2024 Oncology Fellows Program:
New Horizons in Quality Cancer Care™

Team-Based Management of Immunotherapy-Related Toxicities

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Fred Hutchinson Cancer Center

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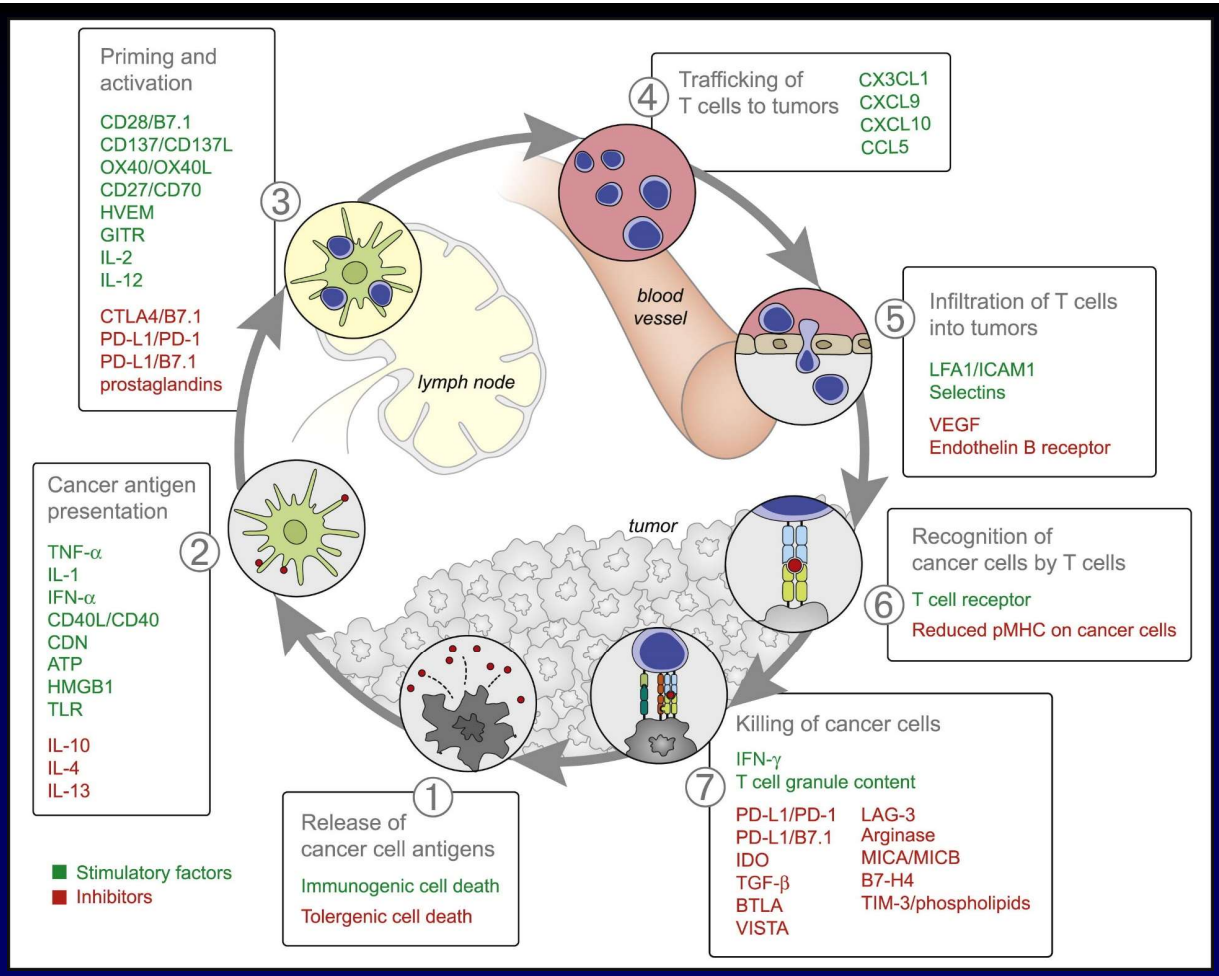
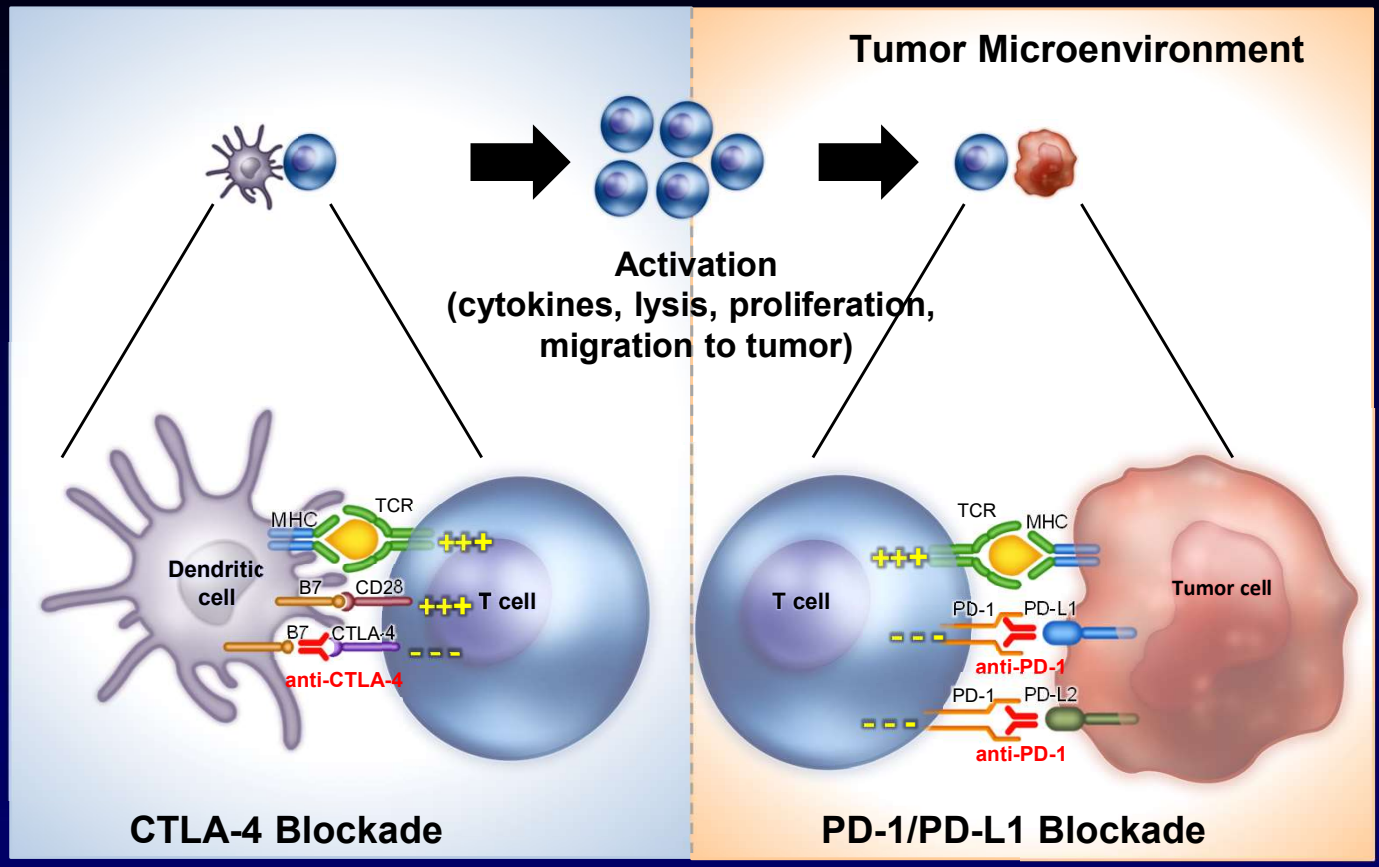
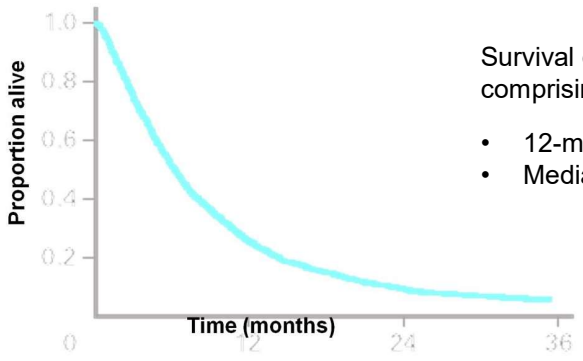


Chen DS and Mellman I
Immunity 39:1, 2013

Mechanism of action of anti-CTLA-4 and anti-PD-1/PD-L1



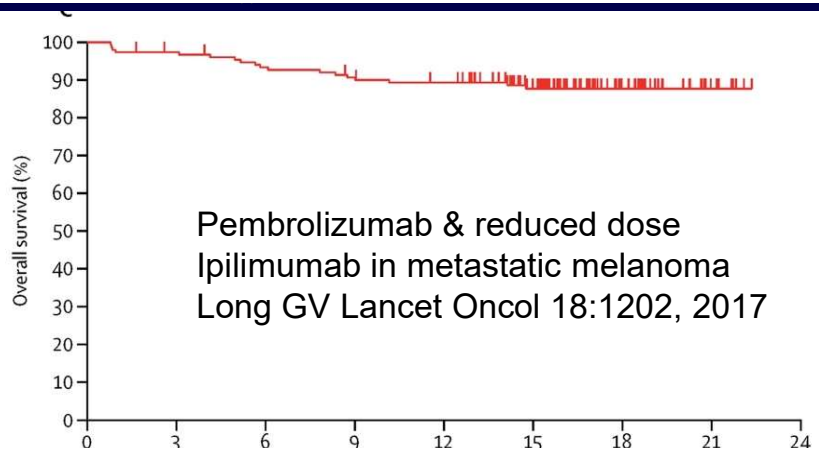
Overall Survival for Metastatic Melanoma before 2011



Adapted from Korn 2008

Survival data from 42 Phase II trials comprising >2100 Stage IV patients

- 12-month OS: 25.5 weeks
- Median OS: 6.2 months



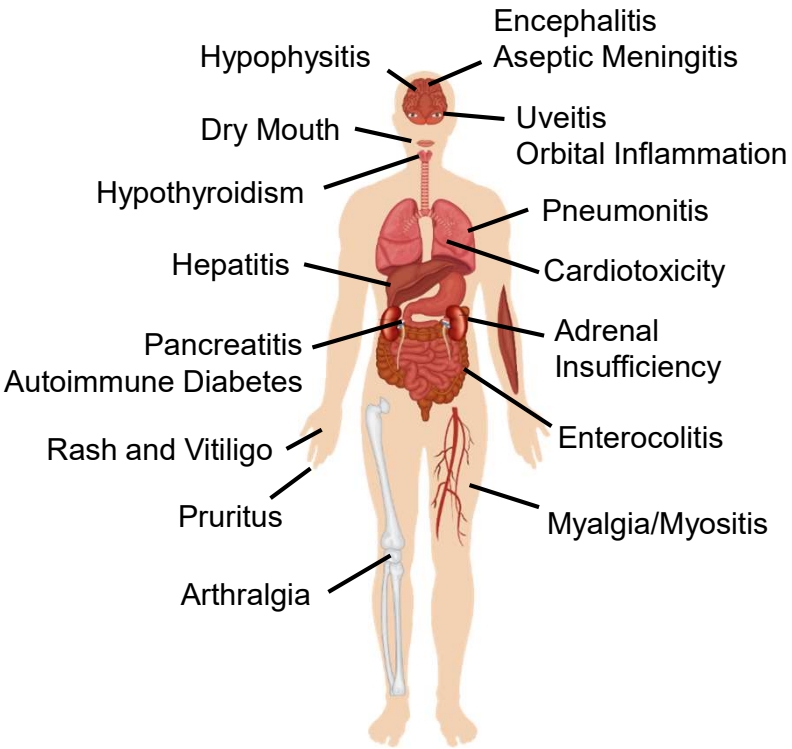
Pembrolizumab & reduced dose Ipilimumab in metastatic melanoma
Long GV Lancet Oncol 18:1202, 2017

