2019
Siegel j, et al. JAAD 2018









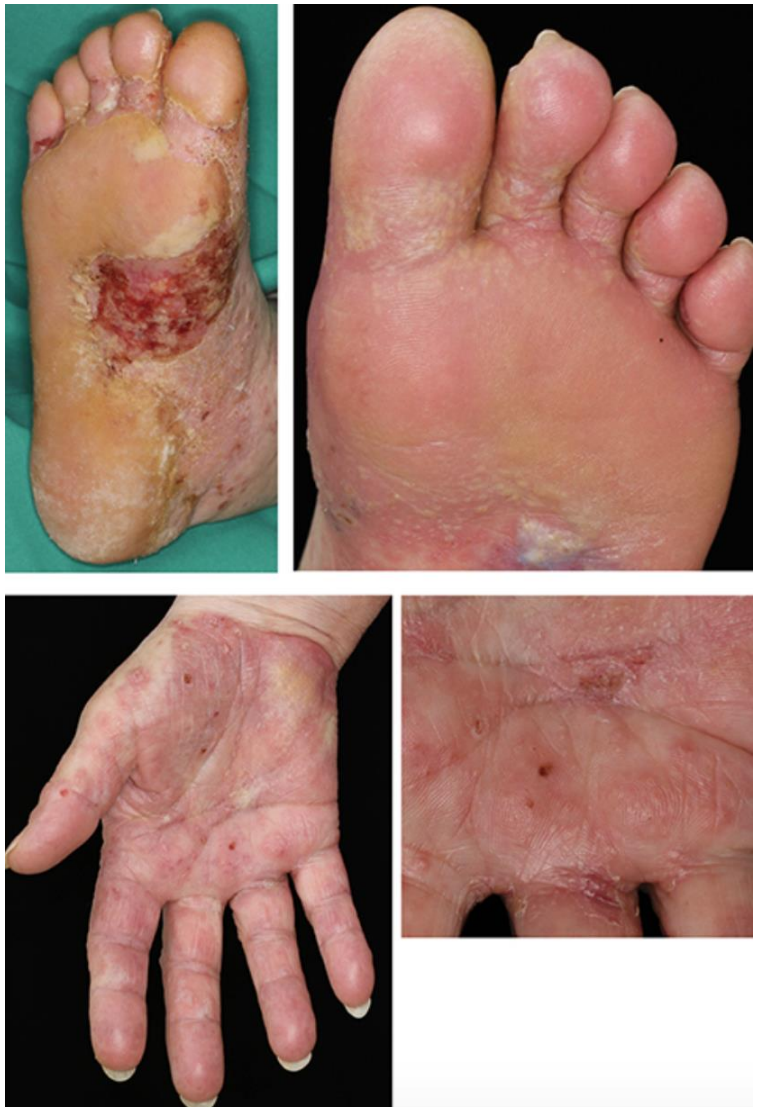
- **The frequency of immunotherapy-associated bullous disorders is unknown; among 1-2 % of patients in single institutional experiences**

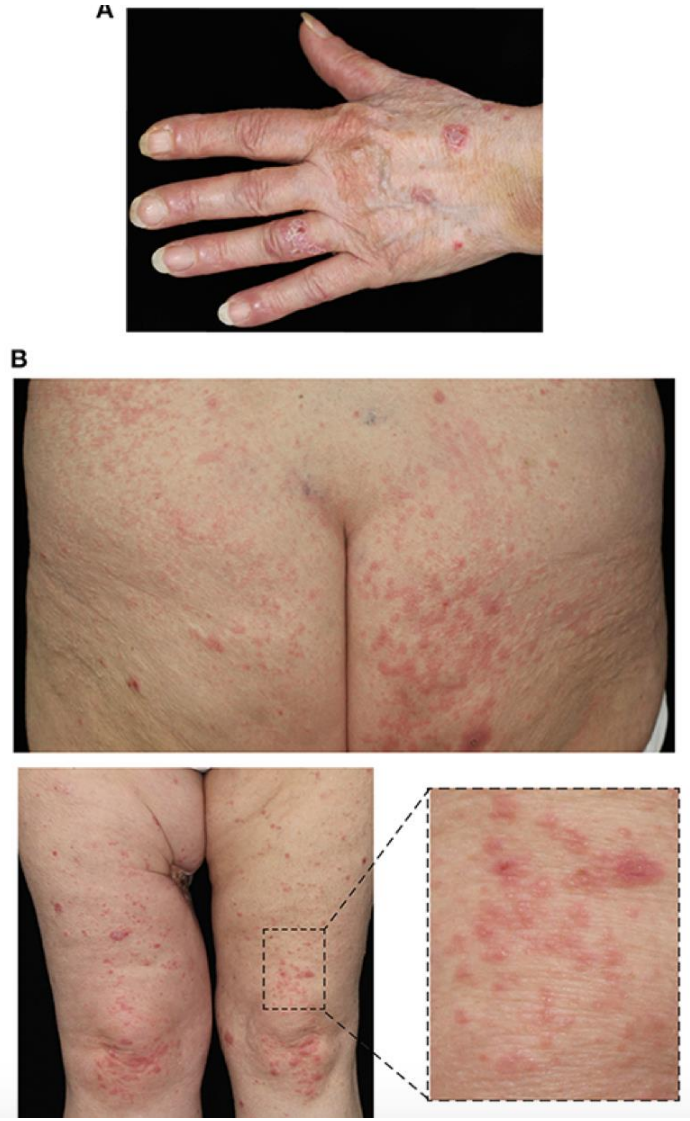
- **The latency of bullous disorders due to immunotherapy is generally longer than that of other cutaneous toxicities (after 14-18 weeks)**

- **Most patients with BP and required temporary or permanent interruption of immunotherapy and management with systemic corticosteroids**

