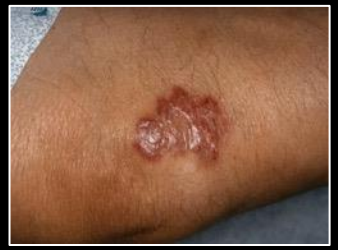
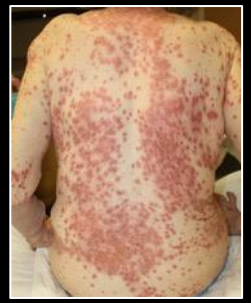
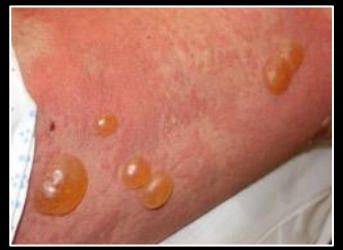
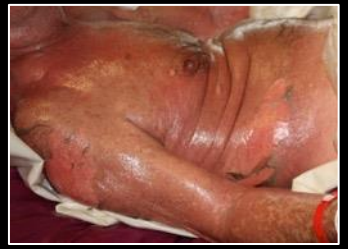
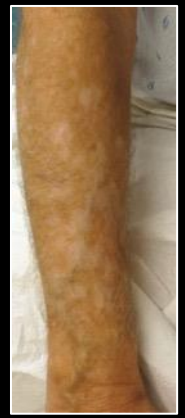
AtlanticDerm CONFERENCE

Cutaneous side effects of immune checkpoint inhibitors

Jean Bolognia, MD

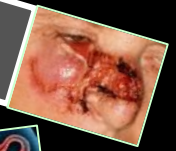






Conflicts of interest – none
Use of trade names – sometimes
Use of off-label indications – yes

Learning Objectives

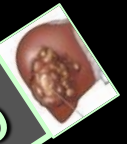
- Recognize the four major groups of cutaneous side effects:
  - morbilliform, lichenoid, eczematous, psoriasiform
  - autoimmune bullous dermatoses, e.g. BP
  - SCARs, e.g. DRESS, SJS/TEN
  - leukoderma
- Have therapeutic options beyond systemic corticosteroids

First introduced to immune checkpoint inhibitors as a treatment for melanoma

cemiplimab 

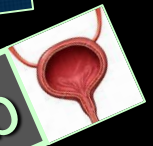
ipilimumab

atezolizumab

tremelimumab 

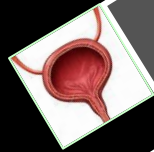
dostarlimab 

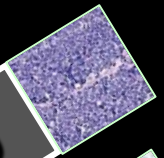
pembrolizumab

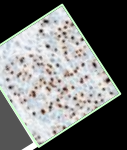
durvalumab 

nivolumab

relatlimab



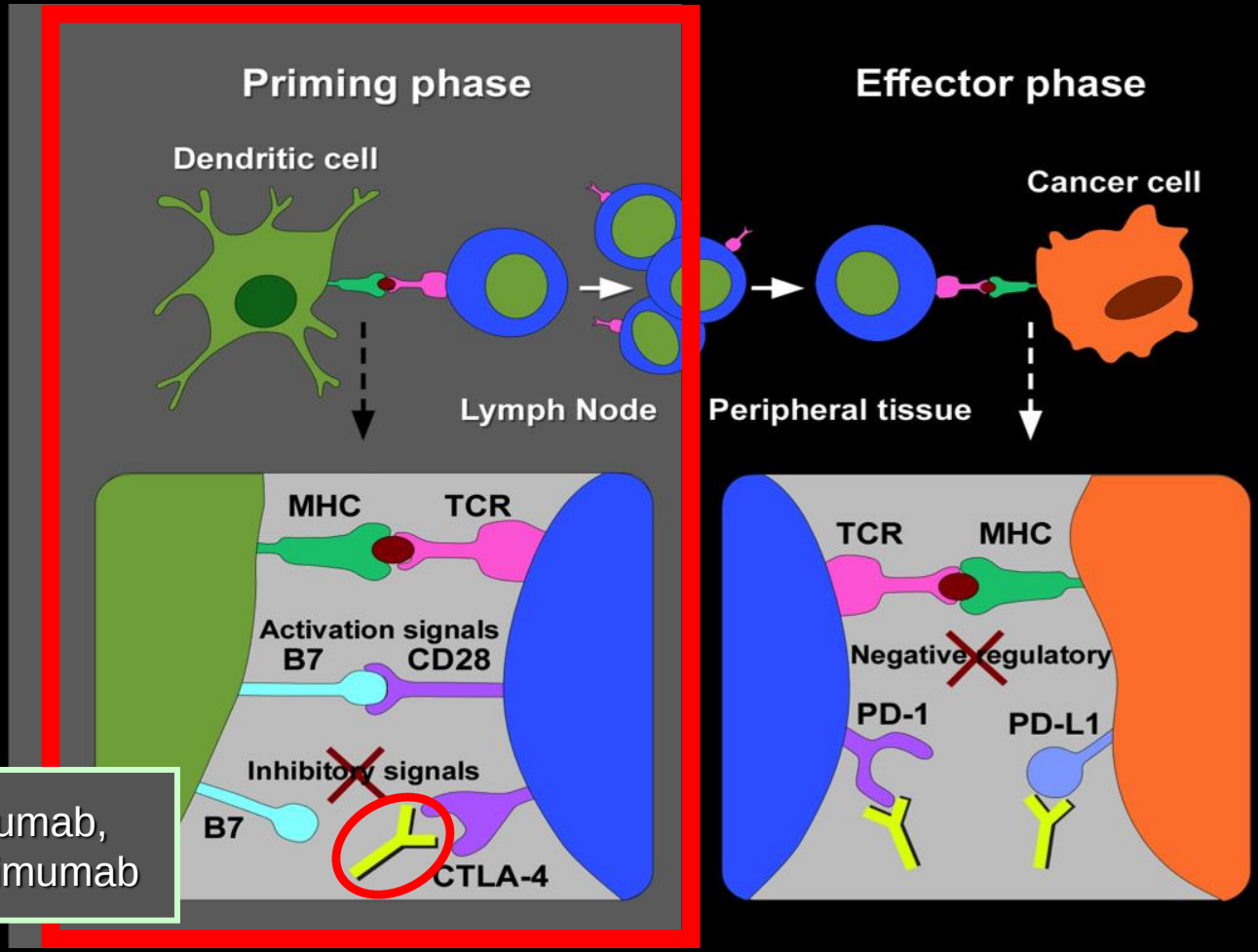
avelumab 

retifanlimab 

T regulatory cells and CTLA-4

- T regulatory (T reg) cells act as the dampeners in the immune system
- T reg cells prevent overproduction of reactive immune cells and risk of autoimmune disease
- CTLA-4 is a protein normally necessary for the T reg cells to suppress overactivation of dendritic cells

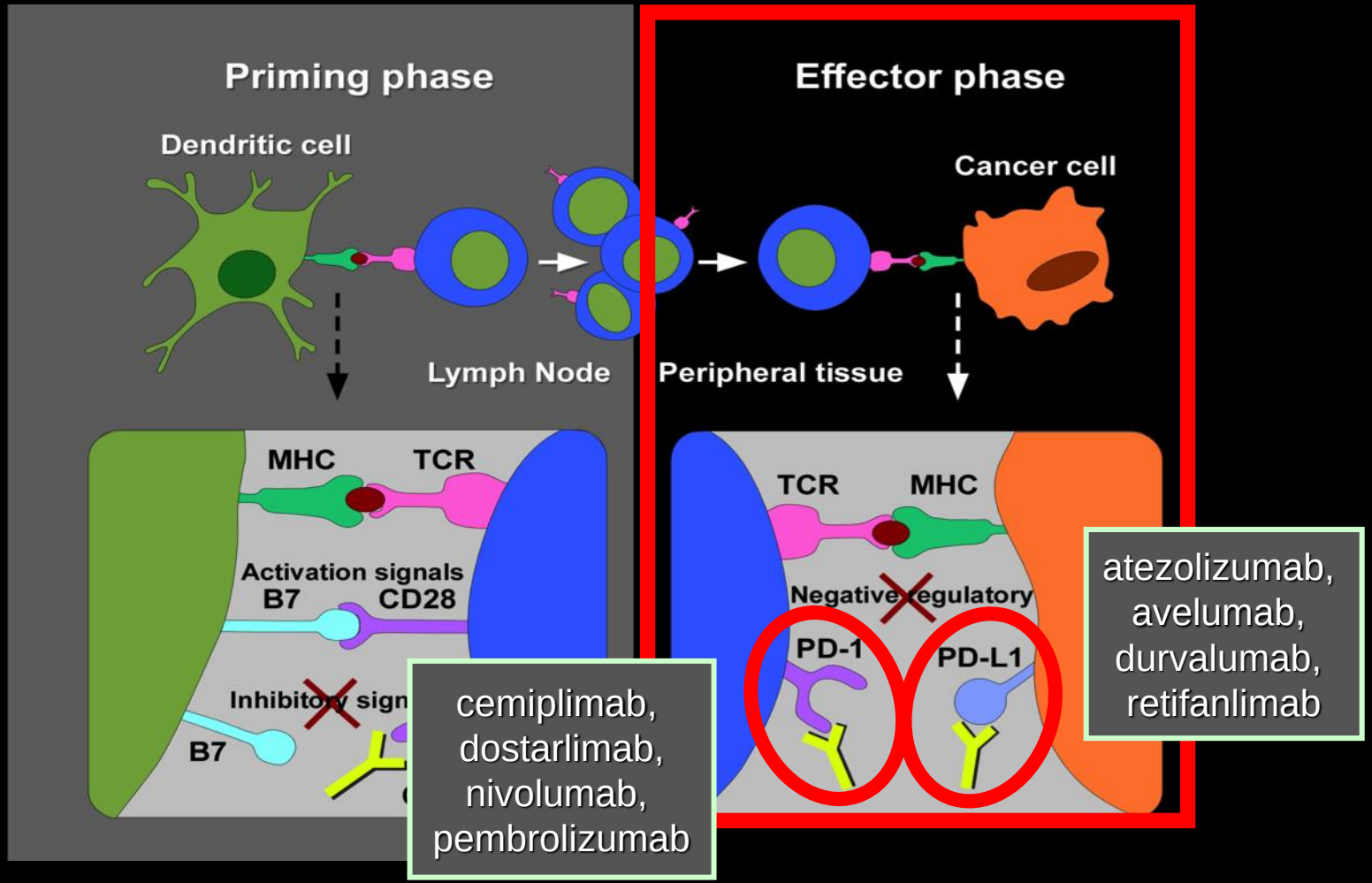
CTLA = cytotoxic T lymphocyte-associated antigen (CD152)