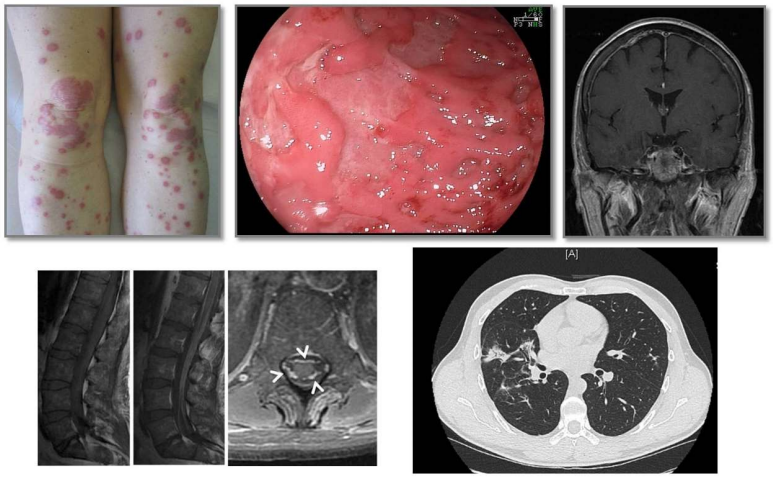
Immune checkpoint inhibitors now approved in:

- ***Melanoma***
- ***Non-small cell lung ca***
- ***Small cell lung ca***
- ***Head & neck squamous cell ca***
- ***Urothelial ca***
- ***Gastric ca***
- ***Esophageal ca***
- ***Mismatch-repair-deficient solid tumors***
- ***Hodgkin lymphoma***
- ***Merkel cell ca***
- ***Squamous cell ca of skin***
- ***Renal cell ca***
- ***Hepatocellular ca***
- ***Endometrial ca***
- ***Cervical***
- ***PMBCL***

Presented by Caroline Robert ASCO 2017

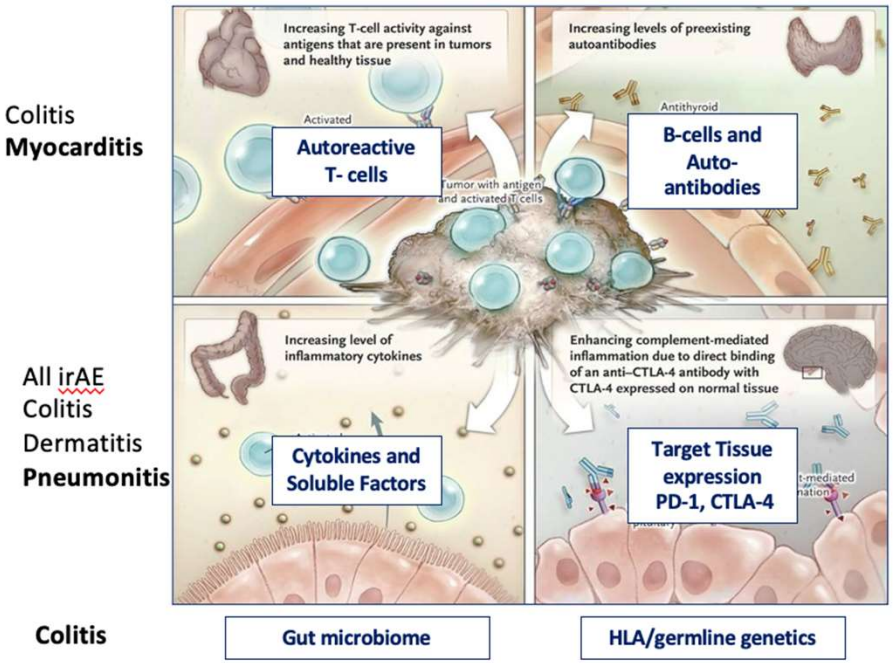
A New Spectrum of Adverse Events





Michot. Eur J Cancer. 2016;54:139. Steven. Rheumatology (Oxford). 2019;58(Suppl 7):vii29. Robert. ASCO 2017. Education session: Checkpoint inhibitor immunotherapy. Clinical images reproduced with permission of Dr. Caroline Robert, MD, PhD.

IRAEs: Unique pathogenic mechanisms



Colitis
Myocarditis

Hypophysitis
Thyroiditis
Skin toxicities
Neurologic irAEs

Severity and Timing irAEs

All irAE
Colitis
Dermatitis
Pneumonitis

Type I DM
Hypophysitis

Colitis

Type I DM
Arthritis

{Postow M et al, *NEJM* 2018}

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2024 — December 7, 2023

NCCN.org

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

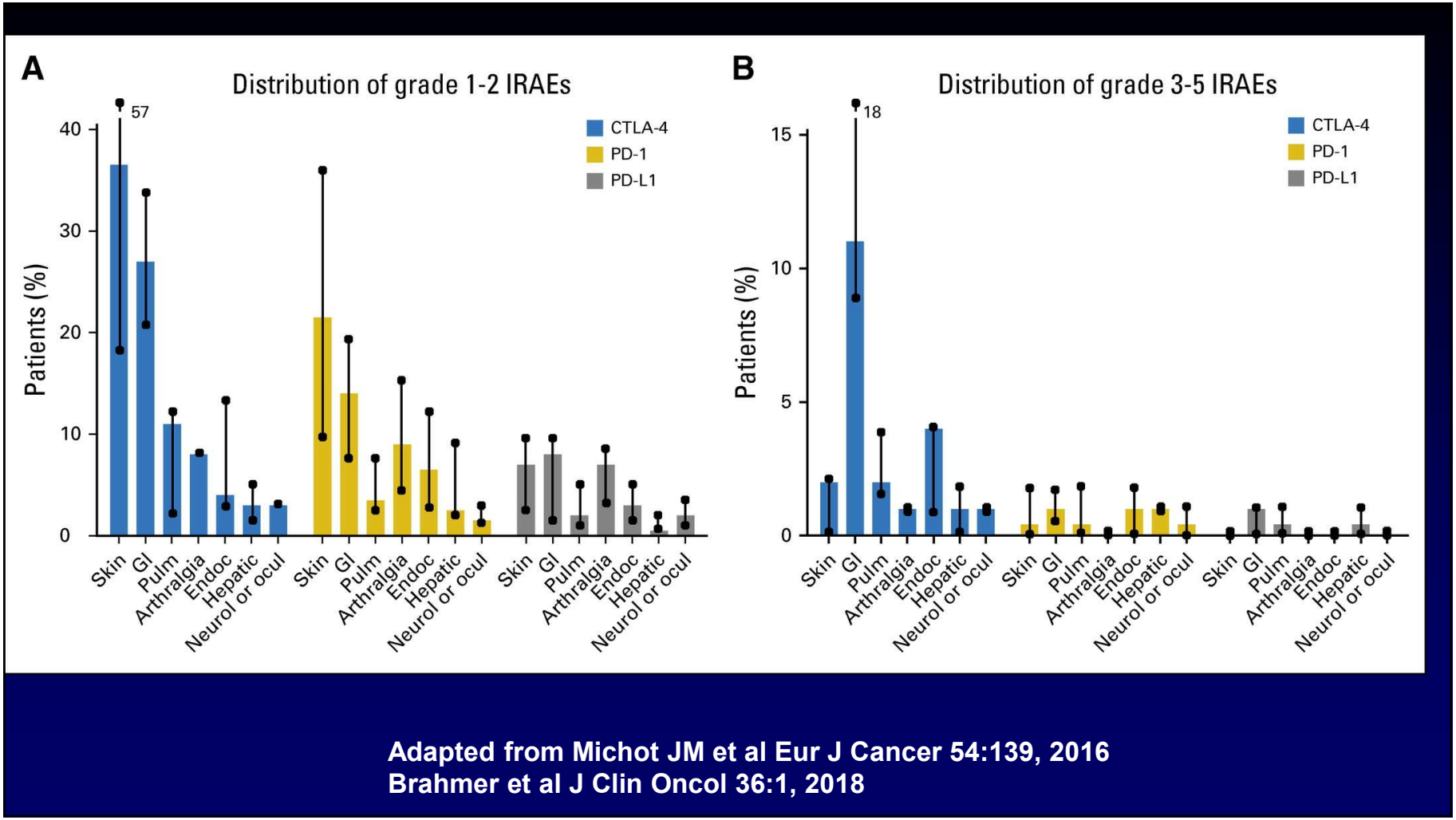
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

Published jco.org Feb 14, 2018

Learning Objectives

- *Describe the different classes of immunotherapies used for cancer treatment*
- *Recognize the immune-related adverse experiences (irAEs) that may occur with cancer immunotherapy*
- *Discuss multidisciplinary approaches to early diagnosis and treatment of irAEs*



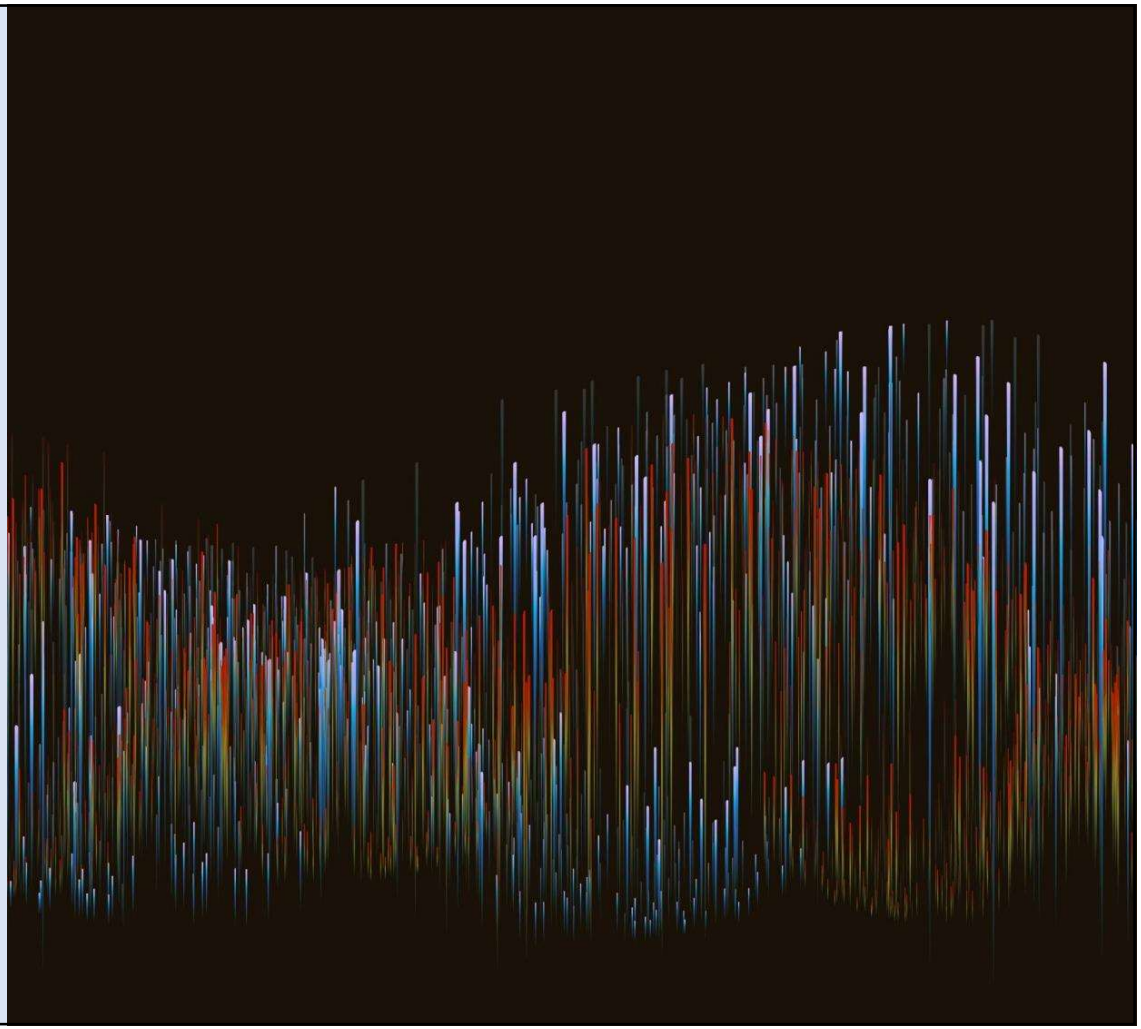
Adapted from Michot JM et al Eur J Cancer 54:139, 2016
Brahmer et al J Clin Oncol 36:1, 2018