BOLLOUS DISEASES

➢ Polimorphyc evolution

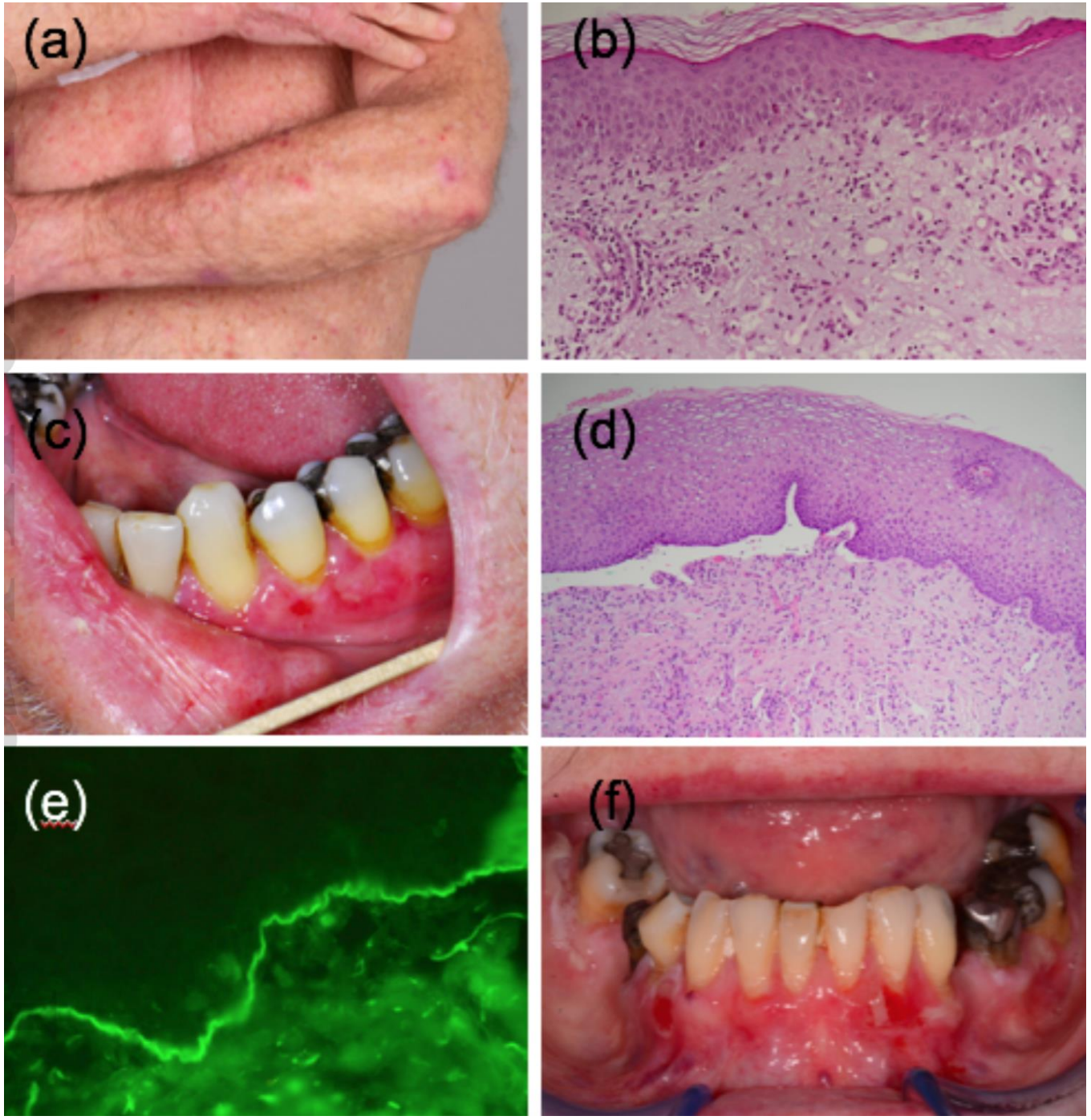




Christian D. Sadik
et al Frontiers Immunol 2019

BOLLOUS DISEASES

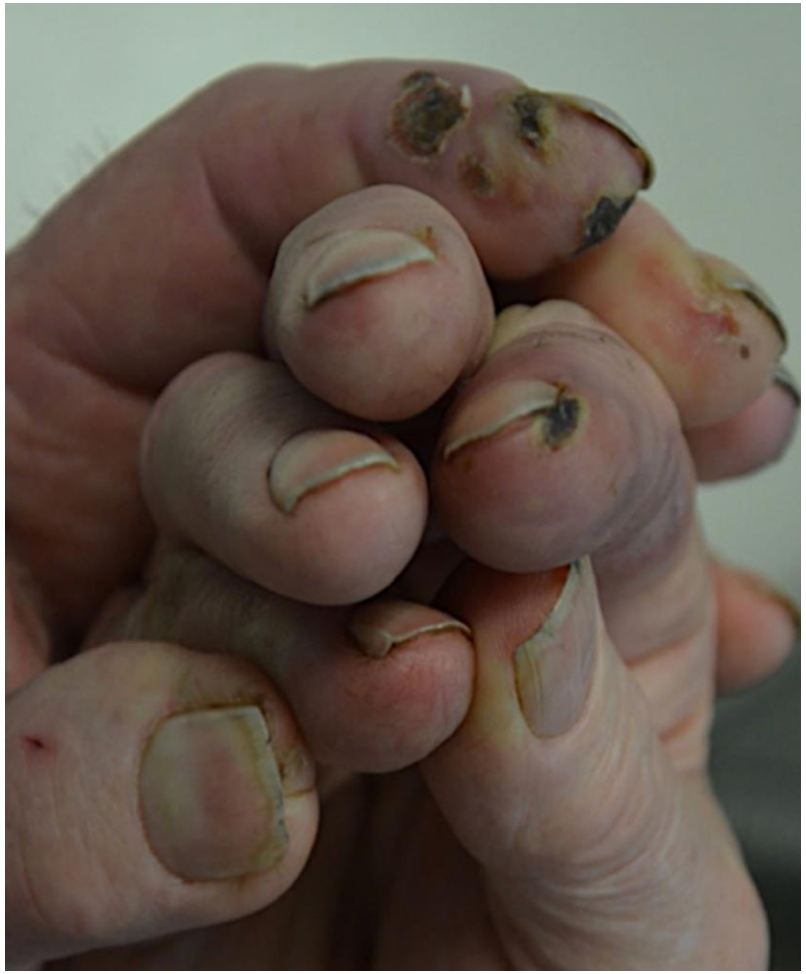
- CPI-related BP may persist for several months after discontinuation of immunotherapy