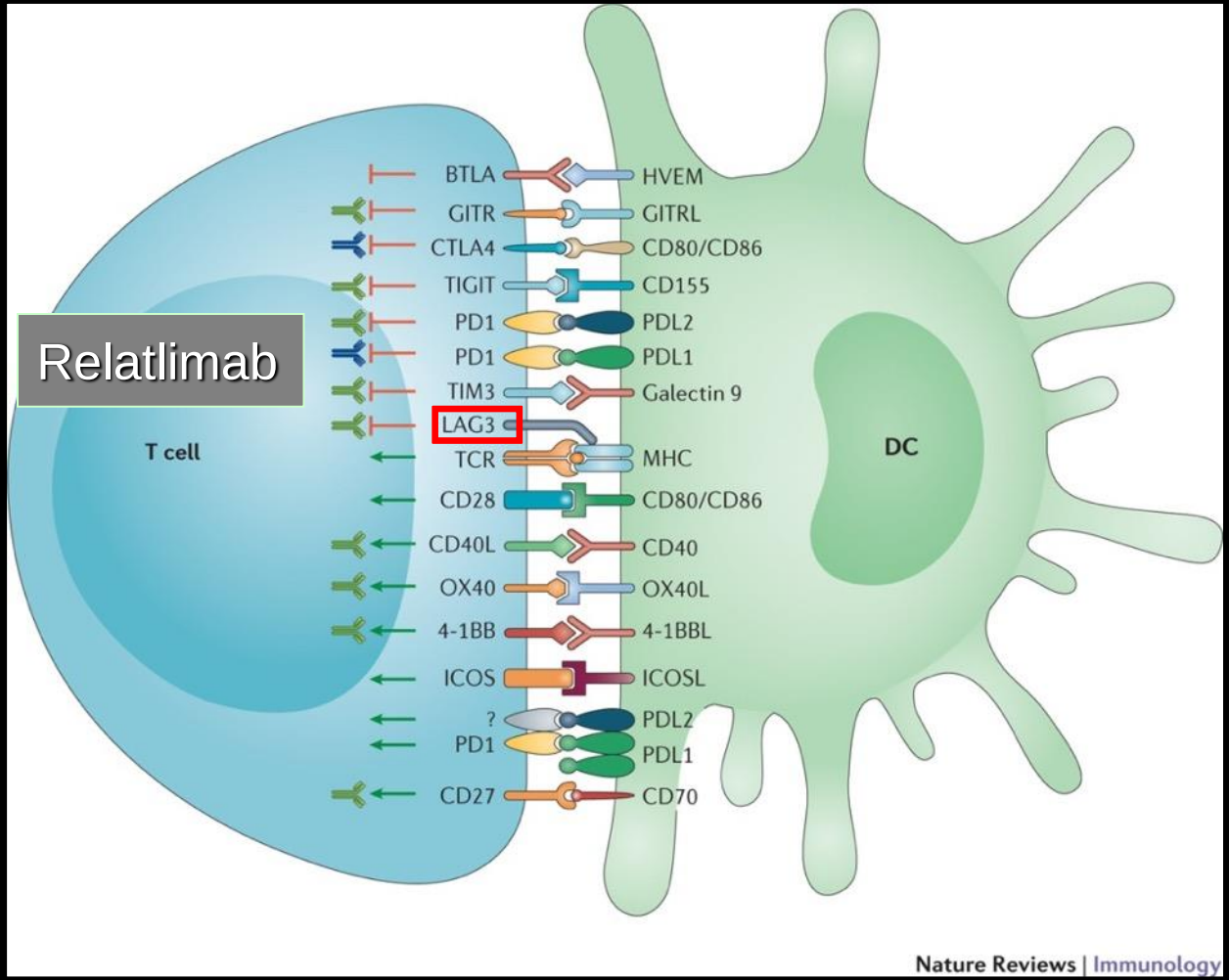


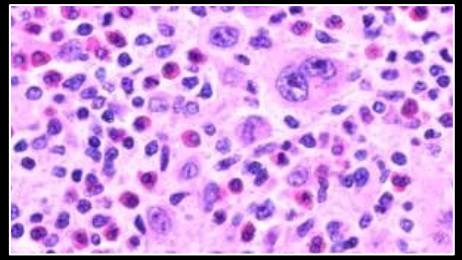
ipilimumab,
tremelimumab

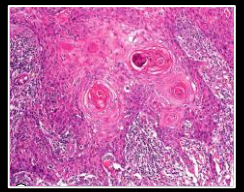
Anti-PD-1 & Anti-PD-L1 Antibodies

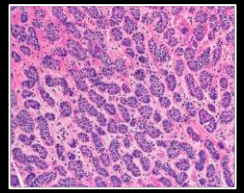
- PD-1 = programmed cell death protein 1
- PD-1 is a T cell co-inhibitory *receptor*
- PD-L1 = ligand of PD-1 expressed on tumors
- Inhibition of the interaction between PD-1 and PDL-1 leads to immune stimulation

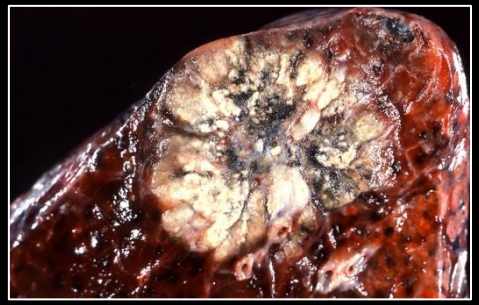

Priming phase
Dendritic cell
Lymph Node
MHC
TCR
Activation signals
B7
CD28
Inhibitory sign
B7
Effector phase
Cancer cell
Peripheral tissue
TCR
MHC
Negative regulatory
PD-1
PD-L1
cemiplimab, dostarlimab, nivolumab, pembrolizumab
atezolizumab, avelumab, durvalumab, retifanlimab

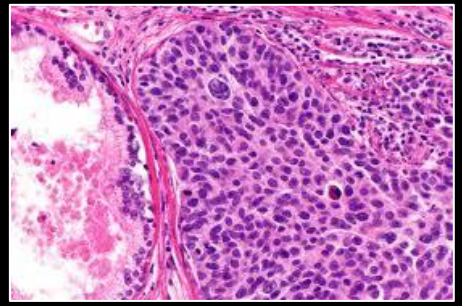

Relatlimab
T cell
DC
BTLA
HVEM
GITR
GITRL
CTLA4
CD80/CD86
TIGIT
CD155
PD1
PDL2
PD1
PDL1
TIM3
Galectin 9
LAG3
TCR
MHC
CD28
CD80/CD86
CD40L
CD40
OX40
OX40L
4-1BB
4-1BBL
ICOS
ICOSL
?
PDL2
PD1
PDL1
CD27
CD70
Nature Reviews | Immunology