The Bottom Line…

- Pt and caregiver education before and during treatment and survivorship.
- High level of suspicion that new symptoms are related to treatment.
- ICPi may continue with close monitoring for grade 1 toxicity (except some neuro, heme, cardiac).
- Hold ICPis for most grade 2 toxicities - consider resuming when revert to grade 1 or less. Prednisone (initial dose of 0.5 to 1 mg/kg/d) may be given.
- Hold ICPis for grade 3 toxicities. Start high-dose prednisone or IV methylprednisolone 1 to 2 mg/kg/d. Taper steroids over at least 4 - 6 weeks. If no improvement after 48 to 72 hours of HD steroids, infliximab may be offered for some toxicities.
- When toxicity reverts to grade 1 or less, resumption of ICPis may be offered; caution advised, esp. in pts with early-onset irAEs. Dose adjustments not recommended.
- In general, grade 4 toxicities warrant permanent discontinuation of ICPis, except endocrinopathies controlled by hormone replacement.

Brahmer et al J Clin Oncol 36:1, 2018

Rheumatic immune-related adverse events



Namrata Singh, MD, MSCI
University of Washington
April 4, 2024

Disclosures

- I do not have any financial relationships with ineligible companies in the past 24 months to disclose
- I will discuss investigational use of various medications in my presentation when discussing ongoing clinical trials

Outline

- Review the spectrum of various rheumatic irAEs
- Compare and contrast differences between ICI-arthritis and classic rheumatoid arthritis
- Briefly discuss options for management of rheumatic irAEs

Clinical Case

59yo F with NSCLC on COSINR clinical trial (Ipilimumab/nivolumab, radiotherapy) for 1.5 years with complete response. She is admitted to hospital with joint pain, swelling at B wrists, B knees and L ankle that did not respond to prednisone 10mg qd x7d. No small joint swelling or stiffness. No fevers, rashes, diarrhea.

Phys Ex: VSS, warm, swollen joints: only R knee with significant (moderate) effusion.

Labs: CRP 98mg/L, slight leukocytosis with high neutrophil count. RF, CCP, ANA negative.

X-rays without erosive changes, no chondrocalcinosis.

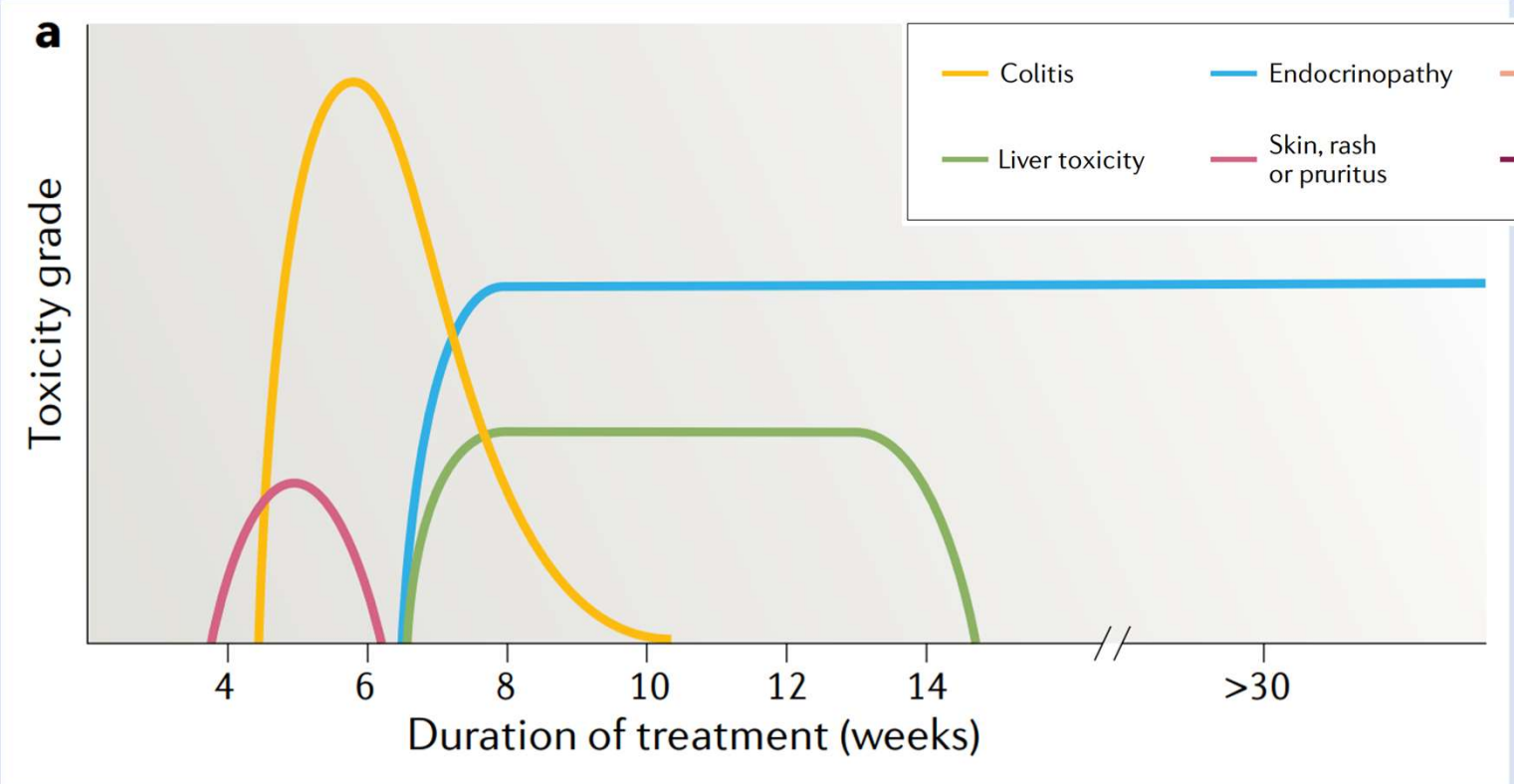
R knee arthrocentesis: WBC of 10k, PMNs predominant, no crystals, neg gram stain. Patient and oncologist would like to continue clinical trial.

Clinical Case: Polling Question

What would you recommend next?

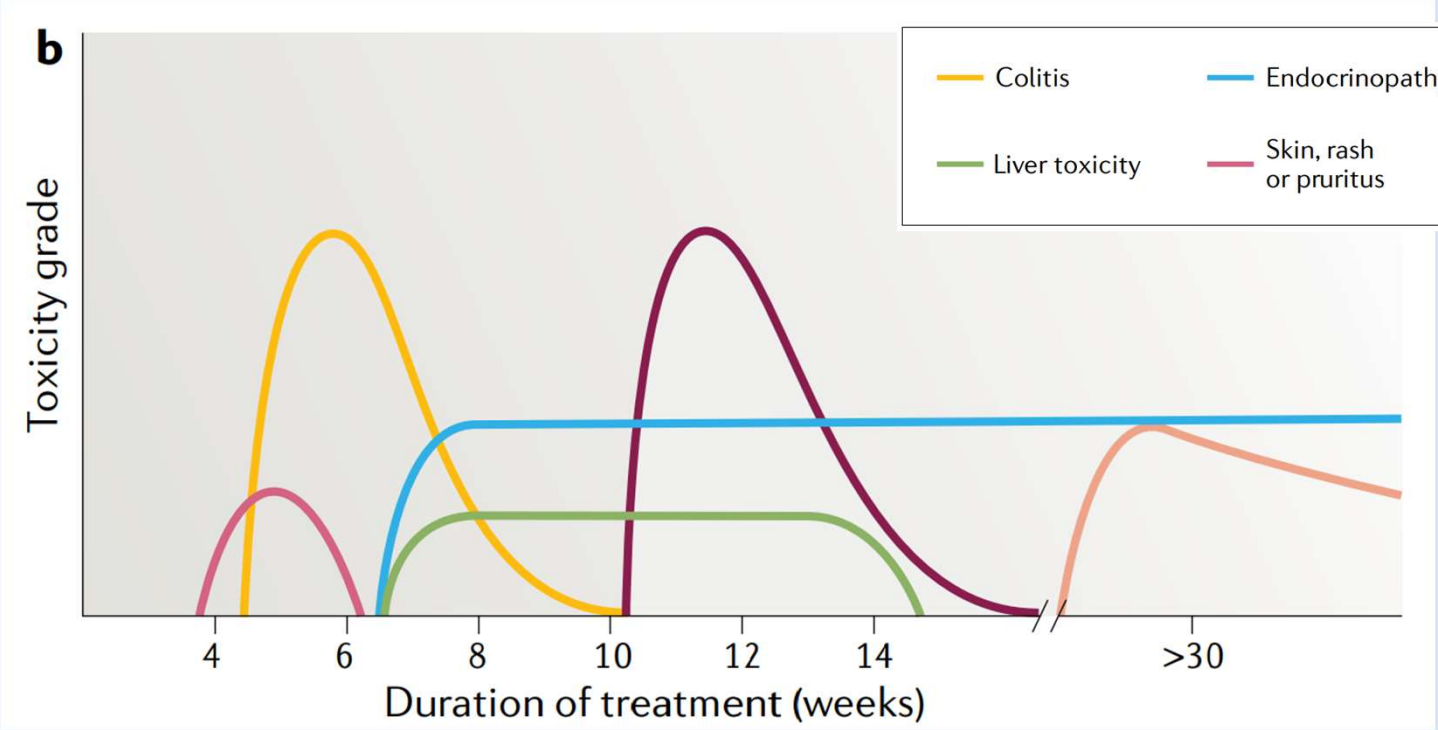
1. Take patient off trial and give 1mg/kg/d systemic steroids monotherapy
2. Keep patient on trial and give 1mg/kg/d systemic steroids and PO methotrexate
3. Take patient off trial, pred 10mg daily, CSIs to all affected joints, start weight-based hydroxychloroquine