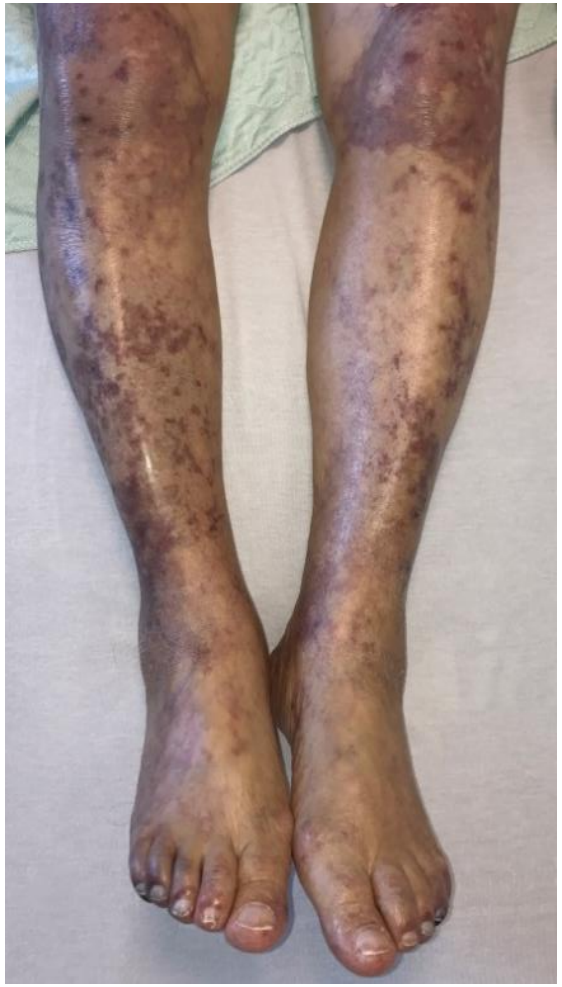


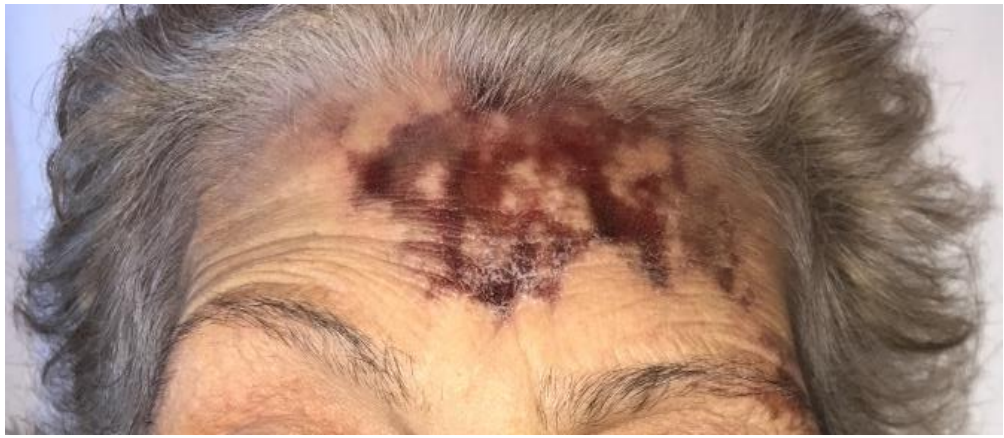
M. Fässler et al. JEADV 2019

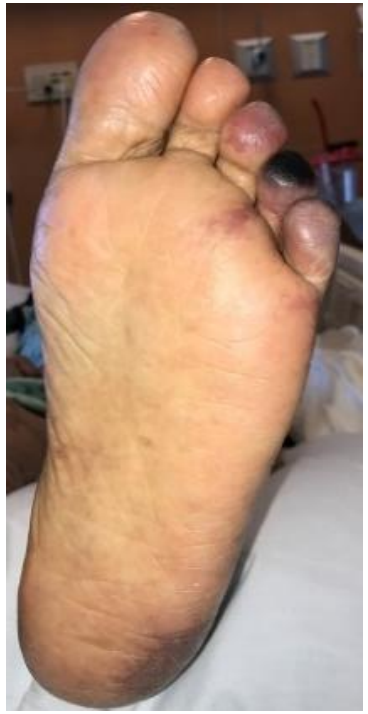
OTHER SKIN
irAE

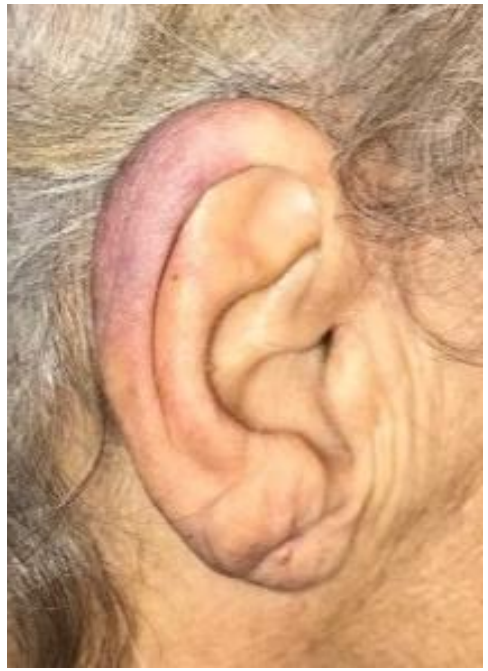
VASCULITIS







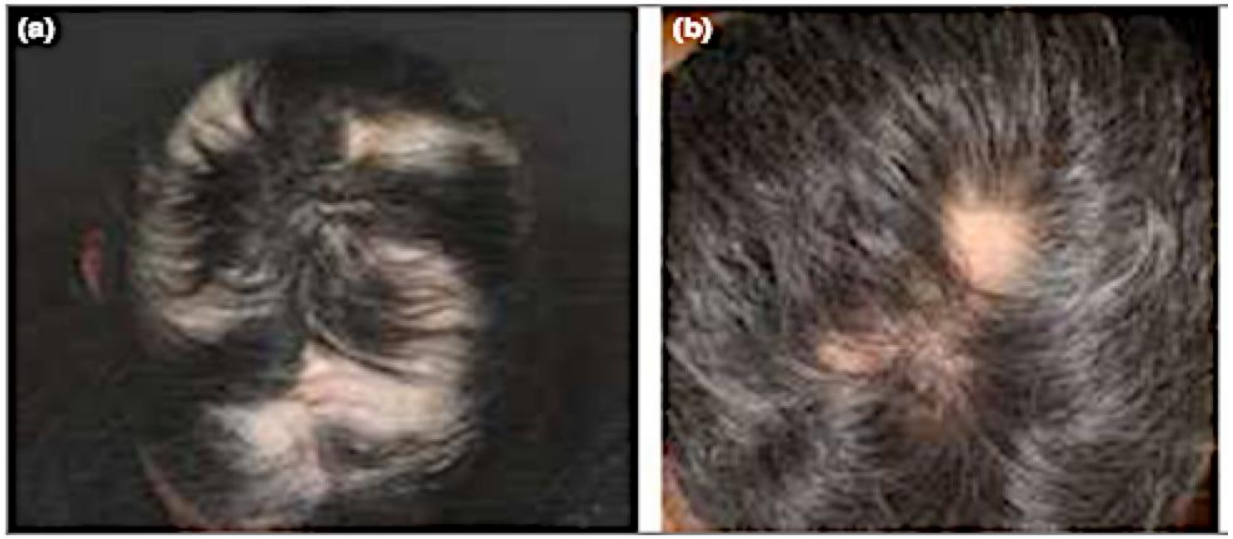




Brown, et al. "Pembrolizumab induced ischemic vasculopathy." in press

ALOPECIA

- Alopecia reported in 1-2%
- Alopecia areata (patchy, totalis, universalis)
- PD-L1 is expressed in the follicular sheath



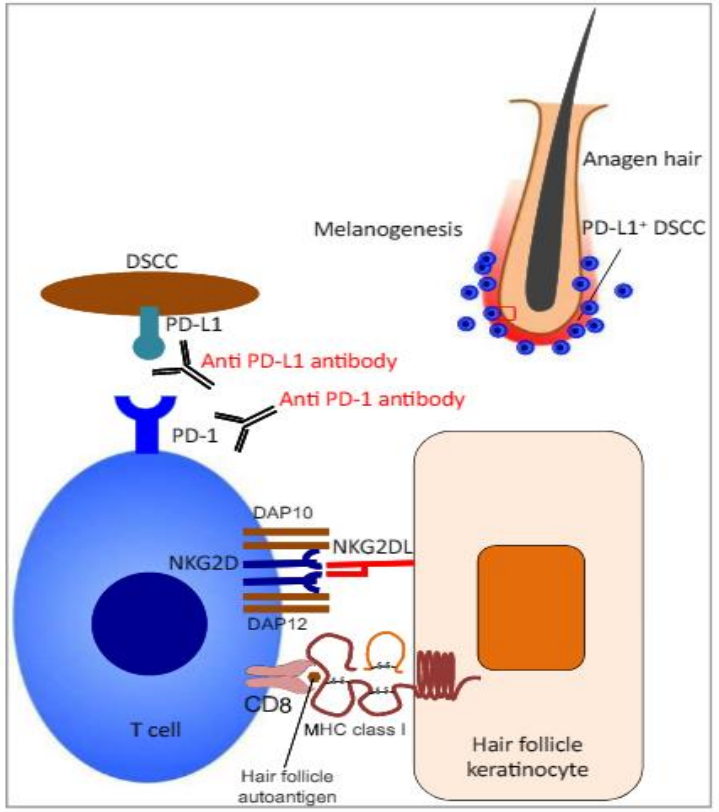


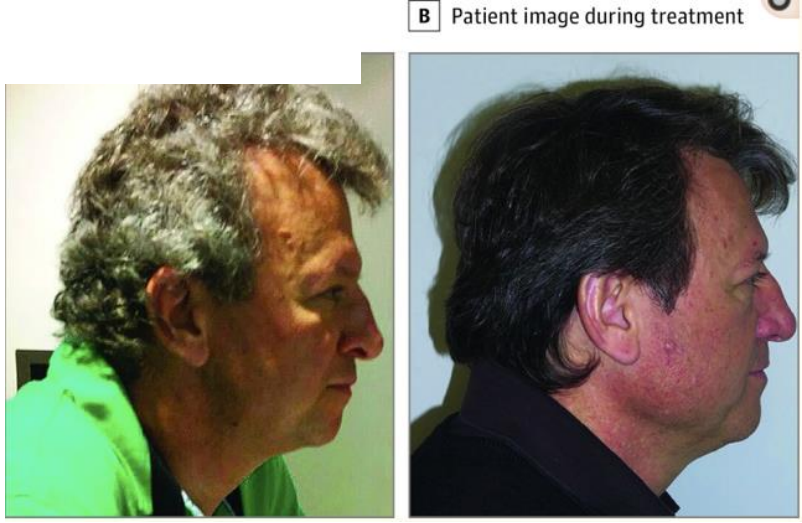
Fig 1. Anti-PD-L1 antibody or anti-PD-1 antibody lead to activation of $NKG2D^{+}CD8^{+}$ T cells, which recognize hair follicle autoantigens via MHC class I on hair follicle keratinocytes. Normally, MHC class I expression is suppressed in the milieu of hair follicle immune privilege. However, activated $NKG2D^{+}CD8^{+}$ T cells produce IFN-γ, which upregulates the expression of MHC class I on the proximal outer root sheath of the hair bulbs. DSCC, dermal sheath cup cells; IFN, interferon; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand.

Zarbo et al. Br J Dermatol 2017; 176:1649–1652
Ito. Br J Dermatol 2017; 176:1444–1445
Antoury L, et al. Dermatol Ther. 2020

JAMA Dermatology | Brief Report

Hair Repigmentation During Immunotherapy Treatment With an Anti–Programmed Cell Death 1 and Anti–Programmed Cell Death Ligand 1 Agent for Lung Cancer

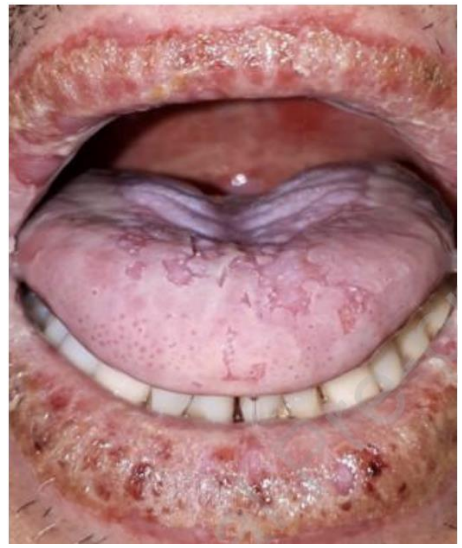
Noelia Rivera, MD[1]; Aram Boada, MD[1]; M. Isabel Bielsa, MD, PhD[1]; et al



- Gray hair follicles still preserve a reduced number of differentiated and functioning melanocytes located in the hair bulb may explain the possibility of repigmenttion
- Repigmentation in correlation with stable disease (treatment response?)- further study needed

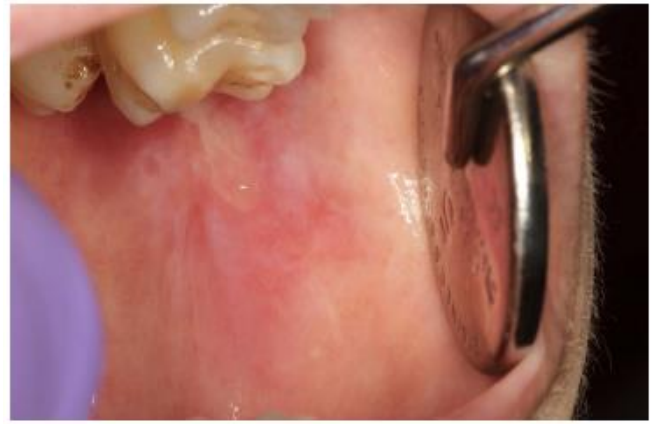
MUCOSAL INVOLVEMENT

- Xerostomia and lichenoid reactions are the most common oral mucosal toxicities



- Although CPI-related mucosal toxicities have not emerged as treatment limiting toxicities in key clinical trials, they nevertheless impact patient quality of life