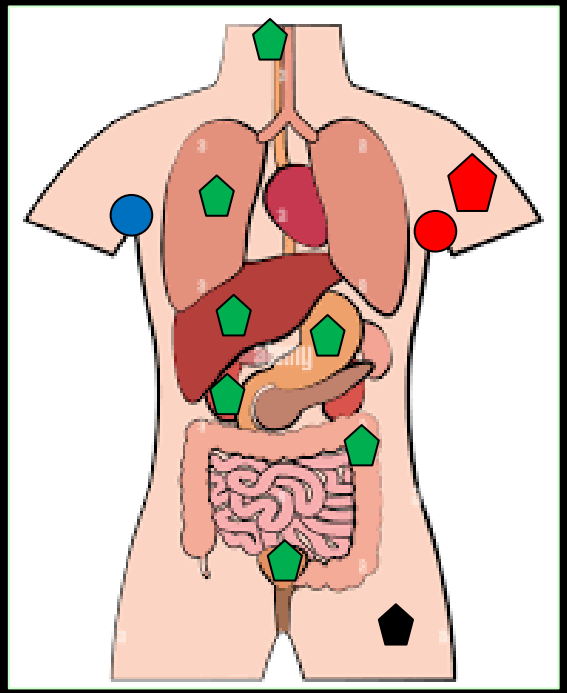


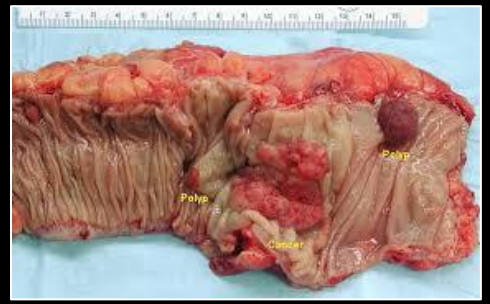


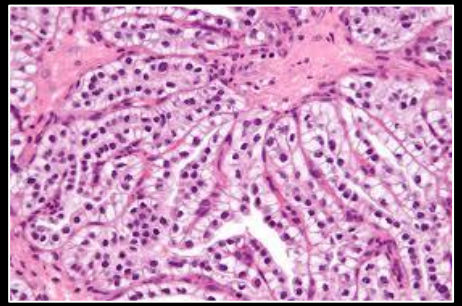


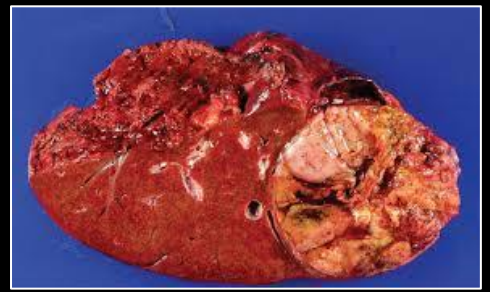


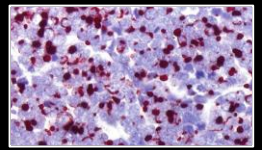


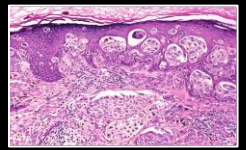



Polyp
Polyp
Cancer









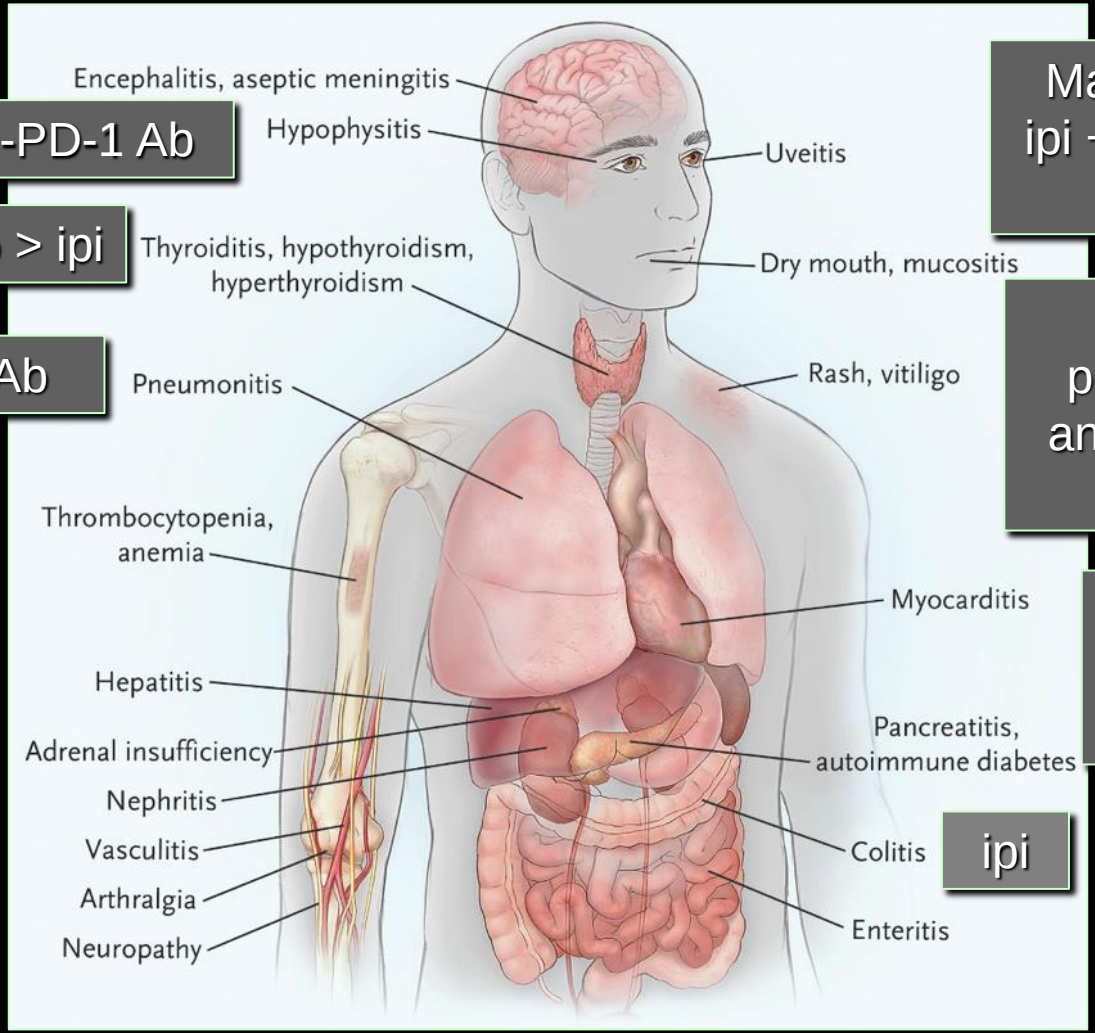
Immune checkpoint inhibitors – major *systemic immune-related adverse events* (irAEs)

- enterocolitis, hepatitis, pancreatitis
- hypopituitarism, hypothyroidism, adrenal insufficiency, type 1 diabetes, uveitis
- pneumonitis, myocarditis, myositis, arthritis, nephritis, sarcoidosis
- peripheral neuropathy, encephalitis

ipi > anti-PD-1 Ab

anti-PD-1 Ab > ipi

anti-PD-1 Ab



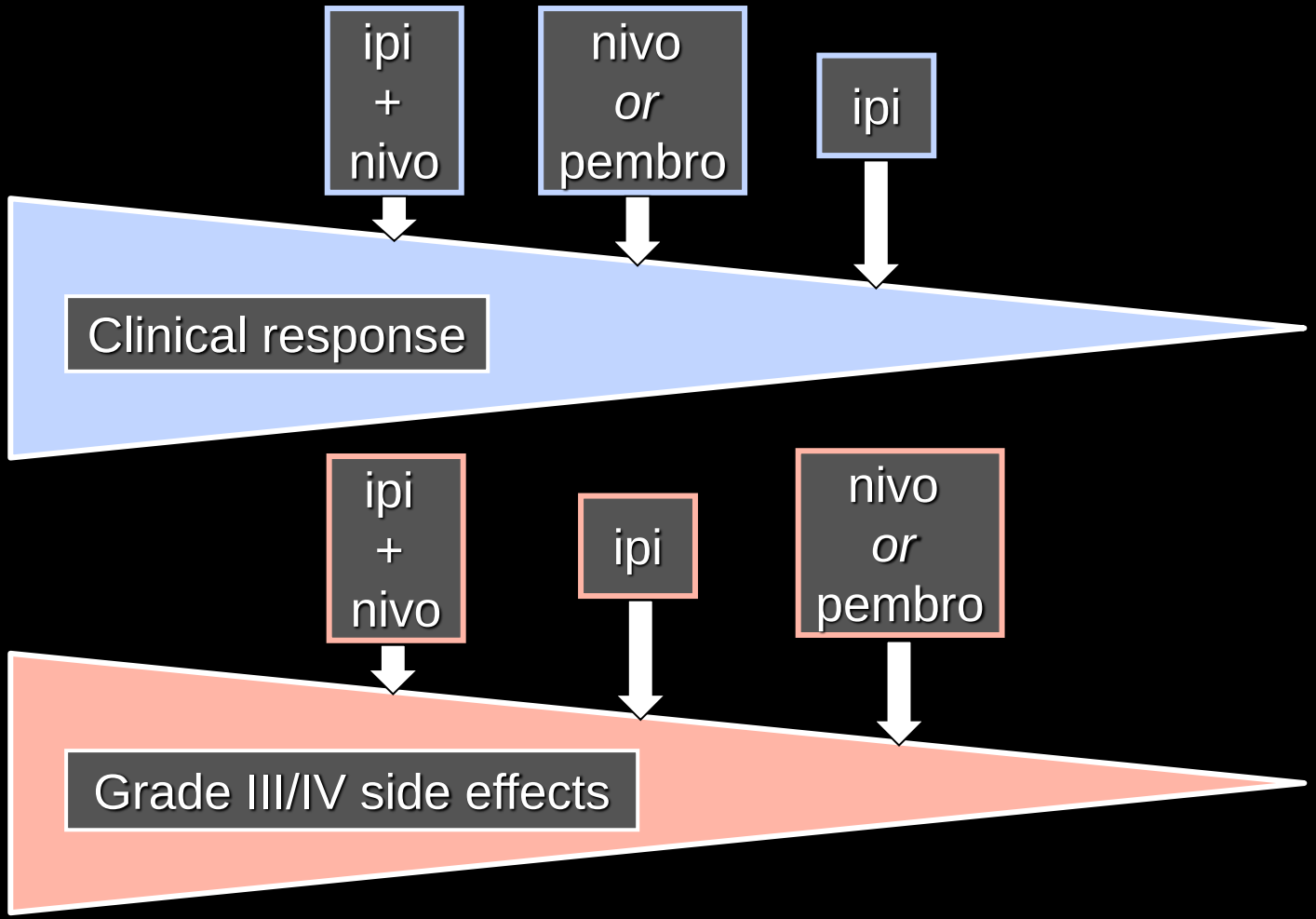
Maculopapular: ipi + nivo 40-60% nivo 20%

bullous pemphigoid: anti-PD-1/PD-L1 Ab

Lichenoid rxs: anti-PD-1/PD-L1 Ab 20%

ipi

NEJM 2018; 378:158-68.

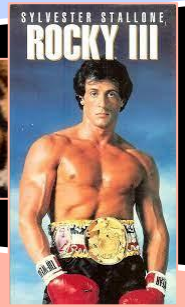

ipi + nivo
nivo or pembro
ipi
Clinical response
ipi + nivo
ipi
nivo or pembro
Grade III/IV side effects

ipi + nivo

nivo *or* pembro

ipi

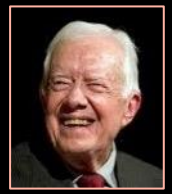
Clinical response



ipi + nivo

ipi

nivo *or* pembro



Grade III/IV side effects

Most common *cutaneous* side effects of immune checkpoint inhibitors (cirAEs)

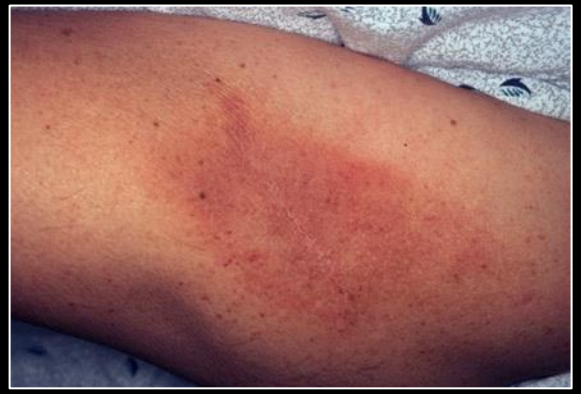
In two retrospective single-institution studies,

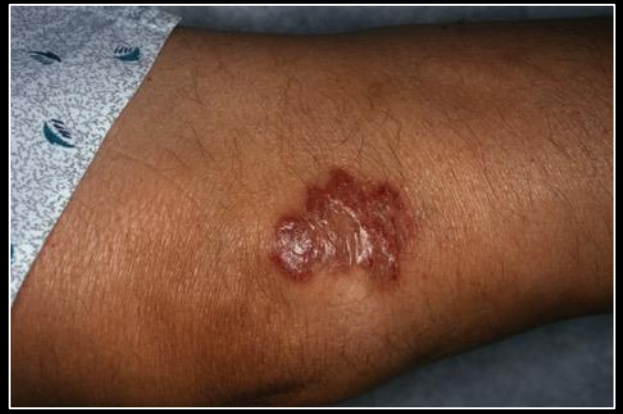
82 patients (anti-PD-1)	**83** patients (pembro)
Any cutaneous SE: 49%	Any cutaneous SE: 42%
Lichenoid dermatitis: 17%	Papular eruptions: 29%
Eczematous dermatitis: 17%	Pruritus: 12%
Vitiligo: 15%	Hypopigmentation: 8%

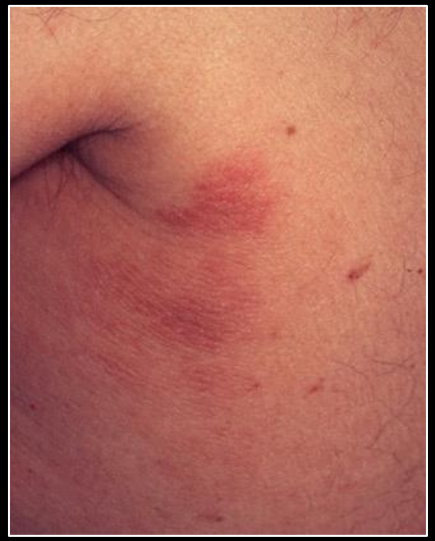
JAAD 2016;74:455-61.
JAMA Dermatol 2015;151:1206-12.