Kinetics of main irAEs with Ipilimumab



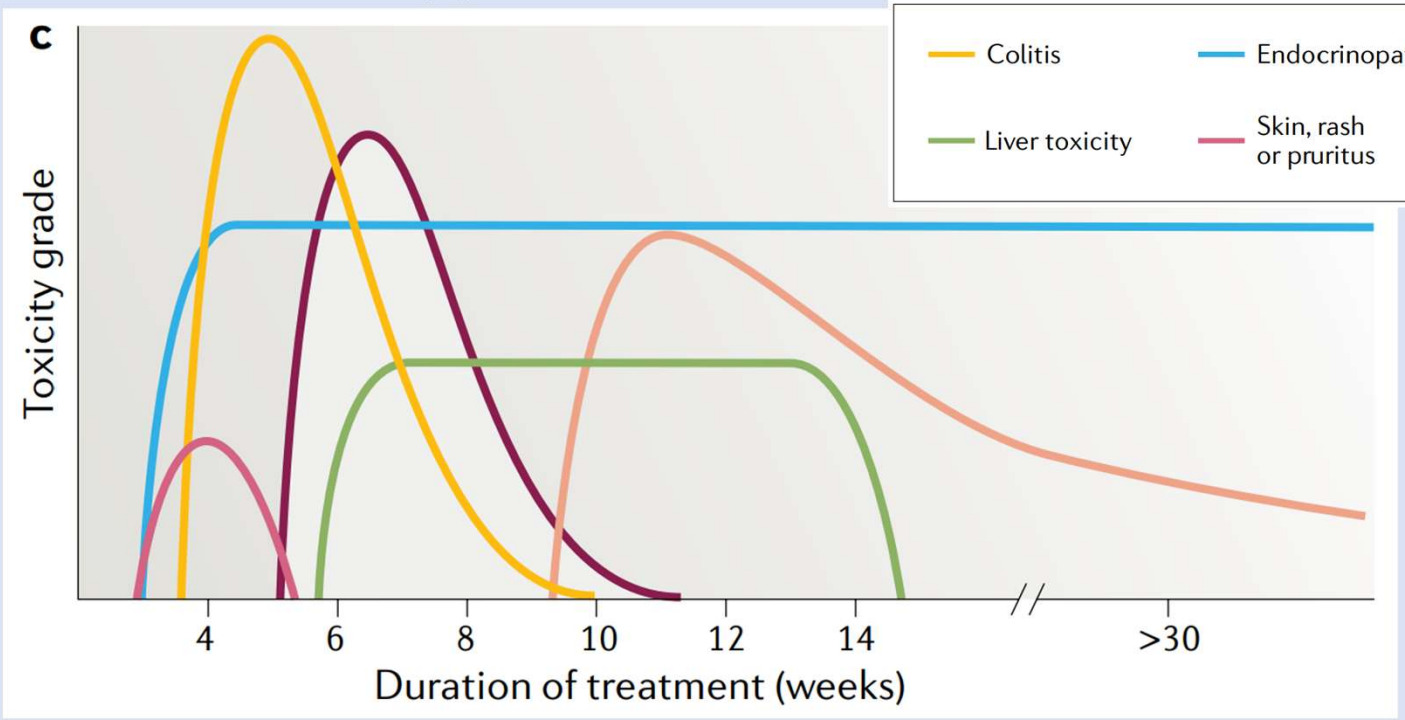
Martins F et al. Nat Rev Clin Oncol. 2019;16(9):563-580.

Kinetics of main irAEs with PD-1 or PD-L1 inhibitors



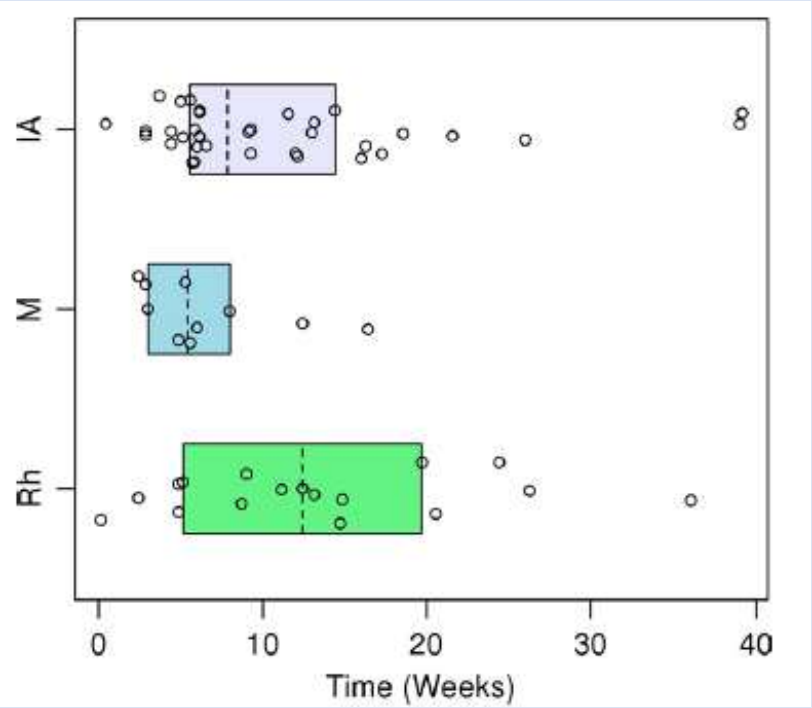
Martins F et al. Nat Rev Clin Oncol. 2019;16(9):563-580.

Kinetics of main irAEs with combination treatment (Ipilimumab + PD-1 inhibitor)



Martins F et al. Nat Rev Clin Oncol. 2019;16(9):563-580.

Time to onset of rheumatic irAEs



Richter MD et al, Arthritis Rheumatol. 2019;71(3):468-475.

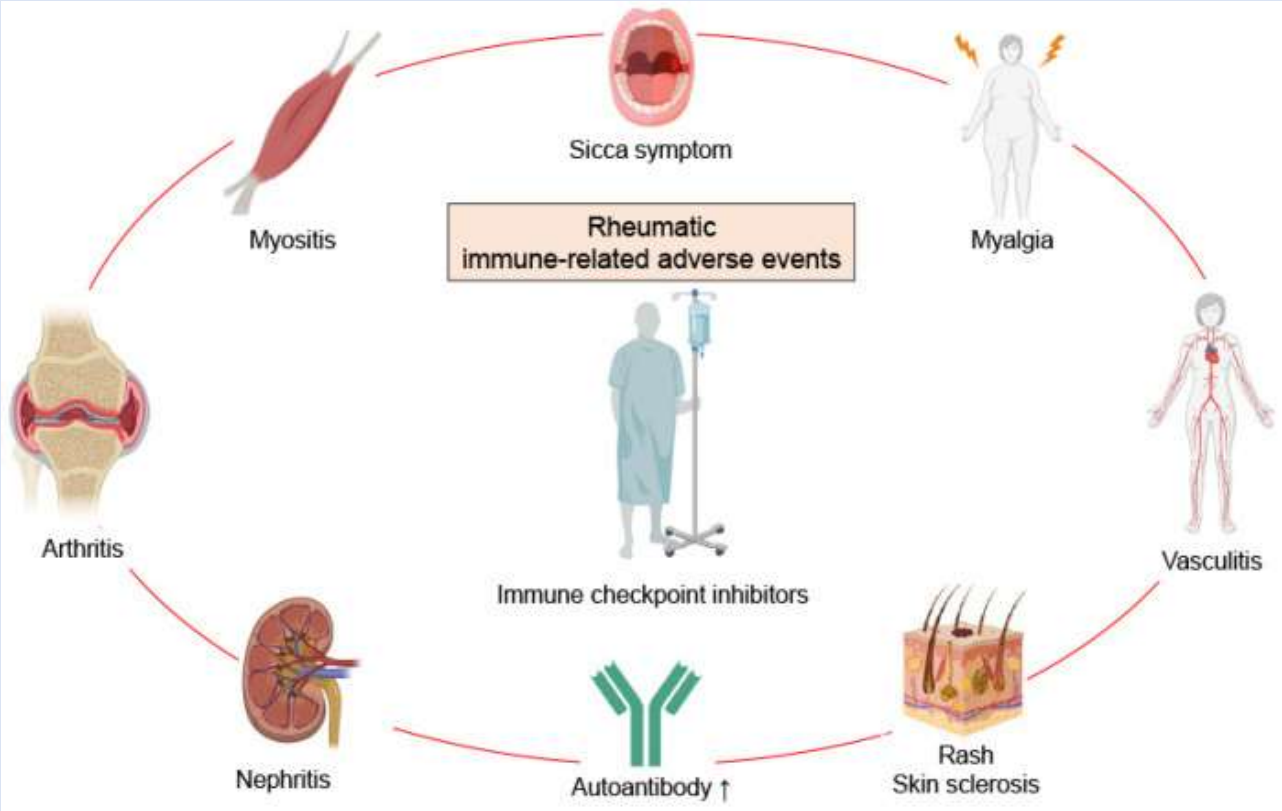
Rheumatic irAEs

- Rheumatic irAE (Rh-irAE) secondary to immunotherapy are likely underreported in clinical trials

- In a systematic review of early clinical trials of irAEs, arthralgias (1-43%) and myalgias (2-20%) were the most commonly reported Rh-irAEs.

Cappelli LC, et al. Arthritis Care Res (Hoboken). 2017;69(11):1751-1763.

Rheumatic irAEs



Int J Mol Sci. 2023 Mar; 24(6): 5643.

ir-Inflammatory arthritis (IA)

Common patterns:

(1) polymyalgia rheumatica (PMR)-like (shoulder and pelvic girdle stiffness),

(2) small joint symmetric inflammatory arthritis (predominantly hand) with diffuse tenosynovitis, and

(3) large joint, asymmetric oligoarthritis

Combination ICIs: large joint involvement plus another IRAE

Monotherapy ICI: small joint involvement & IA as the only IRAE

Cappelli et al

ir-Inflammatory Arthritis differs from classic IA

INVITED REVIEW

Immunological Reviews WILEY

Immune-related adverse events after immune check point inhibitors: Understanding the intersection with autoimmunity

Namrata Singh[1] | Anne M. Hocking[2] | Jane H. Buckner[2]

ir-Inflammatory arthritis (ir-IA) differs from classic IA

- No predilection by sex reported
- Most seronegative
- Frequent enthesitis/tenosynovitis - requires higher doses of corticosteroids than traditionally used
- Although ir-IA have occurred after 1 dose, may occur up to 2 yrs after ICIs.

ir-IA

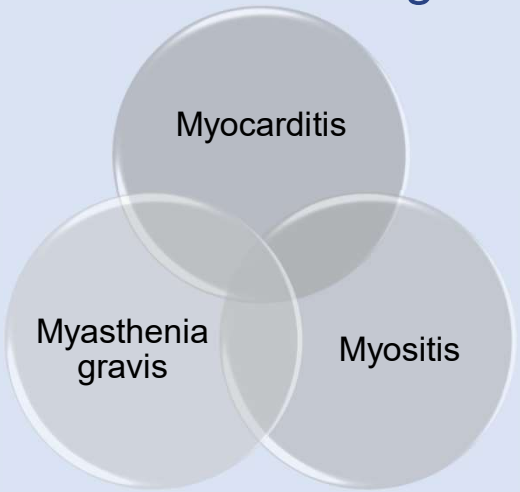
- ir-IA may persist after ICI cessation.
- Often become chronic, despite stopping ICIs, unlike other irAEs such as colitis and pneumonitis.
- Longer ICI exposure, receipt of combination ICI therapy, and a history of other irAEs ⇧ the risk of IA persistence
- Persistent arthritis may be associated with better tumor response

Braaten TJ et al. Ann Rheum Dis. 2020;79(3):332-338.

ir-Myositis

- Ir-Myositis: increasingly recognized irAE although remains relatively uncommon, affecting < 1% of patients exposed to ICI

- **Overlap with myocarditis and myasthenia gravis (3Ms)** more frequent than when observed in the setting of traditional immune myopathies



Touat M et al. Neurology 2018;91(10):e985-e994;
Anquetil C et al. Circulation 2018;138(7):743-745.

ir-Myositis

- Although a less common irAE, it is associated with a high case fatality rate (17%), second only to myocarditis (39.7%).