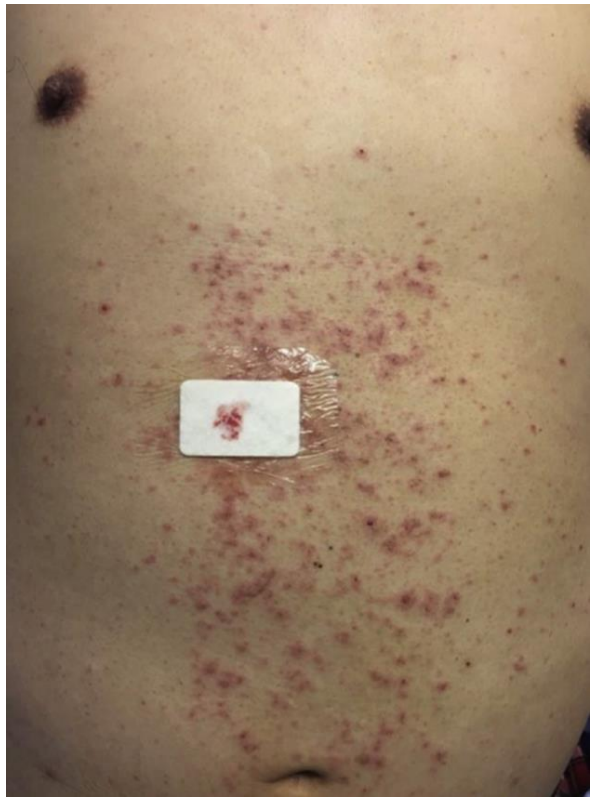
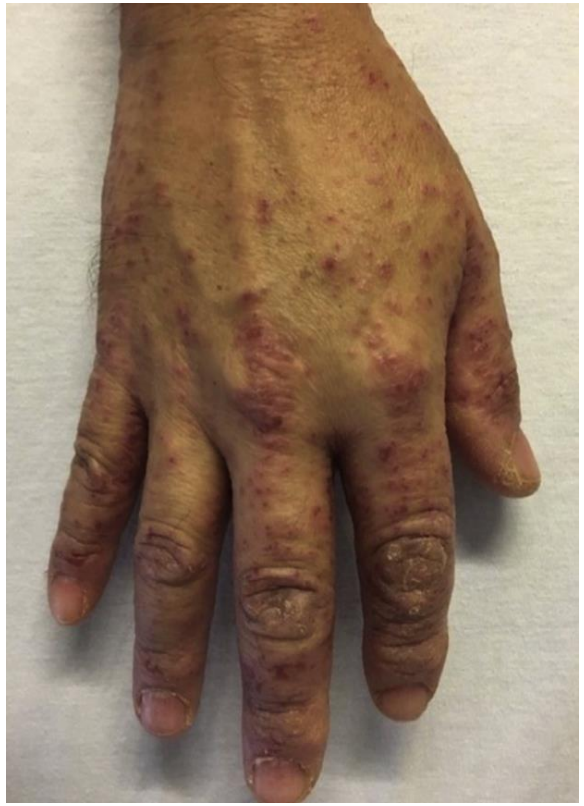
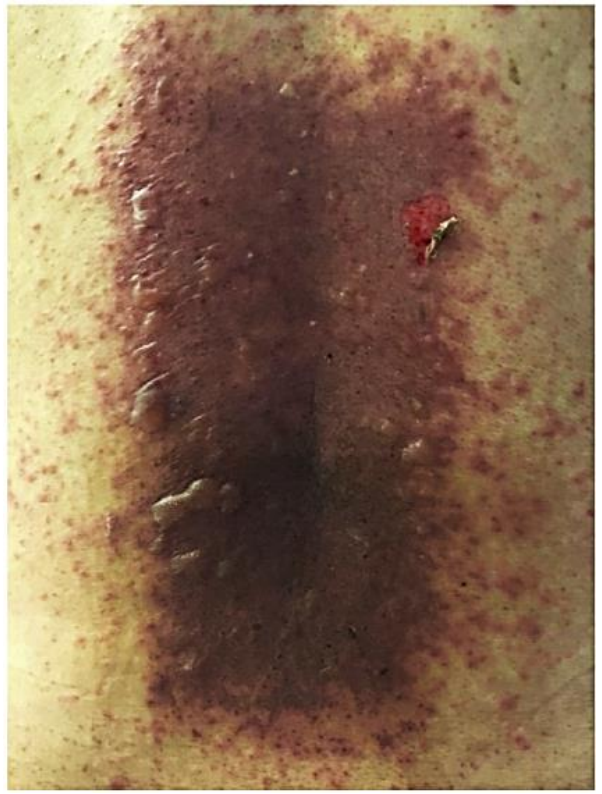
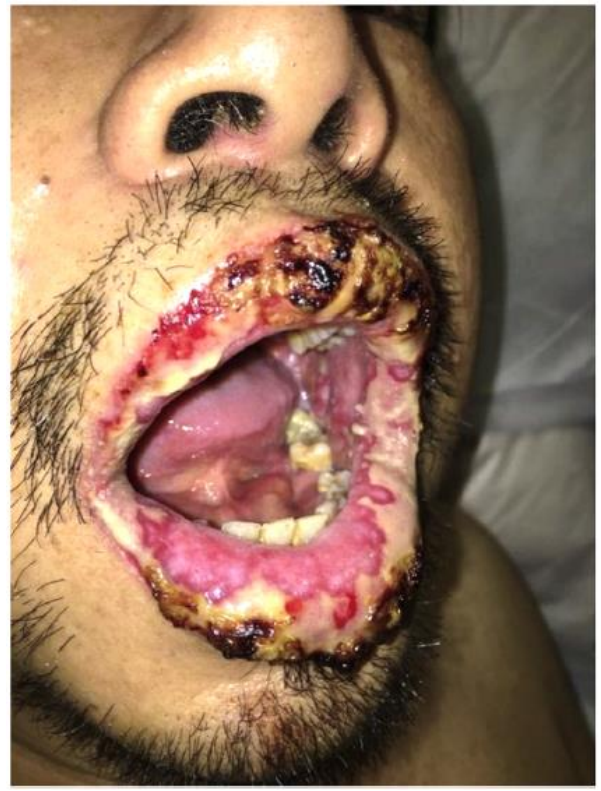
- The lesions may affect dorsal or lateral sides of the tongue, the lips, gingivae, hard palate, buccal mucosa, or perianal and vulvar areas.



- Patients may report pain or soreness, but the lesions can be asymptomatic

Geisler AN, et al. JAAD 2020;S0190-9622(20)30963-4
Yoon SY, et al. Lung Cancer. 2020;147:21-25
Shazib MA, et al. Oral Dis. 2020;26(2):325-333

STEVENS-JOHNSON SYNDROME

Saw, et al. "Pembrolizumab-induced SJS…." Eur J Cancer. 2017.

TOXIC EPIDERMAL NECROLYSIS (TEN)

- Spread measles-like rash → slow progression over weeks/months

- Marked increase of PD-L1 expression in the skin

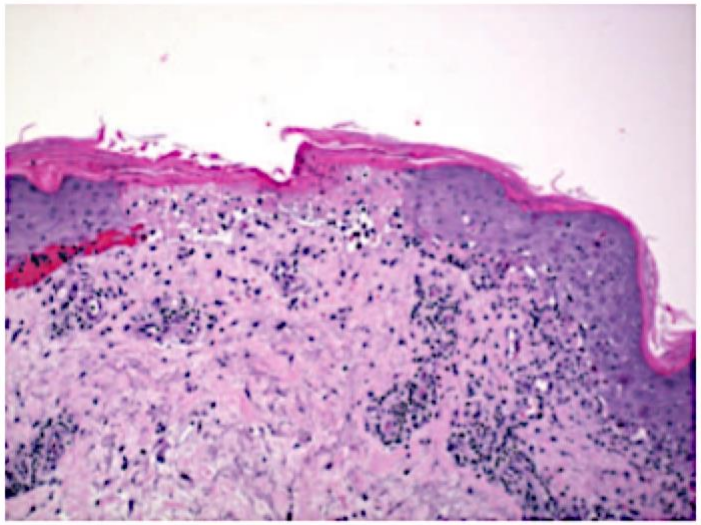


FIGURE 4 Biopsy at time of toxic epidermal necrolysis (TEN) presentation. Routine histology demonstrates interface dermatitis with full epidermal thickness necrosis, ×100.