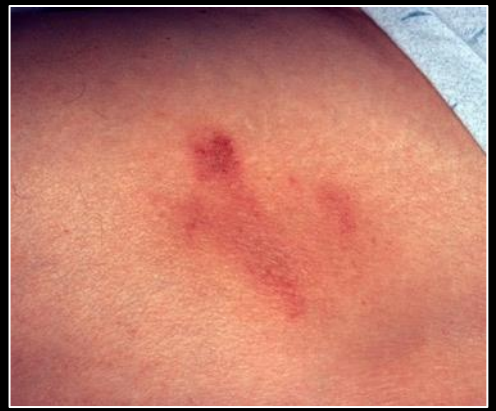
Learning Objectives

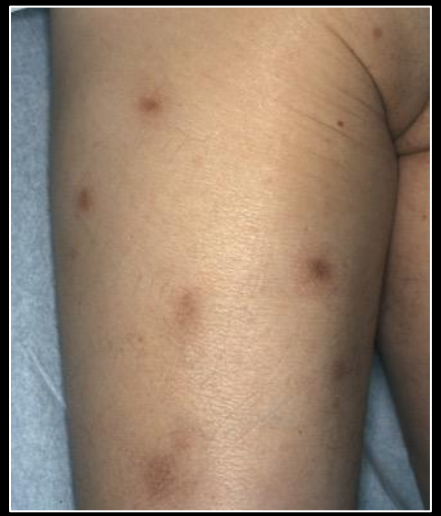
- Recognize the four major groups of cutaneous side effects:
  - morbilliform, lichenoid, eczematous, psoriasiform
  - autoimmune bullous dermatoses, e.g. BP
  - SCARs, e.g. DRESS, SJS/TEN
  - leukoderma
- Have therapeutic options beyond systemic corticosteroids

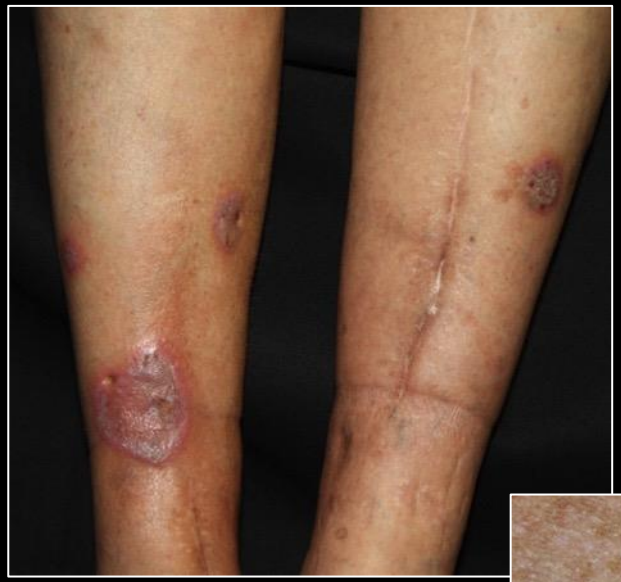




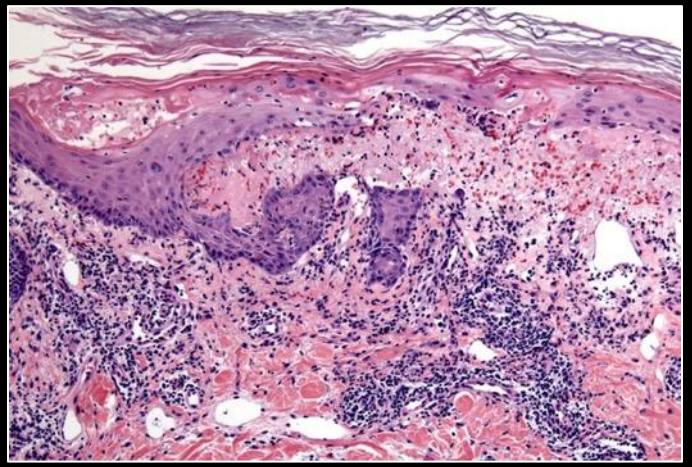


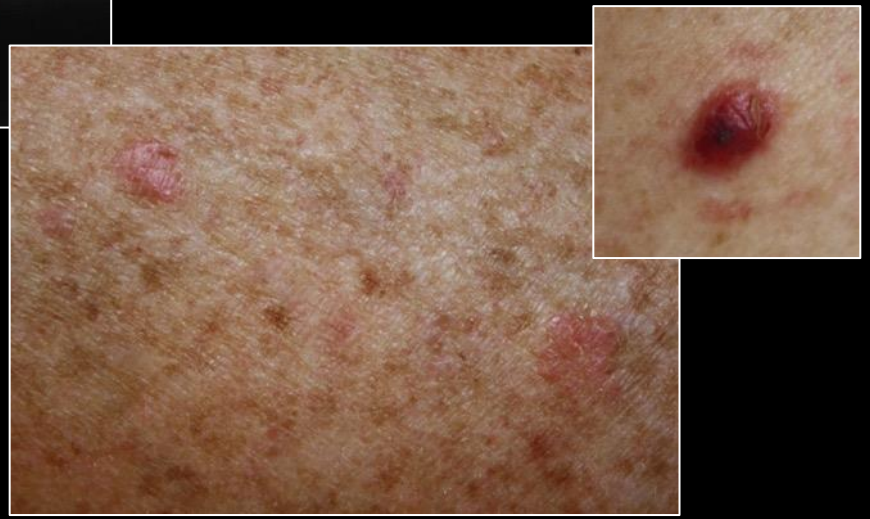




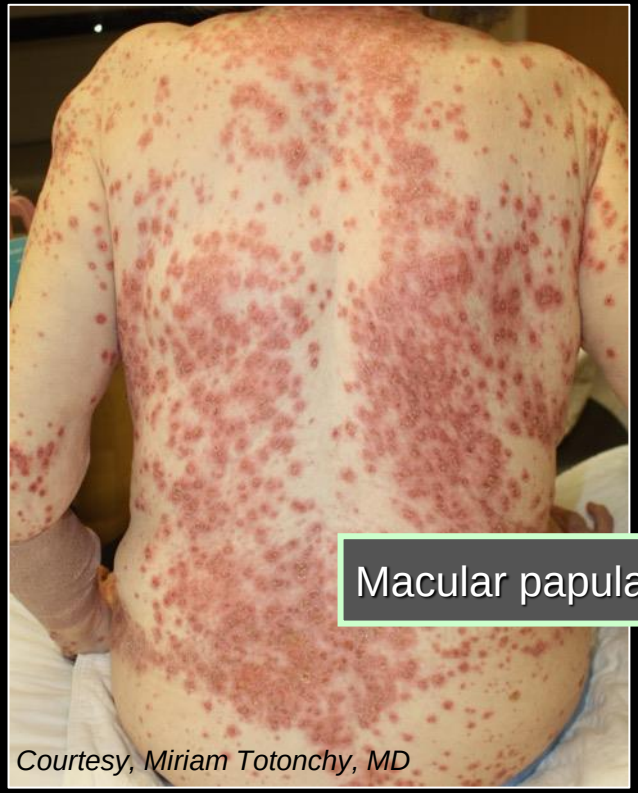


Courtesy, Jeffrey Callen, MD

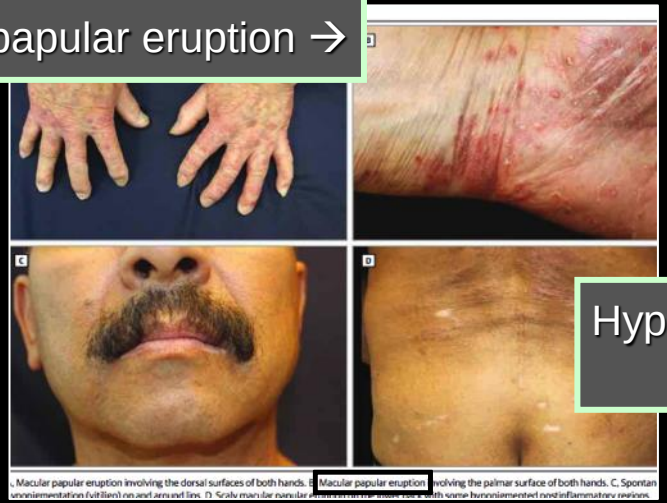




Macular papular eruption →



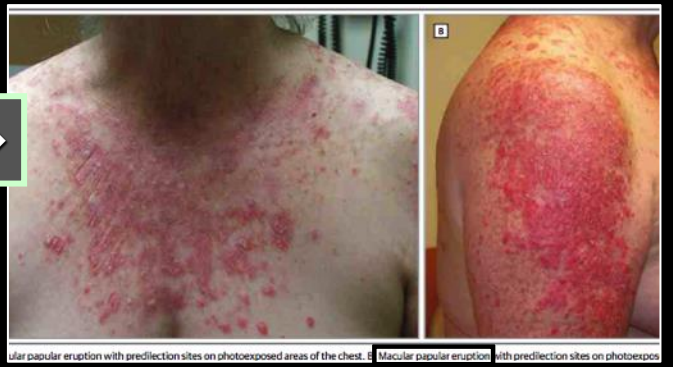
Courtesy, Miriam Totonchy, MD



Macular papular eruption involving the dorsal surfaces of both hands. B Macular papular eruption involving the palmar surface of both hands. C, Spontan

Hypopigmentation (vitiligo)

Macular papular eruption →



ular papular eruption with predilection sites on photoexposed areas of the chest. B Macular papular eruption with predilection sites on photoexpos

Rash NOS – one-third of patients with a cirAE

JAMA Dermatol 2015;151:1206-12.
JAAD 2023;88:1024.

Does a history of psoriasis or eczema influence ICI-induced eruptions?

- Retrospective review (six years), single institution
- Of 296 patients with cirAE, 11 a history of eczema and 18 a history of psoriasis
- 43% with baseline eczema presented with eczematous dermatitis (vs 12% of controls; p = .006)
- 56% with baseline psoriasis presented with psoriasisiform reactions vs 6% of controls; p <.0001)

cirAE, cutaneous immune-related adverse events
JAAD 2023;88:1198.