- Mortality in cases of ir-Myositis overlapping with myocarditis or other neuromuscular symptoms is even higher (over 50% in one study), and results from cardiac or respiratory failure.

ir-Myositis

In a detailed series to date (n = 10), Touat et al described a unique constellation of features that characterize ir-Myositis:

(1) early (within 2 mos of ICI initiation) and severe onset of symptoms;

(2) limb-girdle weakness associated with myalgias, as well as axial and oculomotor weakness;

(3) striking CK elevations with myopathic changes on electromyography;

(4) absence of myositis-specific and anti-acetylcholine receptor antibodies;

(5) necrosis and inflammation on histopathology; and

(6) good response to ICI discontinuation with or without corticosteroid

Touat M et al. Neurology 2018;91(10):e985-e994.

ir-Myositis

Table 2 Electrophysiologic and biological findings in patients with irMyositis (n = 10)

Electrodiagnostic studies, n (%)	
Abnormal test result	9/9 (100)
Electromyography suggestive of myopathic process[a]	9/9 (100)
Abnormal motor and/or sensory conduction	1/9 (11)
Decrement on repetitive stimulation	0/8 (0)
Laboratory tests	
Abnormal CK levels, n (%)	10/10 (100)
Median CK (range), U/L	2,668 (1,059–16,620)
Abnormal troponin T, n (%)	7/9 (78)
Abnormal AST/ALT, n (%)	10 (100)
Abnormal GGT, n (%)	1 (10)[b]
Positive anti-AChR antibodies, n (%)	0/7 (0)
Positive myositis-associated antibodies, n (%)[c]	0/7 (0)
Cardiac MRI with contrast	
Subepicardial enhancement, n (%)	2/4 (50)

Touat M et al. Neurology 2018;91(10):e985-e994.

ir-Vasculitis

- Most frequently reported: large-vessel vasculitis, including giant cell arteritis (GCA) and isolated aortitis, and nervous system vasculitis
- Median duration of ICI therapy preceding symptom onset: 3 months (range 1 week - 18 months)
- Little difference between the clinical, biological, or histopathological presentation of ir-Vasculitis and idiopathic forms of these diseases.

Daxini A, et al. Clin Rheumatol. 2018;37(9):2579-2584.

Special population

- Patients with pre-existing autoimmune disease (AID)

Annals of Internal Medicine

REVIEW

Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease

A Systematic Review

Noha Abdel-Wahab, MD, PhD; Mohsin Shah, MD; Maria A. Lopez-Olivo, MD, PhD; and Maria E. Suarez-Almazor, MD, PhD

- 75% of patients develop an adverse event
  - ❖ Flare occur in 50%, and de novo irAEs in 34%
- No difference in frequency of adverse events in patients with active versus inactive autoimmune disease at ICI initiation
- Patients receiving immunosuppressive therapies at ICI initiation therapy seemed to have fewer adverse events
- Management of adverse events required
  - ❖ High dose corticosteroids in 62%
  - ❖ Disease-modifying antirheumatic drugs (DMARDs) and other immunosuppressive therapies in 16%
  - ❖ Permanent ICI discontinuation in 17%

Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: a retrospective, comparative, cohort study

Kaitlin R McCarter, Taylor Wolfgang, Senada Arabelovic, Xiaosong Wang, Kazuki Yoshida, Emily P Banasiak, Grace Qian, Emily N Kowalski, Kathleen M M Vanni, Nicole R LeBoeuf, Elizabeth I Buchbinder, Lydia Gedmintas, Lindsey A MacFarlane, Deepak A Rao, Nancy A Shadick, Ellen M Gravallese, Jeffrey A Sparks

Lancet Rheumatology May 2023

Study design

- Study of the Mass General Brigham Integrated Healthcare system and Dana-Farber Cancer Institute in Boston; April 2011-April 2021
- Identified those initiating ICI with pre-existing RA
- Matched up to 3 non-RA comparators at the index date of ICI initiation by sex (recorded as male or female), calendar year, ICI target, and cancer type and stage

McCarter KR, et al. *Lancet Rheumatol*. 2023;5(5):e274-e283

Outcomes and analysis plan

- Co-primary outcomes: time from index date to death and time to the first irAE, measured using an adjusted Cox proportional hazards model.

- Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality. Person-time was set as the date of ICI initiation and censored at the time of death or last follow-up.

McCarter KR, et al. *Lancet Rheumatol*. 2023;5(5):e274-e283

Table 1. Baseline Demographics

	Pre-existing rheumatoid arthritis cases (n=87)	Matched non-rheumatoid arthritis comparators (n=203)	p value
Demographics, lifestyle, and comorbidities			
Age, years	72·0 (63·1–77·6)	71·2 (63·2–76·9)	0·55*
Sex	..	..	0·71*
Female	52 (60%)	126 (62%)	..
Male	35 (40%)	77 (38%)	..
Race†	..	..	0·96
White	81 (93%)	187 (92%)	..
Black	3 (3%)	7 (3%)	..
Asian	1 (1%)	2 (1%)	..
Calendar year	2018 (2017–19)	2018 (2017–19)	0·42*
Smoking status	..	..	0·56
Never	24 (28%)	51 (25%)	..
Past	57 (66%)	130 (64%)	..
Current	6 (7%)	22 (11%)	..
Smoking pack-years	20 (0–40)	20 (0–40)	0·90
Body-mass index, kg/m²†	25·8 (22·0–29·4)	26·0 (23·3–31·0)	0·065
Charlson Comorbidity Index	8 (6–9)	8 (3–10)	0·44

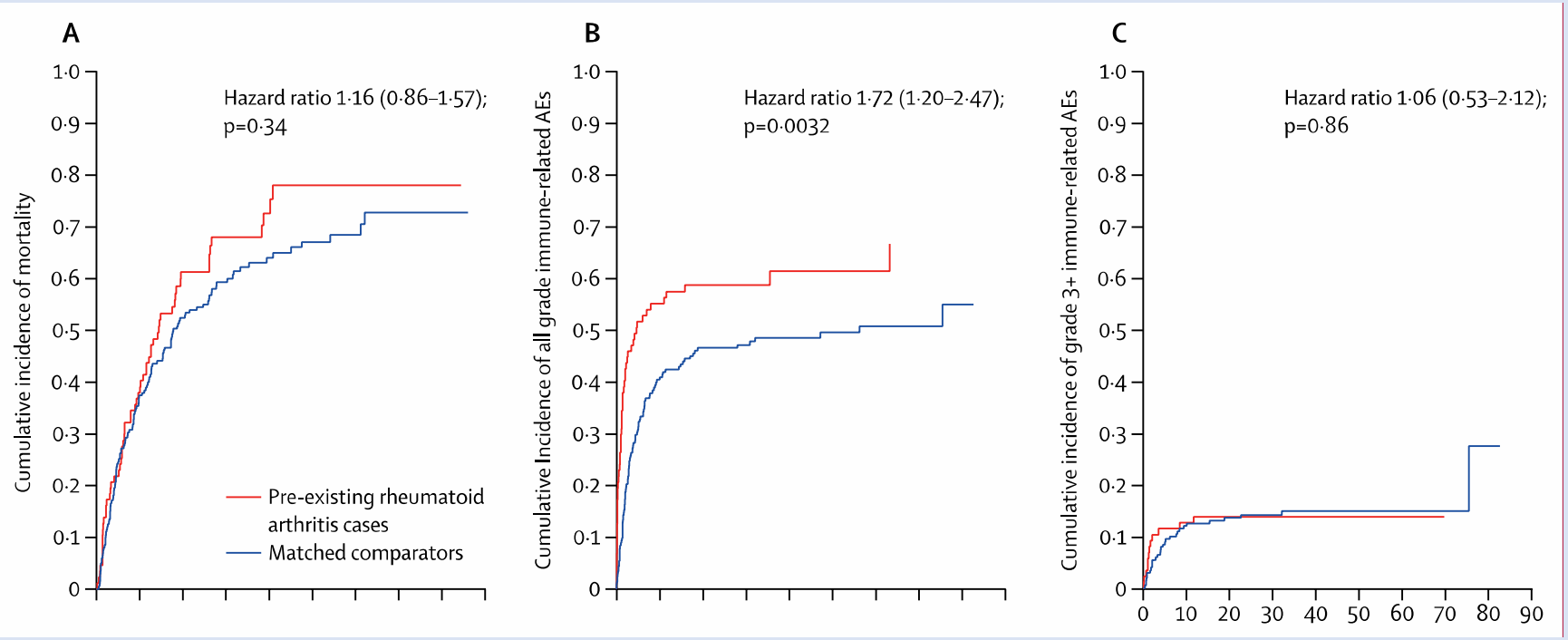
	Pre-existing rheumatoid arthritis cases (n=87)	Matched non-rheumatoid arthritis comparators (n=203)	p value
(Continued from previous page)			
Rheumatoid arthritis characteristics			
Rheumatoid arthritis duration, years	9·4 (4·6–16·5)	..	..
Seropositive	49/71 (69%)	..	..
Positive for anti-cyclic citrullinated peptide	35/57 (61%)	..	..
Positive for rheumatoid factor	37/58 (64%)	..	..
Most recent disease activity within 1 year of index date			
Remission	29/68 (43%)	..	..
Low	25/68 (37%)	..	..
Moderate	11/68 (16%)	..	..
High	3/68 (4%)	..	..
Glucocorticoid	57 (66%)	..	..
Prednisone dose, mg per day	10 (5–26)	..	..
Any DMARD	40 (46%)	..	..
Any conventional synthetic DMARD	31 (36%)	..	..
Methotrexate	19 (22%)	..	..
Hydroxychloroquine	11 (13%)	..	..
Any biological or targeted synthetic DMARD	22 (25%)	..	..
Tumour necrosis factor inhibitor	10 (11%)	..	..
Bone erosions or deformities	27 (31%)	..	..
Interstitial lung disease	13 (15%)	..	..
Rheumatoid vasculitis	1 (1%)	..	..
Sjögren's syndrome	0	..	..
Felty syndrome	0	..	..

McCarter KR, et al. *Lancet Rheumatol*. 2023;5(5):e274-e283

Cancer characteristics			
Target of immune checkpoint inhibitor	..	..	0·94*
PD-1	80 (92%)	188 (93%)	..
PD-L1	4 (5%)	9 (4%)	..
CTLA-4	1 (1%)	1 (<1%)	..
Combination	2 (2%)	5 (2%)	..
Type of cancer			
Lung	43 (49%)	114 (56%)	0·29*
Non-small cell	41 (47%)	112 (55%)	0·21*
Small cell	2 (2%)	2 (1%)	0·27*
Melanoma	21 (24%)	50 (25%)	0·93*
Genitourinary tract	6 (7%)	12 (6%)	0·75*
Gastrointestinal tract	3 (3%)	6 (3%)	0·27*
Head and neck	4 (5%)	7 (3%)	0·22*
Haematological	3 (3%)	3 (1%)	0·19*
Brain	2 (2%)	5 (2%)	0·32*
Other‡	5 (6%)	6 (3%)	0·25*
Cancer duration, years	0·9 (0·1–2·4)	0·6 (0·1–1·9)	0·66
Previous chemotherapy	53 (61%)	91 (45%)	0·012
Previous hormonal therapy	1 (1%)	4 (2%)	0·36
Previous radiation	48 (55%)	71 (35%)	0·0014
Previous stem-cell transplantation	2 (2%)	2 (1%)	0·27
Previous CAR-T therapy	0	1 (<1%)	0·70
Previous chemotherapy, hormonal therapy, radiotherapy, stem-cell transplantation, or CAR-T	53 (61%)	94 (46%)	0·023