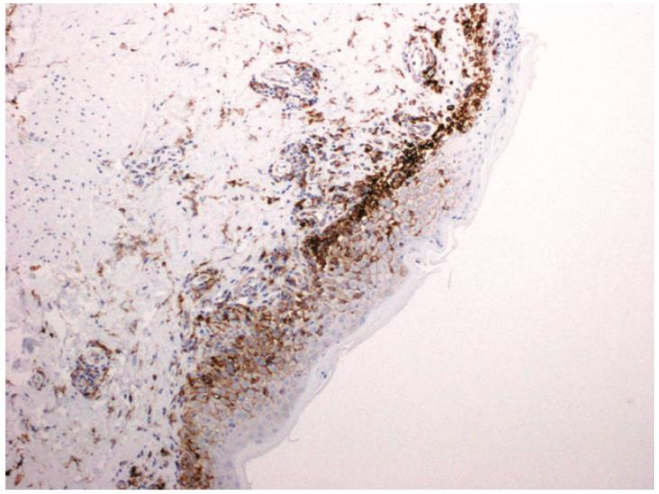
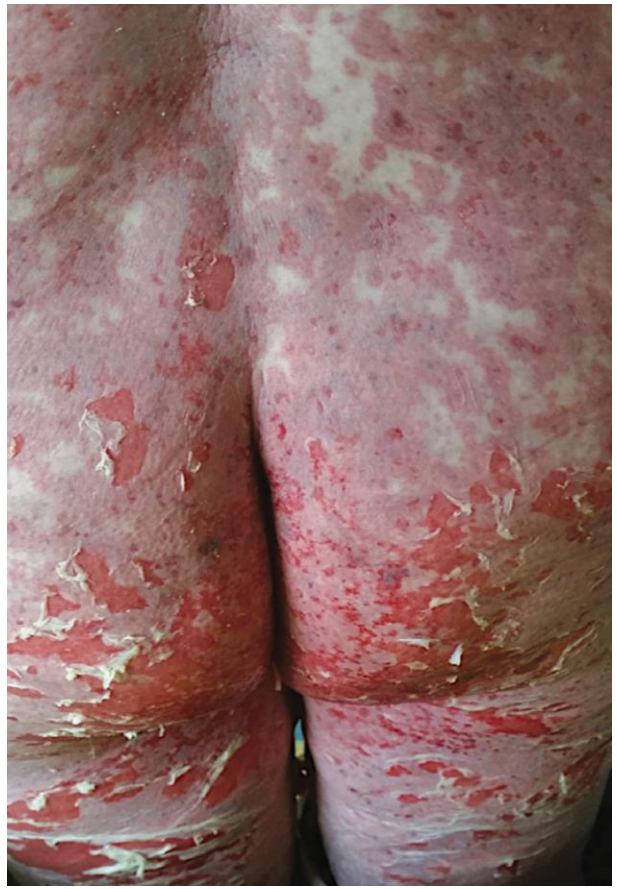


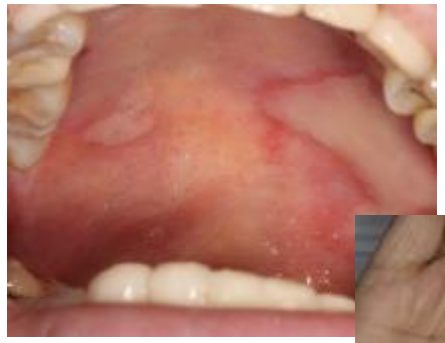
FIGURE 5 Biopsy at time of toxic epidermal necrolysis (TEN) presentation. PD-L1 immunohistochemistry shows dramatic increase of PD-L1 expression in the epidermis, ×100.

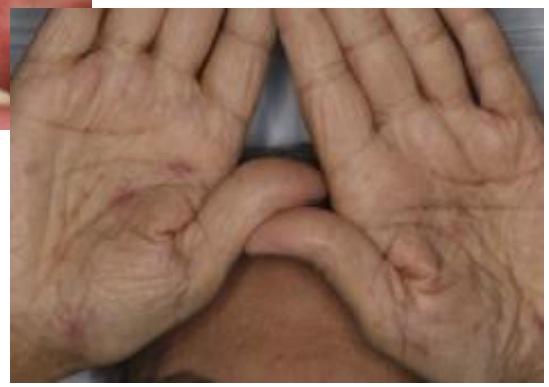


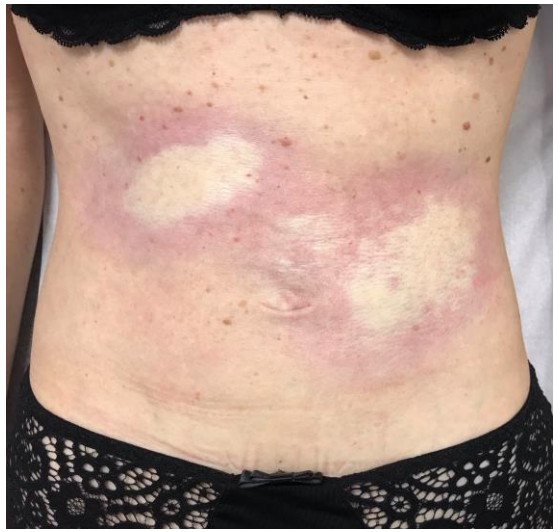
Vivar KL. Et al. J Cutan Pathol. 2017 Apr;44(4):381-384.

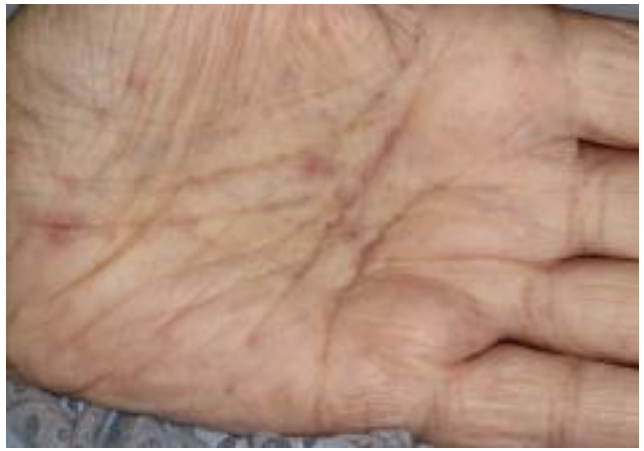
OTHER SKIN irAE

- Hand-foot reaction
- Urticarial reaction
- Skin reactions due to UV radiation hypersensitivity
- Neutrophilic dermatoses
- Morphea
- DRESS syndrome
- ….









Kamińska-Winciorek G. et al. Advances in Dermatology and Allergology 2019
Shazib MA, et al. Oral Dis. 2020;26(2):325-333

irCAE and relation with

irAEs

Pre-existing autoimmune diseases

Age

Treatment outcome

Cancer Immunology, Immunotherapy
https://doi.org/10.1007/s00262-019-02321-z

ORIGINAL ARTICLE

Pre-existing autoimmune disease and the risk of immune-related adverse events among patients receiving checkpoint inhibitors for cancer

Kenneth L. Kehl[1,2] · Shihao Yang[3] · Mark M. Awad[2] · Nathan Palmer[4] · Isaac S. Kohane[4] · Deborah Schrag[1]

The Oncologist®

Immuno-Oncology

Clinical Outcomes of Patients with Advanced Cancer and Pre-Existing Autoimmune Diseases Treated with Anti-Programmed Death-1 Immunotherapy: A Real-World Transverse Study