Table 1. Management of Skin irAEs in Patients Treated With ICPIs

1.0 Skin Toxicities

1.1 Rash/inflammatory dermatitis

Definition: Erythematous macular, papular, or targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others)

Diagnostic work-up
- Pertinent history and physical examination
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder
- If needed, a biologic checkup, including a blood cell count and liver and kidney tests
- Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A(Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms
- Skin biopsy
- Consider clinical monitoring with use of serial clinical photography
- Review full list of patient medications to rule out other drug-induced cause for photosensitivity

Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPIs if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level

1.2 Bullous dermatoses

Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction

Diagnostic work-up
- Physical examination
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease
- If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases
- Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister)
- Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)

Grading	Management
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted When symptomatic bullae or erosions, which are denoted vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations

(continued on following page)

1.0 Skin Toxicities

a for	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions: • Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements • Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
l pain	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc
or	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if [illegible] risk factors, such as neutropenia, etc

nthematous pustulosis, and DRESS/DIHS

s of skin, the appendages of the mucous membranes due to a drug

ng all mucous membranes as well as complete review of systems
as an infection, an effect of another drug, or a skin condition linked to another systemic disease
, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile,

crosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other
reactions, such as acute generalized exanthematous pusulosis
photography
erved on the skin, consider early admission to a burn center for further monitoring and management
se drug reactions:
malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the
ophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of
ain with bowel movements
in examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx,
opathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or
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o the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating
which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN

(continued on following page)

s in Patients Treated With ICPis (continued)

Skin Toxicities

Management
In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations

not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity.
nts and may be prolonged in cases of DRESS/DIHS
ng harms, and strength of recommendations are moderate

Common Terminology Criteria for Adverse Events; DIHS, drug-induced hypersensitivity
, grade; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related
plicable; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome;

American Society of Clinical Oncology *JCO* 2018; 36:1714-68

Guidelines for the treatment of the cutaneous toxicities from immune checkpoint inhibitors (*c*utaneous *i*mmune-*r*elated *a*dverse *e*vents cirAEs)

Common Terminology Criteria for Adverse Events (CTCAE) 4th vs 5th edition

Grade	Clinical
1	Macules/papules **<10% BSA** +/- symptoms (e.g. pruritus, burning)
2	Macules/papules **10-30% BSA** +/- symptoms & limiting ADL
3	Macules/papules **>30% BSA** +/- symptoms & limiting self-care
4	Papulopustular with life-threatening superinfection; SJS, TEN or bullous dermatosis >30% BSA and requiring ICU admission

"… the fact that when >30% of BSA is involved, the rash is automatically graded 3, is subject to discussion. The fifth version of the CTCAE will give a more appropriate classification for skin AEs"

CRCAE is published by the US Dept HHS

Common Terminology Criteria for Adverse Events (CTCAE) 4th vs 5th edition

Grade	Clinical
1	Macules/papules **<10% BSA** +/- symptoms (e.g. pruritus, burning)

Rash maculo-papular pg 138	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-

Definition: A disorder characterized by th[1]e of macules (flat) and p[2]elevated). Also known as m[3]m rash, it is one of the mo[4]on cutaneous adverse events, frequently affecting the u[1]k, spreading centripetall[2]sociated with pruritis.

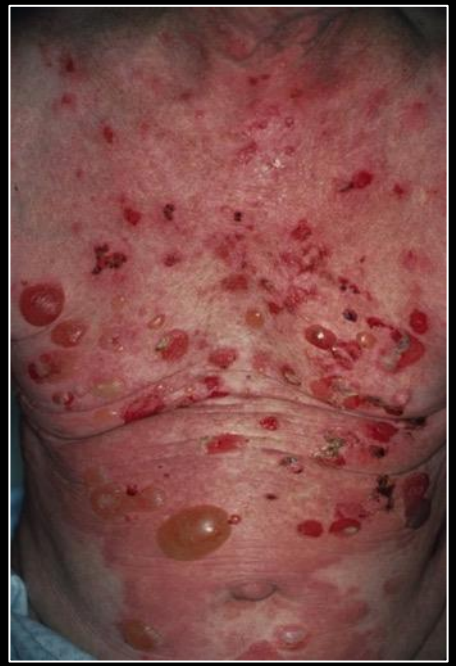
"… the fact that when >30% of BSA is involved, the rash is automatically graded 3, is subject to discussion. The fifth version of the CTCAE will give a more appropriate classification for skin AEs"

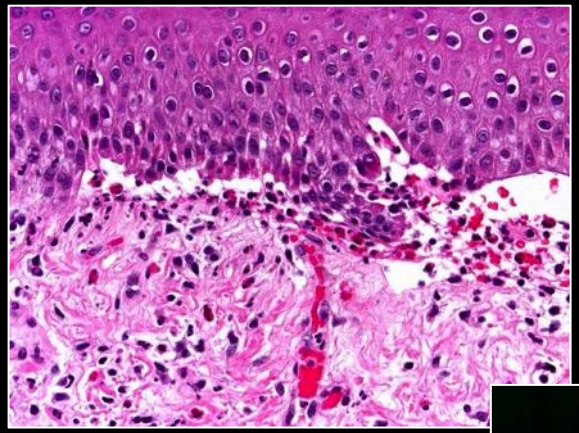
CRCAE is published by the US Dept HHS

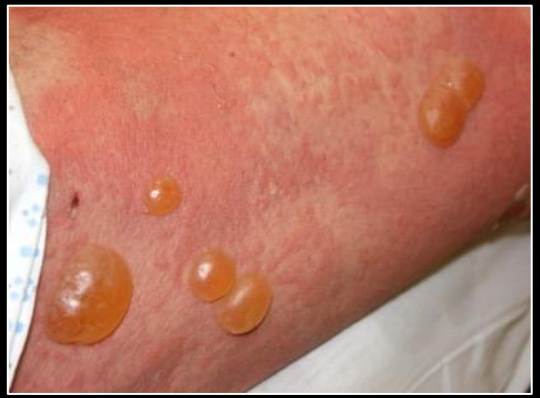
Treatment of morbilliform eruptions (as well as lichenoid, eczematous, & psoriasiform)

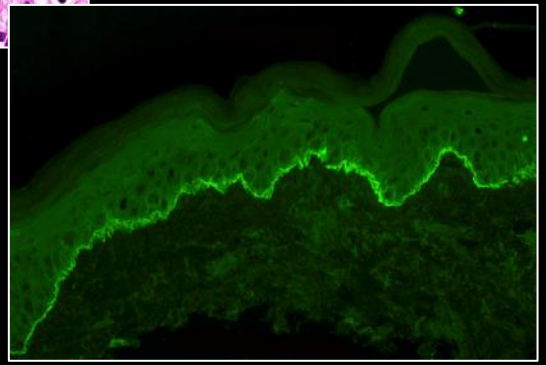
Grade	Clinical	Rx	ICI
1	Symptoms without impact on QOL or controlled with simple Rx	Emollients, mild-to-moderate potency topical CS, oral anti-pruritics *("simple Rx")*	Continue ICPi Avoid skin irritants Minimize sun exposure
2	Impact on QOL and requires intervention	Same as Grade 1 but higher potency CS; consider *oral* CS (e.g. prednisone 1 mg/kg tapered over 2 to ≥4 weeks); *nbUVB, HCQ, acitretin, MTX; dupilumab (eczematous, lichenoid); apremilast, anti-TNF, -IL-17 or -23*	Consider holding ICPi & assess weekly until return to Grade 1; consider 10 mg/day longer term
3	Fails to respond to Grade 2 treatment	Same as Grade 2 but consider higher dose of *oral* CS (e.g. (methyl)prednisolone 1-2 mg/kg)	Hold ICPi & assess in conjunction with dermatologist when to resume
4	Severe, intolerable, fails to respond to Grade 2/3	Hospitalization & *IV* CS (e.g. methylprednisolone 1-2 mg/kg) with slow taper	Same as Grade 3 Consider alternative therapy

Severe reactions – also MMF, IVIg, CSA, infliximab, tocilizumab *Ann Onc* 2017;28:i119*; JCO* 2018;36:1714-68







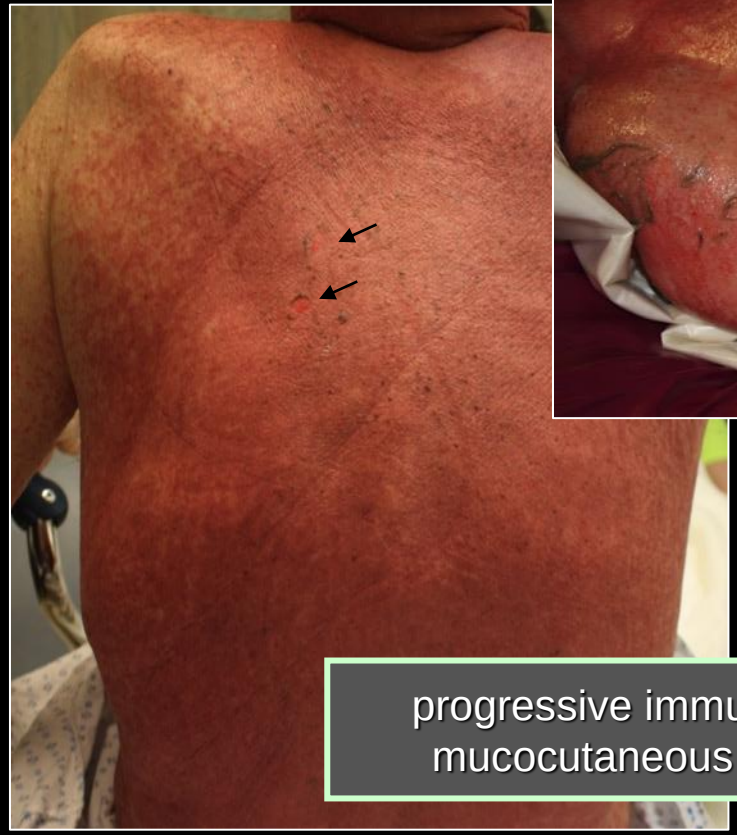


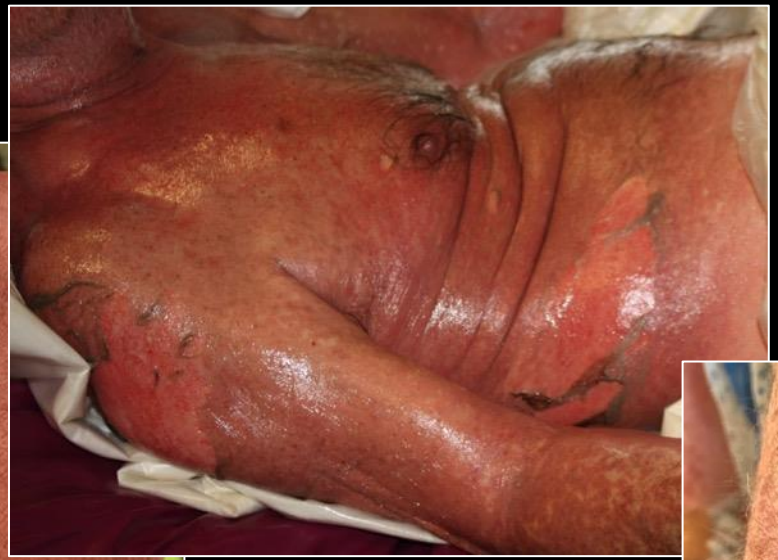
Treatment of bullous eruptions (including autoimmune bullous dermatoses)