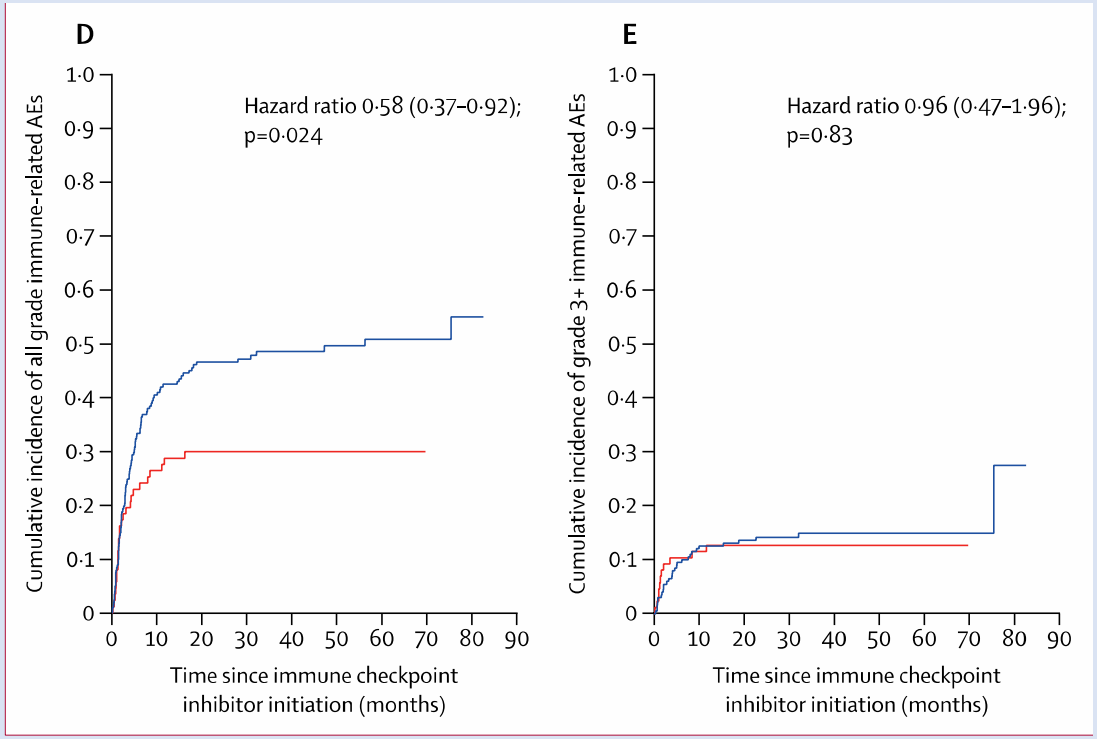
McCarter KR, et al. *Lancet Rheumatol*. 2023;5(5):e274-e283

Cumulative incidence curves after ICI initiation



McCarter KR, et al. *Lancet Rheumatol*. 2023;5(5):e274-e283

Cumulative incidence curves after ICI initiation



McCarter KR, et al. *Lancet Rheumatol*. 2023;5(5):e274-e283

Strengths and Limitations

Strengths

- Well-designed comparative cohort study
- Important data on ICI use among patients with pre-existing RA receiving ICIs for cancer

Limitations

- Only analyzed patients with pre-existing RA whose oncologists chose to use ICIs, so no data presented on patients whose cancer was not treated with ICIs perhaps due to active RA or the perceived risk of poor outcomes. Thus, these findings might not apply to all patients with RA, particularly those with high disease activity or those whose oncologist chose not to initiate ICIs.
- Could not examine whether changes in immunosuppression affected outcomes.
- Single health-care system, so results might not be generalizable to other geographic areas.

Treatment of irAEs

Over the past few years, multiple groups have released clinical guidelines on management of irAE secondary to immunotherapy, based on expert consensus:

- National Comprehensive Cancer Network (NCCN)
- Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group
- European Society of Medical Oncology (ESMO)
- American Society of Clinical Oncology (ASCO)

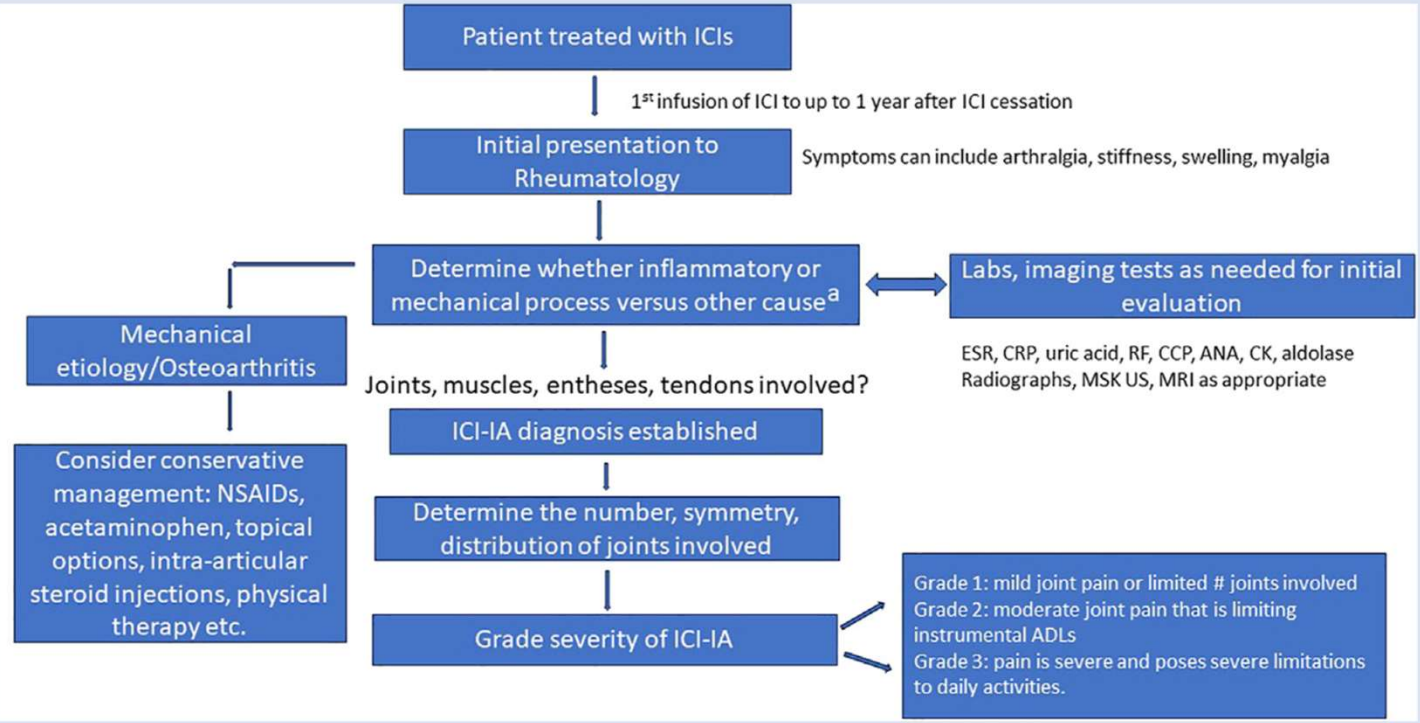
Management of ir-IA

Inflammatory Arthritis due to Immune Checkpoint Inhibitors

Current Approaches to Management

Namrata Singh, MD, MSCI[a], Anupama Shahane, MD, MPH[b], Jeffrey A. Sparks, MD, MMSc[c], Samuel Bitoun, MD, PhD[d], Laura C. Cappelli, MD, MHS[e,*]

Approach to management of ir-IA



Singh, N et al. RDCI 2024

National Comprehensive Cancer Network®

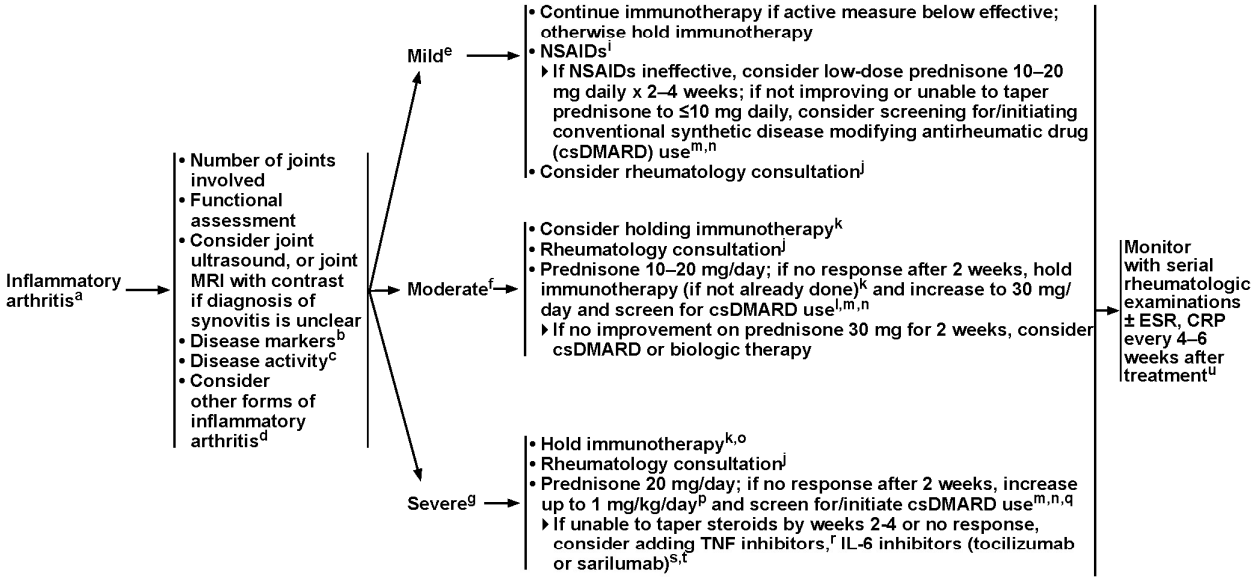
NCCN Guidelines Version 1.2024
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

MUSCULOSKELETAL ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT[h]



Footnotes on ICI_MS-1A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Management of Immune Checkpoint Inhibitor-Related Toxicities

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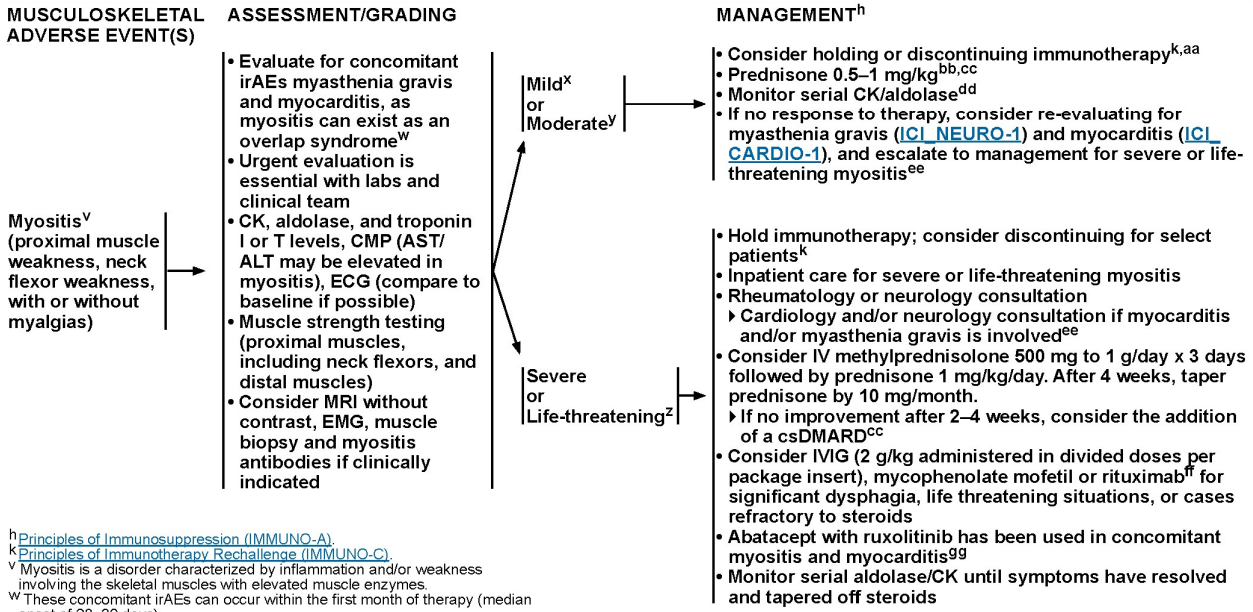

[h] Principles of Immunosuppression (IMMUNO-A).
[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[v] Myositis is a disorder characterized by inflammation and/or weakness involving the skeletal muscles with elevated muscle enzymes.
[w] These concomitant irAEs can occur within the first month of therapy (median onset of 28–30 days).
[x] CPK elevation less than 1000 mcg/L, mild weakness and minimal impairment of ADLs; no myasthenia gravis and/or myocarditis co-existing with myositis.
[y] Moderate pain associated with objective weakness and/or elevation of muscle enzymes (CK or aldolase) limiting self-care ADLs.
[z] Urgent intervention is indicated.
[aa] Would not recommend holding ICI if no elevation in CPK or evidence of active myositis.
[bb] If improving after 2–4 weeks, begin slow prednisone taper by 5 mg/week. If unable to taper, or no response, add csDMARD.
[cc] Methotrexate (with folic acid) as a steroid-sparing agent to speed up taper. If contraindication to methotrexate, consider mycophenolate mofetil or azathioprine.
[dd] Do not need to trend aldolase unless aldolase elevation is the only evidence of myositis (CPK normal). Aldolase can be falsely elevated if blood sample is hemolyzed.
[ee] There have been case reports of a life-threatening triad of myositis, myocarditis, and myasthenia gravis.
[ff] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[gg] Salem JE, et al. Cancer Discov 2023;13:1100-1115.