Number ICI-treated patients 4438

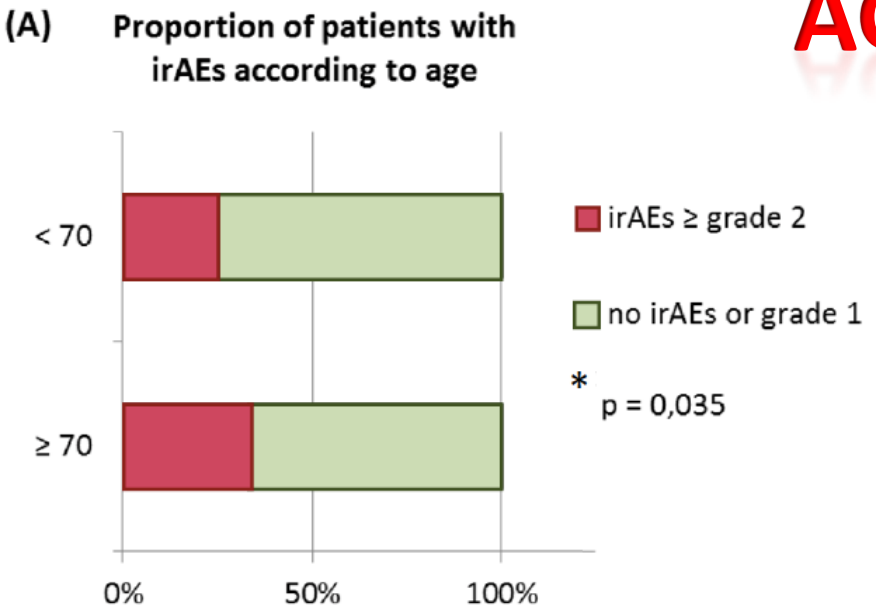
Pre-existing autoimmune disease

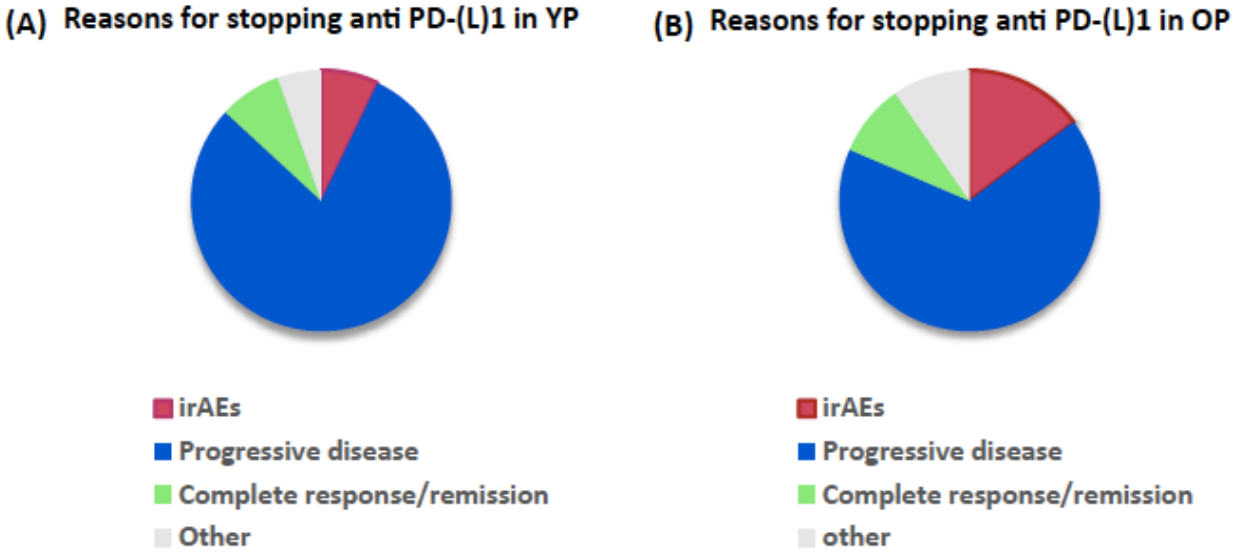
- No 3976
- Yes 462

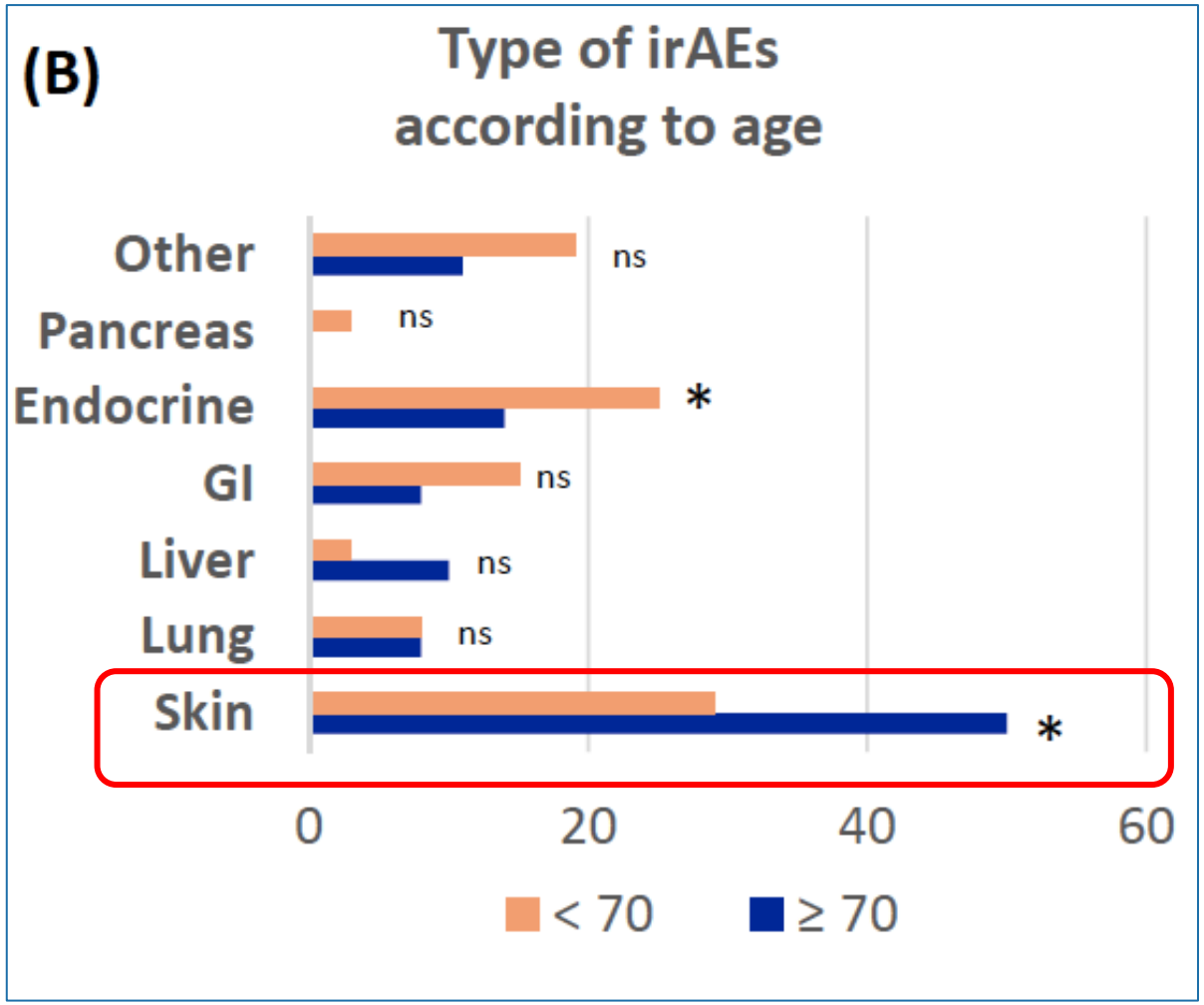
Pre-existing autoimmune disease, after 3 months of ICI treatment:

- Do not change the risk of a grade 3/4 irAE
- Increase the incidence of hospitalization with irAE +
- Increase the incidence of prednisone prescriptions ++

AGE and irAEs







C. Baldini et al. European Journal of Cancer 129 (2020) 71e79

Cutaneous irAE and treatment outcome

JAAD
Journal of the American Academy of Dermatology

486
screened patients
in treatment with PD1/PDL1 i

94 no skin AE

20 case patients

Characterization of dermatitis after PD-1/PD-L1 inhibitor therapy and association with multiple oncologic outcomes: A retrospective case-control study

Charles Kyung Min Lee, BS[a], Shufeng Li, MS[b], Duy Cong Tran, BS[a], Gefei Alex Zhu, MD[b], Jinah Kim, MD, PhD[b], Bernice Y. Kwong, MD[b], and Anne Lynn S. Chang, MD[b]