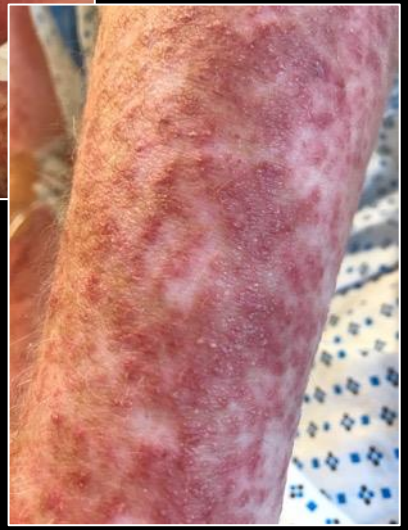
Grade	Clinical	Rx	Immune checkpoint inhibitor
1	No symptoms, blisters **<10% BSA**, no erythema	Local care Consider other etiology	Continue ICPi
2	Symptomatic blisters or erosions, impacting QOL **10-30% BSA**	Local care & class I topical CS *Doxycycline +/- nicotinamide* Low threshold for *oral* CS (e.g. prednisone 0.5-1 mg/kg tapered over ≥4 weeks)	Hold ICPi Evaluation for autoimmune bullous dermatosis & observe for progression to SCAR*
3	~~Skin sloughing~~ *Blisters or erosions* **>30% BSA** plus pain and ADLs impacted	Hospitalization & *IV* CS (e.g. methylprednisolone 1-2 mg/kg) with slow taper; if BP, consider rituxumab *dupilumab, omalizumab, MTX*	Hold ICPi & assess in conjunction with dermatologist regarding appropriateness of resuming
4	Blisters *or erosions* **>30% BSA** plus fluid or electrolyte abnormalities	Same as Grade 3	Permanently discontinue ICPi

*SJS/TEN, DRESS, AGEP

JCO 2018;36:1714-68; *Support Care Cancer* 2020;28:6119







progressive immunotherapy-related mucocutaneous eruption (PIRME)

YDRSC

Treatment of severe cutaneous adverse reactions (SCARs, e.g. SJS/TEN, DRESS)

Grade	Clinical	Rx	Immune checkpoint inhibitor
1	N/A	Monitor closely for improvement or worsening	Consider holding ICPi
2 *DRESS* *SJS*	Morbilliform eruption **10-30%** BSA plus systemic symptoms, LN, or facial swelling	Moderate-to-high dose topical CS Consider *oral* CS (e.g. prednisone 0.5-1 mg/kg tapered over ≥4 weeks)	Consider holding ICPi & assess weekly until return to Grade 1
3 *SJS*	Skin sloughing **<10% BSA** plus mucosal involvement	Hospitalization & *IV* CS (e.g. methylprednisolone 0.5-1 mg/kg initially then switch to oral) ~~High potency topical CS~~ *TNF inh*	Hold ICPi & assess in conjunction with dermatologist when to resume *or alternative therapy*
4 *SJS/ TEN*	Skin erythema & blistering/sloughing **≥10% BSA** *or* concerning lab abnormalites (*DRESS*)	Hospitalization & *IV* CS (e.g. methylprednisolone 1-2 mg/kg), with taper when toxicity resolves to normal +/- IVIG or cyclosporine *TNF inh*	Permanently discontinue ICPi

JCO 2018;36:1714-68; *JAMA Onc* 2022;8:130

Time to onset of cutaneous IrAEs (weeks)					
0-3	4-6	7-9	10-12	13-15	16+
Psoriasiform eruption	Morbilliform eruption	Lichenoid eruption (can involve mucosa)		Bullous pemphigoid	
	Pruritus			Alopecia	
		Vitiligo-like hypopigmentation or depigmentation			
SJS/TEN/DRESS					

Geisler AN, et al. *JAAD* 2020;83:1255-68.

Acute toxic epidermal necrolysis reaction post single dose pembrolizumab with preceding cephalosporin exposure: successful rechallenge with anti-PD-1 therapy

Lomax AJ, et al. *Intern Med J* 2019;83:1051-3.

Hx of at least 1 drug allergy – increased risk of nonspecific rash (OR 1.95 [1.12-3.38]); hx 3 or more drugs allergies - increased risk of grade 2-4 cirAEs (OR 6.57 [1.77-24.42] *BJD* 2022;187:424.

Following interruption of ICB Ab due to inflammatory cutaneous irAEs, what are the chances of recurrence?

- Single-institution retrospective analysis
- 103 inflammatory eruptions in 98 patients with a latency of 0.2-18 months
- 24% (25/103) required disruption in therapy
  - *immunobullous: 7/8*
  - lichenoid: 8/26
  - morbilliform: 6/18
  - *SJS: 2/2*
- 19% (3/16) had grade 2 or 3 flare on rechallenge

Coleman E et al. *JAAD* 2019;80:990

Impact of Dermatology Consult on Skin irAEs

- *Inpatients – retrospective cohort study*:
  - interruption of ICB Ab therapy ⬇ (0% [derm] vs 36%)
  - use of systemic immunosuppression ⬇ (18% [derm] vs 55%)
- *Outpatients – retrospective cohort study (included anticancer and targeted therapies)*:

REFERRING CLINICIAN RECOMMENDS INTERRUPTION		DERM RECOMMENDS INTERRUPTION	
		NO	YES
	NO	104	2
	YES	**40** ⇦	4

Chen ST et al. *JAAD* 2020;82:994
Barrios DM et al. *JEADV* 2020;34:1340

Use of ICIs in immunosuppressed patients

- Retrospective review (ten years), single institution
- 23 HIV-positive* & 8 renal transplant patients who received ICI
- 3 patients develop 4 cirAEs – 3 pruritus & 1 vasculitis/vasculopathy
- Kidney rejection in 37.5% at a median of 34 days (range, 15-59)

Histopathologic correlations

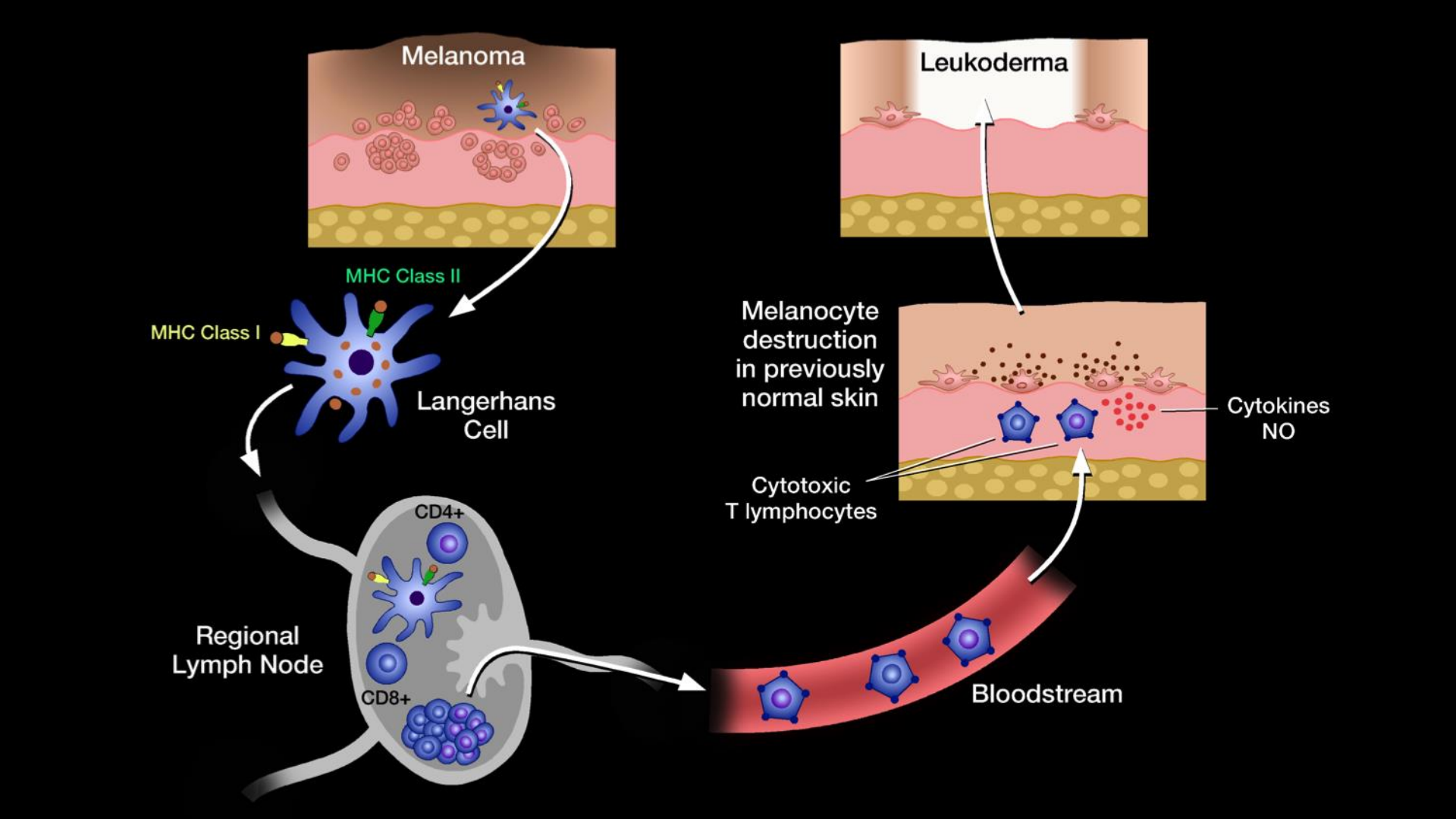
- Retrospective review (nine years), single institution
- 95 patients who developed cirAEs underwent a skin biopsy
- Vacuolar/interface histology associated with pneumonitis (p = .01)
- Psoriasiform a/w noncutaneous irAEs (p = .02), MS (p = .002)

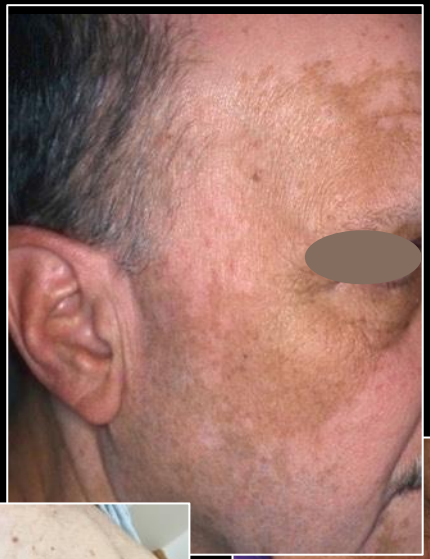
*≤20 copies/ml – 82% at onset; 66% during Rx
MS - musculoskeletal

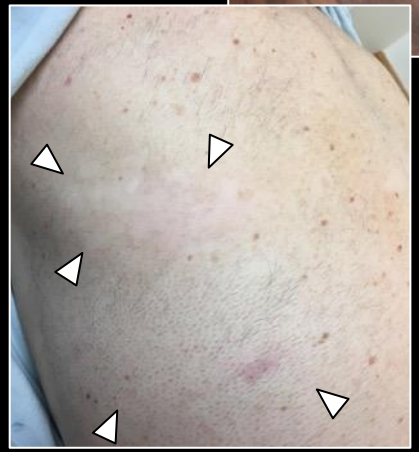
cirAE, cutaneous immune-related adverse events
JAAD 2022;86:172; *JAAD* 2022;87:651.