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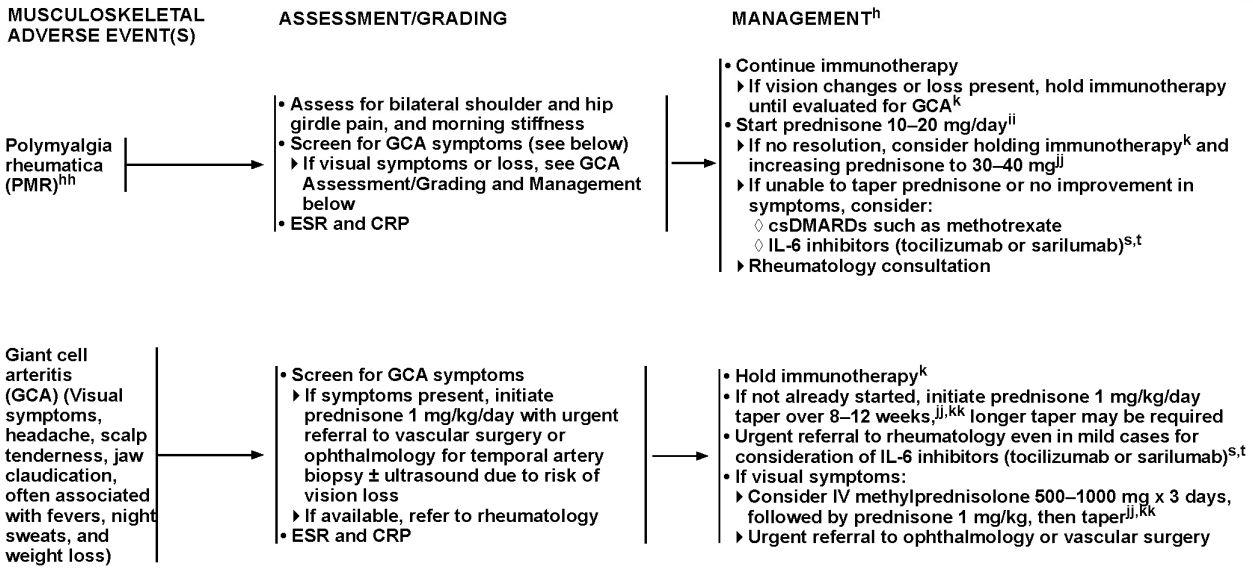

[h] Principles of Immunosuppression (IMMUNO-A).
[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[s] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab or sarilumab), screen for diverticular disease prior to initiating therapy and use with caution in patients with clinically active diverticular disease.
[t] An FDA-approved biosimilar is an appropriate substitute for tocilizumab.
[hh] Pain and/or stiffness in the morning usually involving bilateral shoulders and hip girdle region that limits instrumental or self-care ADLs.
[ii] PMR requires a slow taper. If improving in 4 weeks, taper by 2.5 mg every 2–4 weeks.
[jj] PJP prophylaxis if it is anticipated that patient will be treated with >20 mg prednisone for >4 weeks.
[kk] GCA requires a slower taper. Goldstein BL, et al. Arthritis Rheumatol 2014;66:768-769; Micaily I, et al. Ann Oncol 2017;28:2621-2622; Calabrese LH, et al. Nat Rev Rheumatol 2018;14:569-579.

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IL-6i for management of irAEs

Journal for ImmunoTherapy of Cancer

Selective immune suppression using interleukin-6 receptor inhibitors for management of immune-related adverse events

Faisal Fa'ak,[1] Maryam Buni,[2] Adewunmi Falohun,[2] Huifang Lu,[2] Juhee Song,[2] Daniel H Johnson,[3] Chrystia M Zobniw,[2] Van A Trinh,[2] Muhammad Osama Awiwi,[2] Nourel Hoda Tahon,[2] Khaled M Elsayes,[2] Kaysia Ludford,[2] Emma J Montazari,[2] Julia Chernis,[4] Maya Dimitrova,[1] Sabina Sandigursky,[1] Jeffrey A Sparks,[5] Osama Abu-Shawer,[5] Osama Rahma,[5] Uma Thanarajasingam,[6] Ashley M Zeman,[6] Rafee Talukder,[7] Namrata Singh,[7] Sarah H Chung,[7] Petros Grivas ,[7] May Daher,[2] Ala Abudayyeh,[2] Iman Osman,[1] Jeffrey Weber ,[1] Jean H Tayar,[2] Maria E Suarez-Almazor,[2] Noha Abdel-Wahab,[2,8] Adi Diab [2]

1. This is the largest study assessing the impact of anti-interleukin-6 receptor (anti-IL-6R) therapy on irAE and antitumor immune response.
2. Early introduction of anti-IL6-R therapy resulted in a rapid irAE improvement compared with delayed treatment as a second line of therapy. Also, comparable efficacy was achieved with SC and IV administrations of anti-IL-6R therapy in the largest irAE subgroup of patients with ICI-induced arthritis.
3. Anti-IL-6R therapy did not seem to compromise the ICI-induced tumor response.

Multidisciplinary collaborations at the UW

1. **irAE listserv** –Sometimes clinicians want to touch base for a quick discussion amongst subspecialists
2. **Tumor board** – Generally 2-3 cases are discussed. Once q2 months
3. **Expert panel** – We have a short list of dedicated experts who are willing to serve as faculty discussants
4. **Dedicated clinics** – Rheum-irAE clinic at the UW Roosevelt site

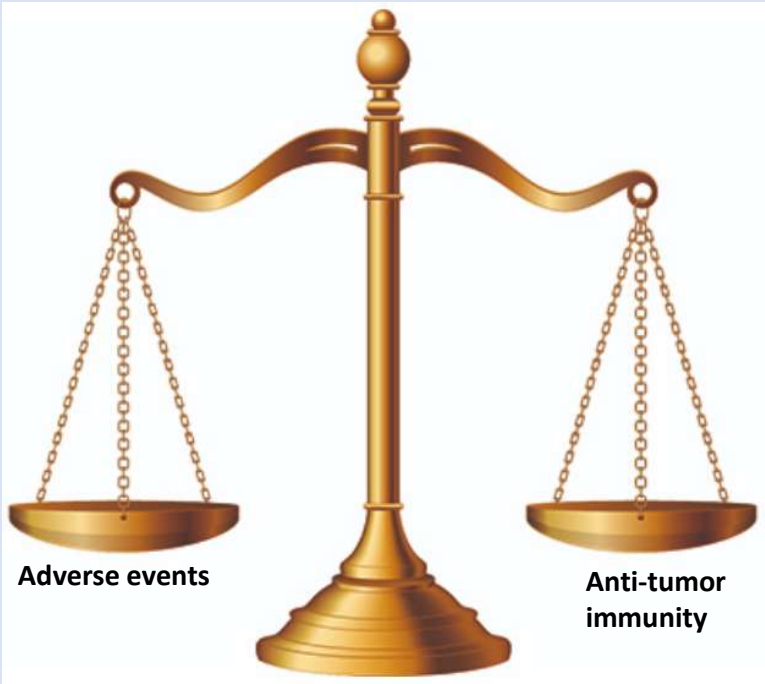
Restarting ICI after an irAE

- Depends on—
  - type and severity of irAE,
  - stage and response of underlying malignancy,
  - alternative treatment options, and
  - needs discussion between the patient, oncologist and other specialists.

Effect of irAE treatment on cancer outcomes

- No prospective, randomized controlled trials evaluating whether concomitant immunosuppressive therapy negates the anti-tumor response of immunotherapy

- Long-term data are needed, in larger populations, across various cancer types, and manifesting with different AE



Current Clinical Trials for Management of irAEs

Clinical Trials	Trial ID
Study of Rituximab or Tocilizumab for Patients With Steroid-Dependent Immune- Related Adverse Events (irAEs)	NCT04375228
Checkpoint Inhibitor Induced Colitis and Arthritis - Immunomodulation With IL-6 Blockade and Exploration of Disease Mechanisms	NCT03601611
A Phase II Study of the Interleukin-6 Receptor Inhibitor Tocilizumab in Combination With Ipilimumab and Nivolumab in Patients With Unresectable Stage III or Stage IV Melanoma	NCT03999749
TNF-Inhibitor as Immune Checkpoint Inhibitor for Advanced MELanoma (TICIMEL)	NCT03293784
Infliximab or Vedolizumab in Treating Immune Checkpoint Inhibitor-Related Colitis in Patients With Genitourinary Cancer or Melanoma	NCT04407247
Role of Gut Microbiome and Fecal Transplant on Medication- Induced GI Complications in Patients With Melanoma or Genitourinary Cancer	NCT03819296

Future directions

- Better clinical correlates
- Predictive biomarkers, diagnostic codes
- Predictors of steroid responsiveness
- Systematic literature review on steroid-sparing agents used for irAE therapy, with specific focus on tumor outcome (in addition to irAE outcome) → ONGOING
- Multi-institutional prospective cohort study comparing outcomes
- More clinical trials assessing risks and benefits of ICI and cytokine-targeted immunosuppression

Clinical Case

59yo F with NSCLC on COSINR clinical trial (Ipilimumab/nivolumab, radiotherapy) for 1.5 years with complete response. She is admitted to hospital with joint pain, swelling at B wrists, B knees and L ankle that did not respond prednisone 10mg qd x7d. No small joint swelling or stiffness. No fevers, rashes, diarrhea.
Phys Ex: VSS, warm, swollen joints: only R knee with significant (moderate) effusion.
Labs: CRP 98mg/L, slight leukocytosis with high neutrophil count. RF, CCP, ANA negative.
X-rays without erosive changes, no chondrocalcinosis. R knee arthrocentesis: WBC of 10k, PMNs predominant, no crystals, neg gram stain. Patient and oncologist would like to continue clinical trial.

What would you recommend next?

A. Take patient off trial and give 1mg/kg/d systemic steroids monotherapy
B. Keep patient on trial and give 1mg/kg/d systemic steroids and PO methotrexate
C. Take patient off trial, pred 10mg daily, CSIs to all affected joints, start weight-based hydroxychloroquine

Conclusions

- irAEs represent an emerging field in autoimmunity and many questions remain unanswered.
- From a research perspective, there is need for understanding pathogenesis of these disorders.
- In terms of therapy, the potential of targeted therapies is largely untapped and research as to whether they are capable of effectively treating immune-mediated toxicities while not hampering desired antitumor responses is needed.