[a]Stanford University School of Medicine, Redwood City, California

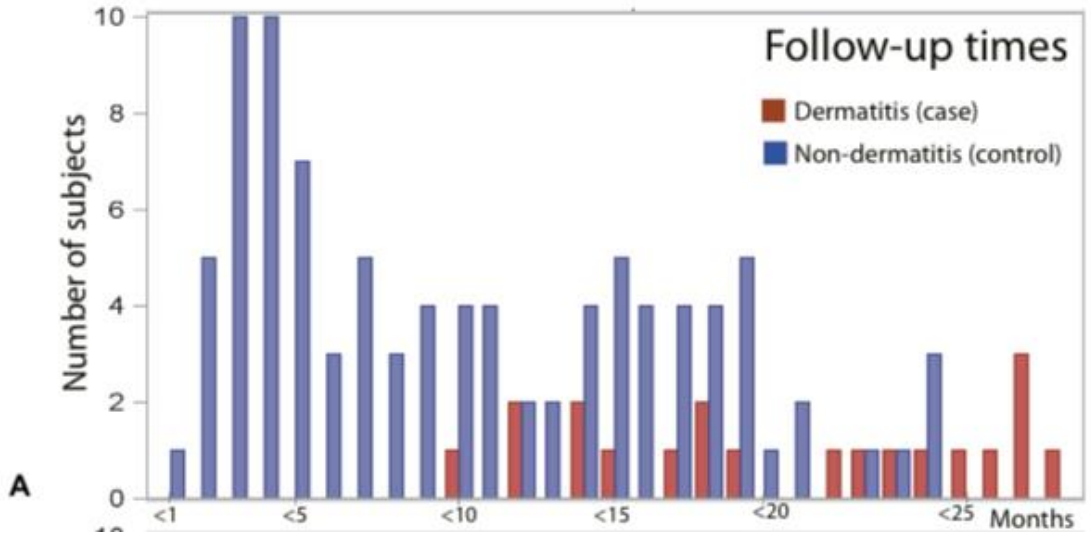
[b]Department of Dermatology, Stanford University School of Medicine, Redwood City, California

Dermatitis is significantly associated with a more favorable

- response rate

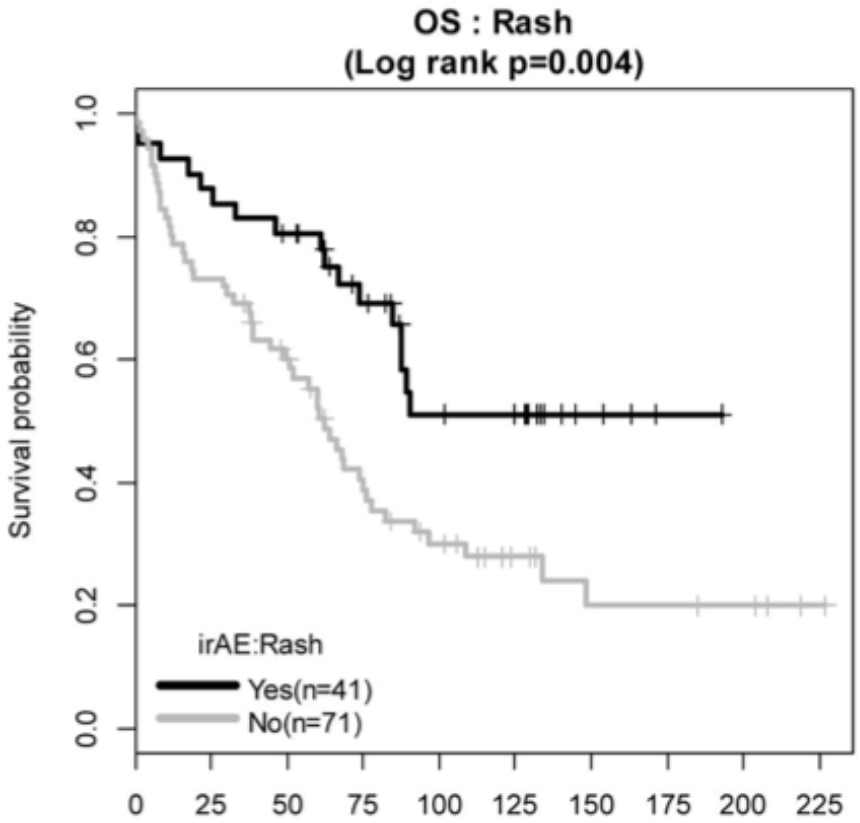
- progression-free survival

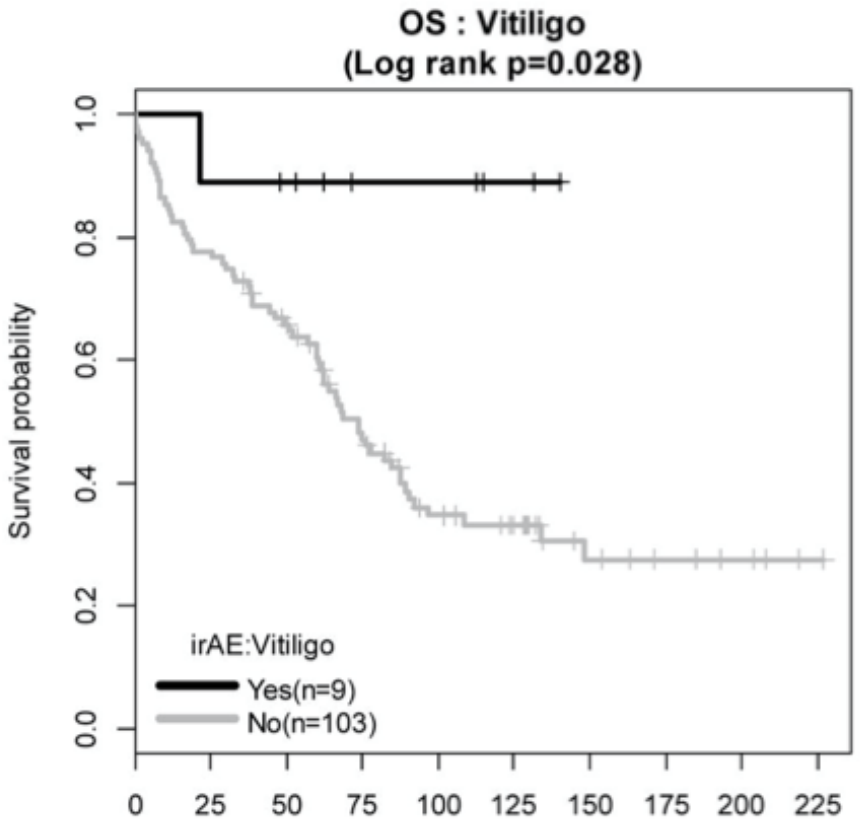
- overall survival



Min Lee et al. JAAD 2018. 79(6): 1047–1052

irAE and treatment outcome:
relation with *type* of skin irAE





112 patients
with metastatic melanoma
treated with Nivolumab

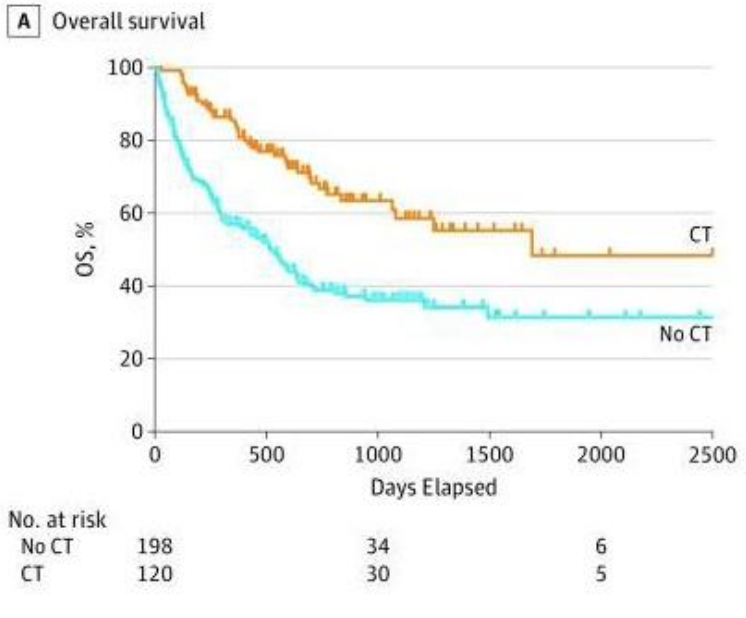
Freeman-Keller M, et al. Clin Cancer Res 2016;22: 886–894.