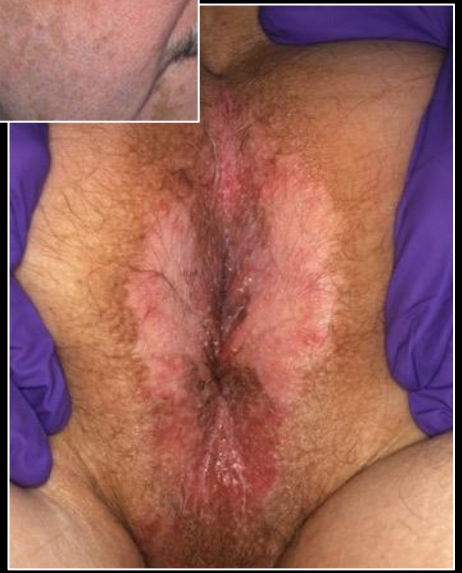
Learning Objectives

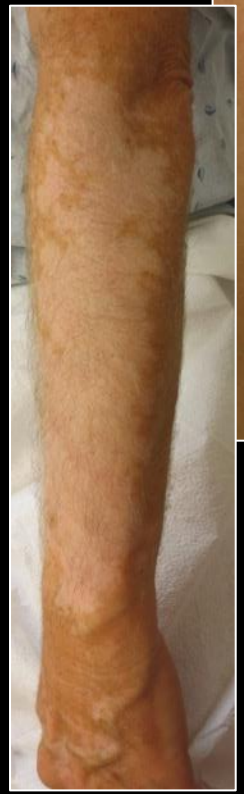
- Recognize the four major groups of cutaneous side effects:
  - morbilliform, lichenoid, eczematous, psoriasiform
  - autoimmune bullous dermatoses, e.g. BP
  - SCARs, e.g. DRESS, SJS/TEN
  - leukoderma
- Have therapeutic options beyond systemic corticosteroids

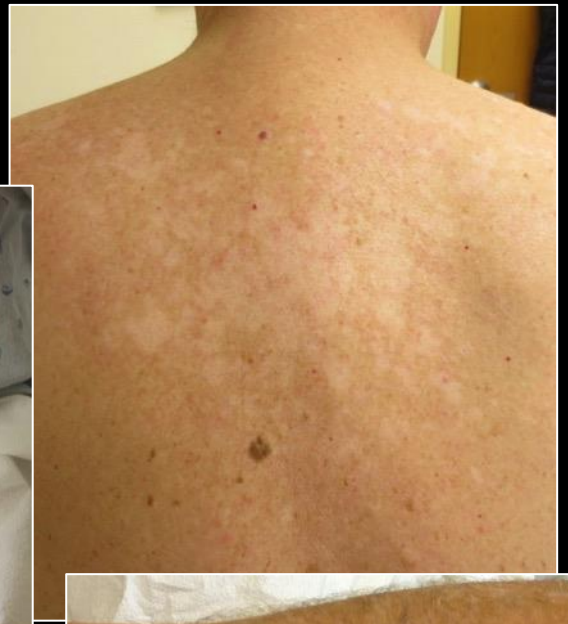

Melanoma
MHC Class II
MHC Class I
Langerhans Cell
CD4+
CD8+
Regional Lymph Node
Bloodstream
Leukoderma
Melanocyte destruction in previously normal skin
Cytokines
NO
Cytotoxic T lymphocytes

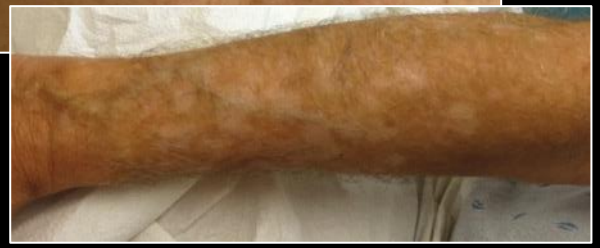


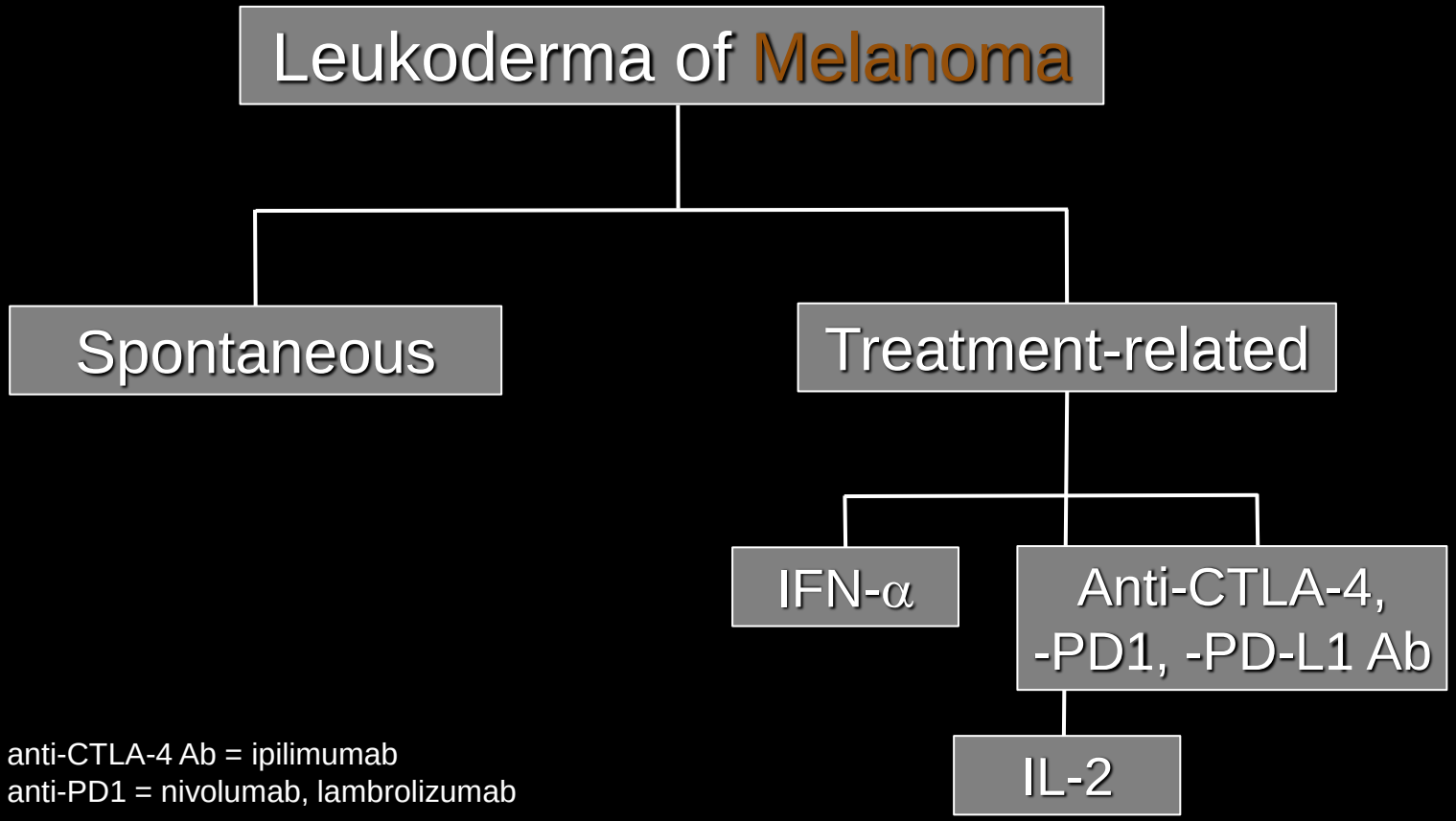








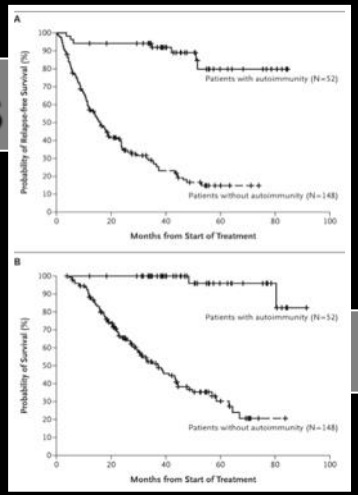




anti-CTLA-4 Ab = ipilimumab
anti-PD1 = nivolumab, lambrolizumab

Leukoderma of Melanoma

Spontaneous

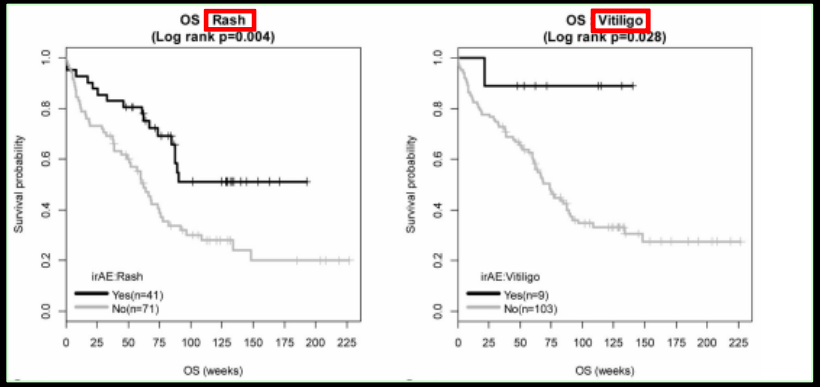


Gogas H. NEJM 2006; 354:709

Treatment-related

- IFN-α
- Anti-CTLA-4, -PD1, -PD-L1 Ab
- IL-2

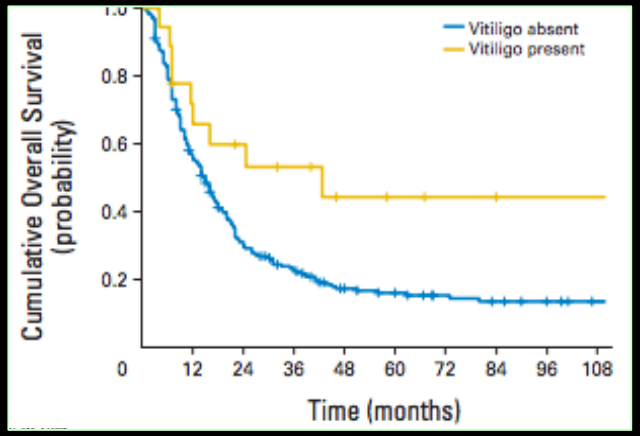
Improved overall survival in patients treated with nivolumab who developed cutaneous adverse events



- Of 148 patients,
  - 43% developed a “rash”
  - 13% developed “vitiligo”
- All patients being treated for melanoma

Clin Cancer Res 2016;22:886.

Improved overall survival in patients treated with immune checkpoint-blocking Ab who developed vitiligo-like depigmentation



- Meta-analysis of 5,737 patients
- 3.4% developed vitiligo-like depigmentation
- All patients being treated for melanoma

J Clin Oncol 2015;33:773-81.

Pruritus, morbilliform eruption
SCARs (DRESS, AGEP, SJS/TEN)

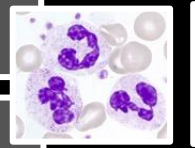
Lichenoid eruption, *SCLE, dermatomyositis, PLEVA- or PLC-like, lichen nitidus, lichen sclerosus,*

Psoriasiform, eczematous, PRP

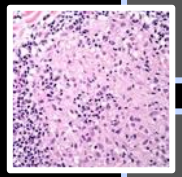
Immunobullous eruptions (BP, LPP > PV)

Leukoderma, *poliosis, alopecia areata*

Vasculitis, neutrophilic dermatoses



Acneiform/follicular lesions



Panniculitis, EN-like

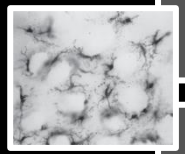
Sarcoidosis, GA, IGD, pHZ

Eruptive keratoacanthomas

Oral ulcers

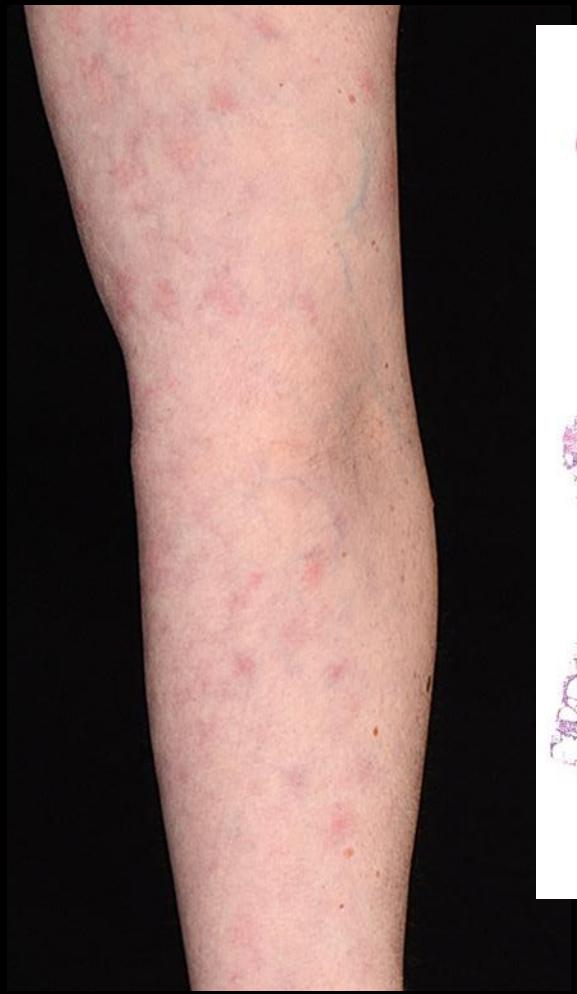
Generalized lipodystrophy

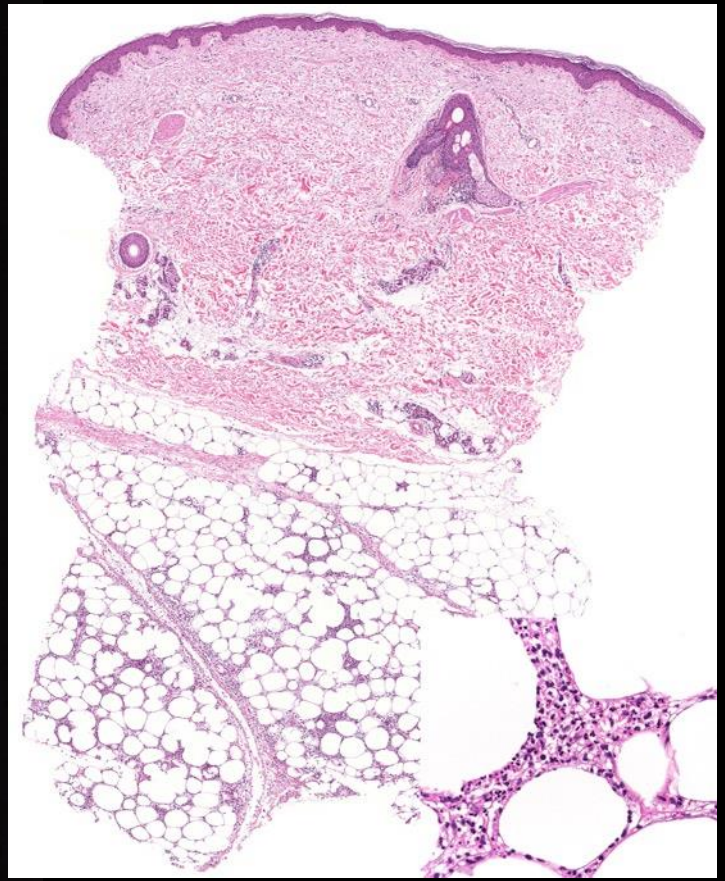
Morphea, eosinophilic fasciitis



Repigmentation of gray hair

Regressed melanocytic nevi

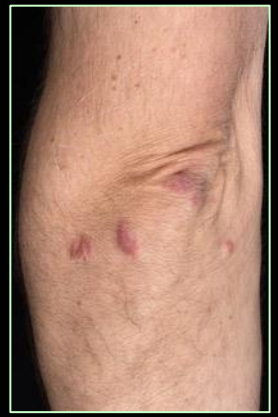


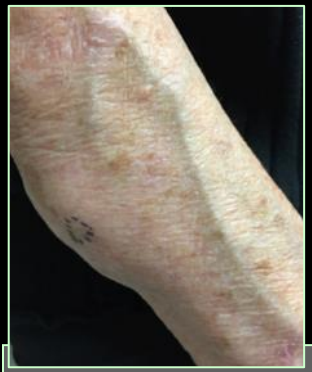


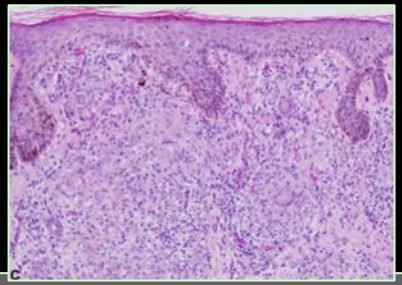
Courtesy, Lorenzo Cerroni, MD

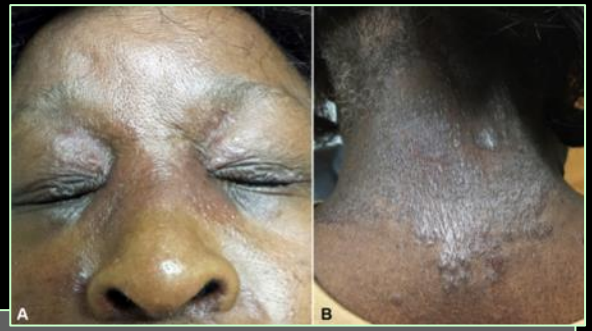
Martel J, et al.
Human Pathology
Doi:10.1016/
j.humpath.
2023.04.016

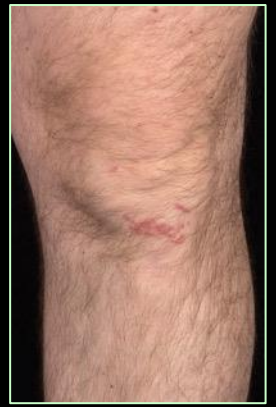
Immune checkpoint inhibitor-induced sarcoidosis *vs* post-immunotherapy reaction *vs* sarcoid-like granulomatous reaction









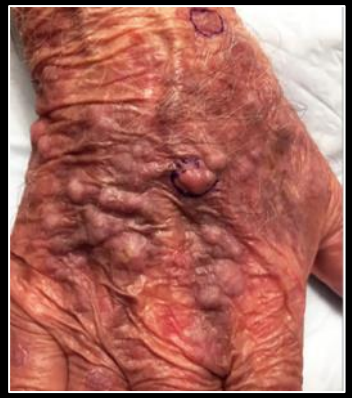


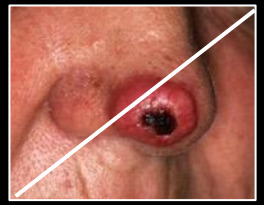
- Seen with ipilimumab, nivolumab, & pembrolizumab
- However, PD-1 overexpression has been observed in sarcoidosis patients
- Systemic involvement: pulmonary, lymph nodes, uveitis

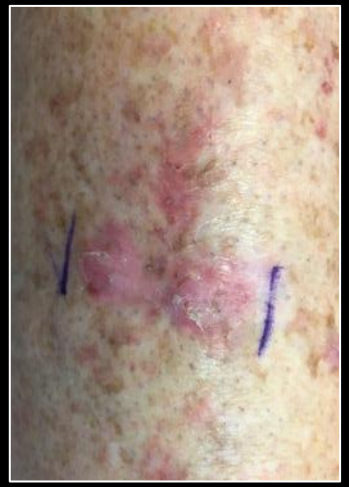
Courtesy, Lorenzo Cerroni, MD

JAAD Case Rep 2017;3:208-11
JAAD Case Rep 2016;2:290-3

Atypical squamous proliferation*







Class I CS

ILK

5-FU injection

50 mg/ml

MTX injection

25 mg/ml

*Preferred over keratoacanthoma-like squamous proliferations

JAMA Dermatol 2017;153:694-97.
JEADV 2018;32:e58-e59.

Immune checkpoint-blocking antibodies – cutaneous side effects

BE FLEXIBLE