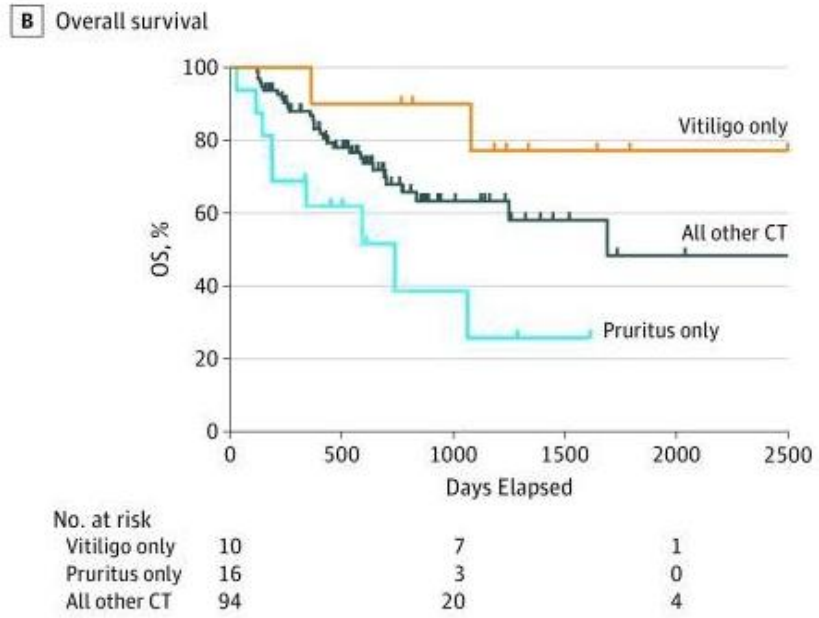
irAE and treatment outcome:
relation with *type* and *time of onset*

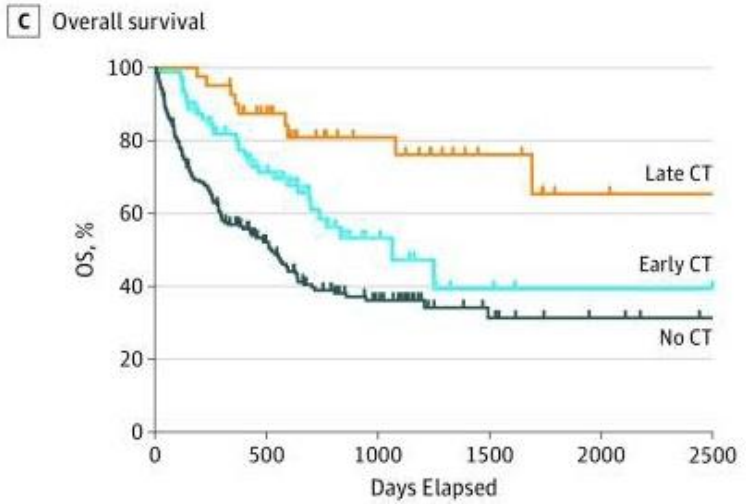
318 patients
in treatment with
anti-PD1 monotherapy or IPI+NIVO

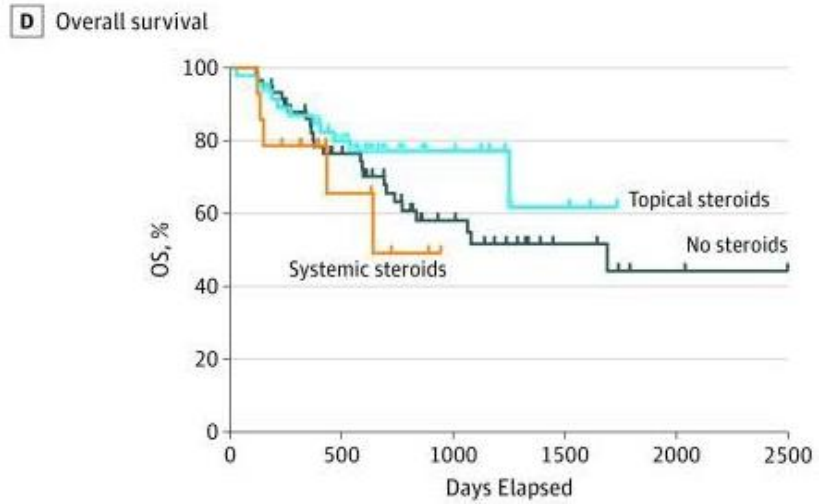
120 patients
with cutaneous toxicity

198 patients
without CT









Quach HT, et al. JAMA Oncol. 2019;5(6):906-908.

MANAGEMENT

- The treatment of skin irEAs depends on the severity of the event

- Severity determined according to Common Terminology Criteria for Adverse Event (CTCAE) scale

Common Terminology Criteria

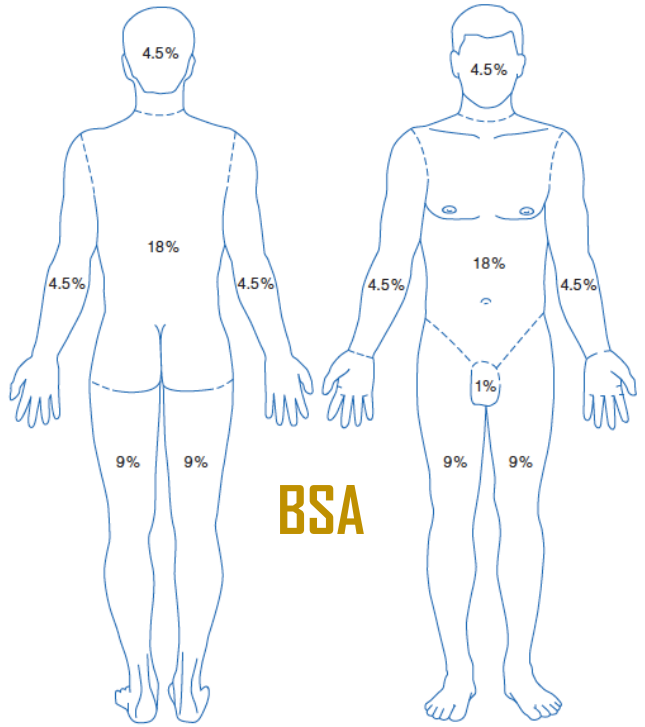
for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

It grades adverse events based on severity on a scale from 1 to 5



CTCAE for cutaneous ir ADVERSE EVENTs

- **Grade 1:** **Mild**; macules/papules covering <10% body surface area (BSA), with or without symptoms (eg. Pruritus, burning, tightness).

- **Grade 2:** **Moderate**; macules/papules covering 10%-30% BSA, with or without symptoms (eg. Pruritus, burning, tightness); limiting instrumental activities of daily living (iADLs)

- **Grade 3-4:** **Severe** or medically significant but not immediately life-threatening; macules/papules covering >30% BSA, with or without symptoms; limiting self-care activities of daily living (ADLs)

- **Grade 5:** **Death** related to AE.

MANAGEMENT GUIDELINES

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

Management of Immunotherapy-Related Toxicities, Version 1.2019

John A. Thompson, MD[1,*,†]; Bryan J. Schneider, MD[2,*,†]; Julie Brahmer, MD, MSc[3,*,†]; Stephanie Andrews, MS, RN, ANP-BC[4]; Philippe Armand, MD, PhD[5]; Shailender Bhatia, MD[1]; Lihua E. Budde, MD, PhD[6]; Luciano Costa, MD, PhD[7]; Marianne Davies, MSN, DNP[8]; David Dunnington, MA[9]; Marc S. Ernstoff, MD[10,†]; Matthew Frigault, MD[11]; Brianna Hoffner, MSN[12]; Christopher J. Hoimes, MD[13]; Mario Lacouture, MD[14]; Frederick Locke, MD[4]; Matthew Lunning, DO[15]; Nisha A. Mohindra, MD[16]; Jarushka Naidoo, MD[3]; Anthony J. Olszanski, MD, RPh[17]; Olalekan Oluwole, MD[18]; Sandip P. Patel, MD[19]; Sunil Reddy, MD[20]; Mabel Ryder, MD[21]; Bianca Santomasso, MD, PhD[14]; Scott Shofer, MD, PhD[22]; Jeffrey A. Sosman, MD[16]; Momen Wahidi, MD[22]; Yinghong Wang, MD, PhD[23,†]; Alyse Johnson-Chilla, MS[24]; and Jillian L. Scavone, PhD[24]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. B. A. G. Haanen, F. Carbonnel, C. Robert, K. M. Kerr, S. Peters, J. Larkin & K. Jordan, on behalf of the ESMO Guidelines Committee

JAAD Journal of the American Academy of Dermatology

REVIEW ARTICLE | ARTICLES IN PRESS

CME Part II: Immune checkpoint inhibitor-related dermatologic adverse events

Amaris N. Geisler, BS • Gregory S. Phillips, BS • Dulce M. Barrios, MS • ... Andrea P. Moy, MD • Jeffrey A. Kern, MD • Mario E. Lacouture, MD • Show all authors

Published: May 22, 2020 • DOI: https://doi.org/10.1016/j.jaad.2020.03.132

CONCLUSION

Dermatologic toxicities are common with new oncologic therapies and are often mild to moderate in severity (Grade 1-2)

Patient education and proactive manegement of AEs are crucial:

- Possible use of topical treatments in early stage
- **Improved quality of life and overall survival of patients**

BASIC KIT FOR PATIENTS STARTING CANCER TREATMENT

Moisturizing cream
± urea

Anti UVB & UVA
Sunscreen

Cleanser PH ~5

Repair
Cream/ointment

Cancer is a word, not a sentence.

John Diamond

Thank You

ANY QUESTIONS?