Thank You!

Questions??

- https://forms.office.com/r/R7PiPNw0Ef

Management of ir-IA

Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis

Anne R Bass [1,2] Noha Abdel-Wahab,[3] Pankti D Reid [4] Jeffrey A Sparks [5] Cassandra Calabrese [6] Deanna P Jannat-Khah [7,8] Nilasha Ghosh [1,2] Divya Rajesh,[9] Carlos Andres Aude [7] Lydia Gedmintas,[10] Lindsey MacFarlane,[10] Senada Arabelovic,[10] Adewunmi Falohun,[3] Komal Mushtaq,[11] Farah Al Haj,[12] Adi Diab,[13] Ami A Shah,[14] Clifton O Bingham [15] Karmela Kim Chan [1,2] Laura C Cappelli [15]

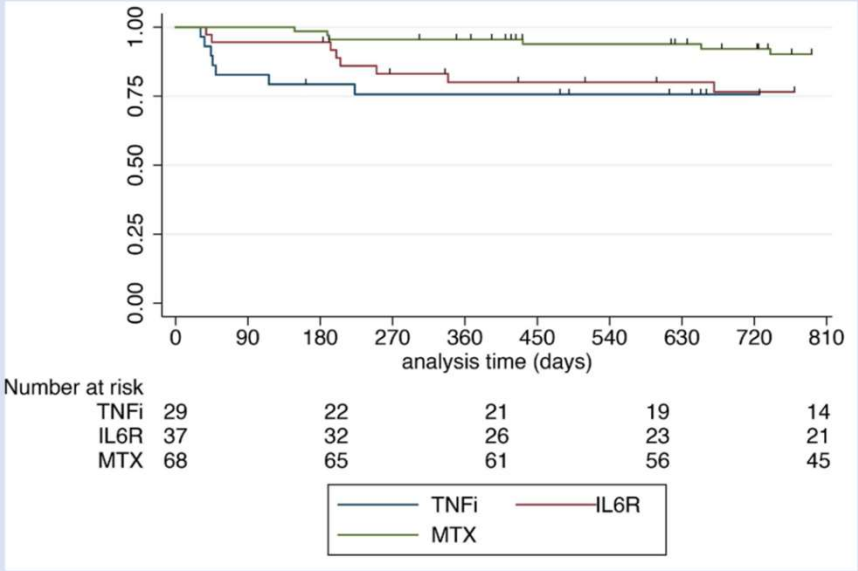


Figure 1 Kaplan-Meier survival estimates: time to cancer progression from immune checkpoint inhibitor initiation. Patients whose cancer progressed prior to disease-modifying antirheumatic drug (DMARD) initiation were excluded. IL6R, interleukin-6 receptor; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.

Bass AR, *et al*. *Ann Rheum Dis* 2023

Team-Based Management of Cutaneous Immunotherapy-Related Adverse Events

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Vice-Chair, Department of Dermatology
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Member, NCCN Panel on Management of Immunotherapy-Related Toxicities

The Ohio State University
Wexner Medical Center

DERM: Bullous dermatitis	Inflammation of the skin and the presence of bullae, which are filled with fluid. The most common immune-related bullous dermatitis is bullous pemphigoid. May be intense or widespread; intermittent; skin changes from scratching (eg, edema, excoriations, lichenification, oozing/crusts); limiting instrumental activities of daily living (iADLs).
DERM: Maculopapular rash (morbilliform rash)	Macules (flat) and papules (elevated)
DERM: Pruritus	Itching sensation, with or without rash
DERM: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% body surface area (BSA), respectively
DERM: Lichen planus	Violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
DERM: Psoriasis and psoriasiform disease	Thick red scaly plaques, accentuated on extensor surfaces, scalp, umbilicus, postauricular surfaces
DERM: Oral mucosa inflammation	Irritated gums and/or oropharynx, red/white lesions and/or ulcers, lichen planus, mucositis
DERM: Dry mouth (Sicca syndrome)	Dry mouth, oral sensitivity, dysarthria, dysphagia, dysgeusia, dental caries/erosion with prolonged salivary hypofunction, dry eye, lack of lubrication
DERM: Oral dysesthesia	Pain most often described as "burning" in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

Morphologies of Skin Rashes Associated with Immunotherapy

	Demographics		Immunotherapy class			Rash Characteristics			
Rash type	Pts, no. (M, F)	Age, mean, y	Anti-CTLA-4	Anti-PD-1 or PD-L1	Both	Latency, mean, mo (range)	Pruritus	Grade, median (range)	Other irAE,^ no.
Lichenoid	26 (17, 9)	64	2	23	1	6.2 (0.5-20)	25	1 (1-3)	9
Maculo-papular	18 (5, 13)	61	2	11	5	1.0 (0.2-5.7)	16	2 (1-3)	7
Psoriasiform	17 (8, 9)	67	1	12	4	5.7 (0.2-28.8)	10	1 (1-3)	8
Eczematous	12 (6,6)	66	0	9	3	5.8 (0.6-25)	12	1 (1-3)	5
Immuno-bullous	8 (4, 4)	68	0	8	0	4.5 (0.5-10)	8	3 (2-3)	2
Prurigo	7 (3, 4)	71	0	6	1	10.1 (1.8-16)	7	1 (1-3)	3
Grover's-like	4 (4, 0)	71	0	4	0	4.2 (0.2-14.4)	4	1 (1-2)	1
Acneiform	4 (3, 1)	47	0	4	0	4.3 (0.2-11)	1	1 (1-2)	1
Granulomatous	3 (0, 3)	65	0	2	1	17.7 (7-36)	0	1	0
SJS-like	2 (1,1)	62	0	0	2	1.4	2	4	2
PR-like	1 (1, 0)	75	0	1	0	0.2	1	2	0
PRP-like	1 (1, 0)	63	0	1	0	0.46	1	3	0
Total	103 (54, 49)	65	5	81	17	5.13 (0.1-36)	77	1 (1-4)	36*

Coleman E, et al. Inflammatory eruptions associated with immune checkpoint inhibitor therapy. *J Am Acad Dermatol*. 2019;80(4):990-997. doi:10.1016/j.jaad.2018.10.062.

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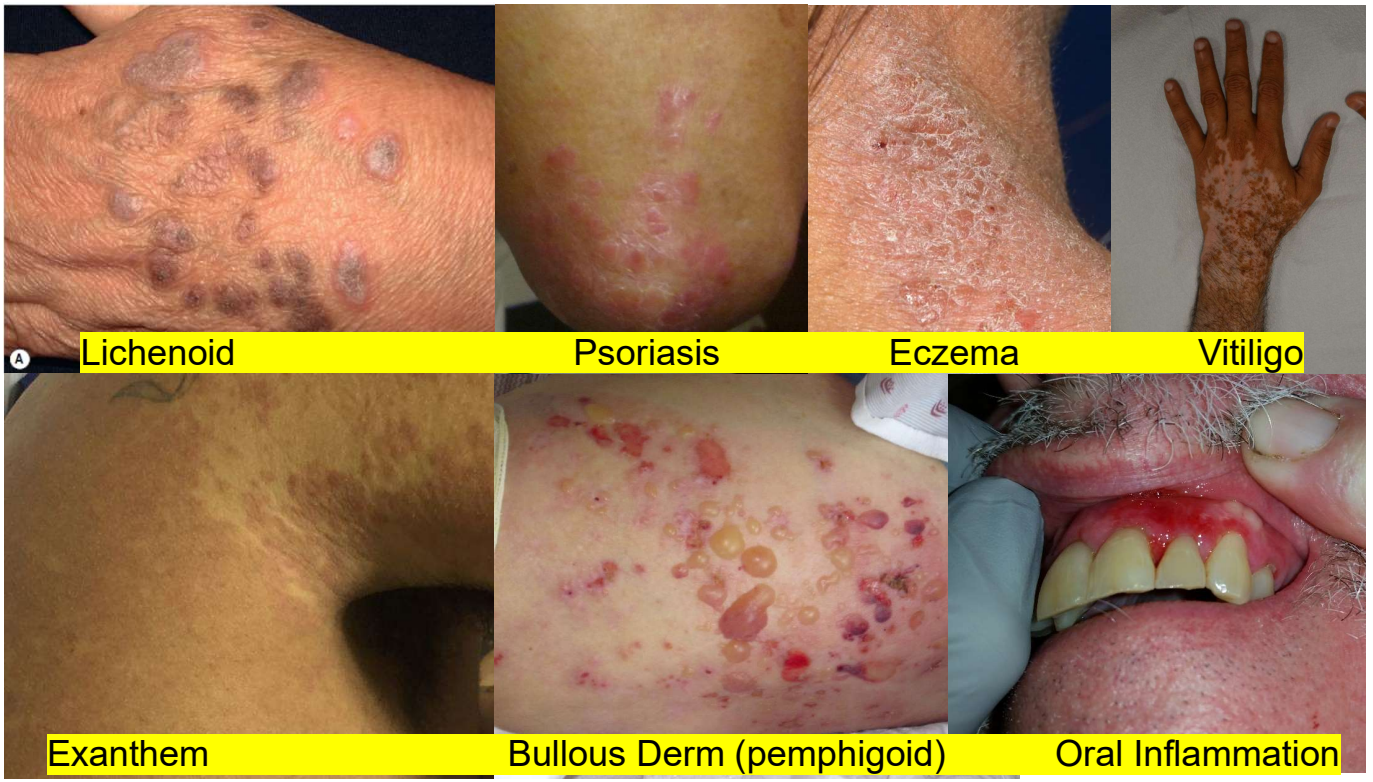
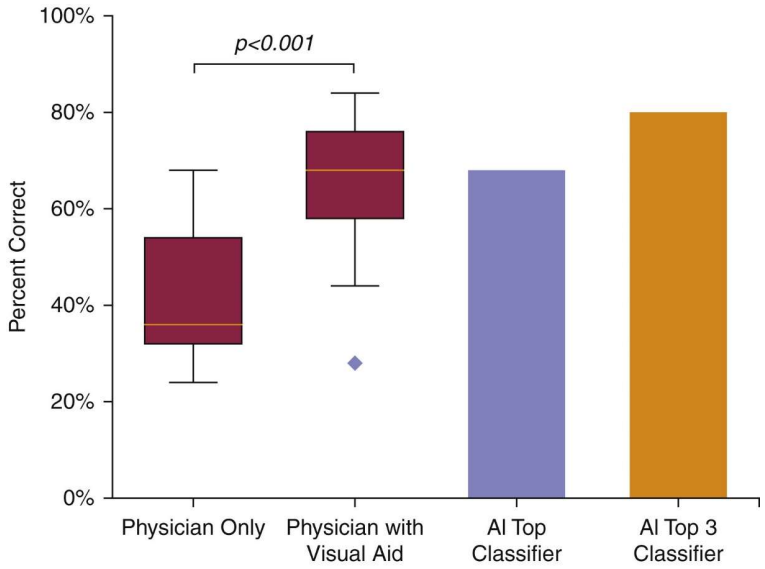
Morphologies of Skin Rashes Associated with Immunotherapy



Long-Term Goal:
Point-of-Care Image Classification Assistance



Dulmage B, Tegtmeyer K, Zhang MZ, Colavincenzo M, Xu S. A Point-of-Care, Real-Time Artificial Intelligence System to Support Clinician Diagnosis of a Wide Range of Skin Diseases. J Invest Dermatol. 2021 May;141(5):1230-1235. doi: 10.1016/j.jid.2020.08.027. Epub 2020 Oct 14. PMID: 33065109.

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Patient Management Question 1

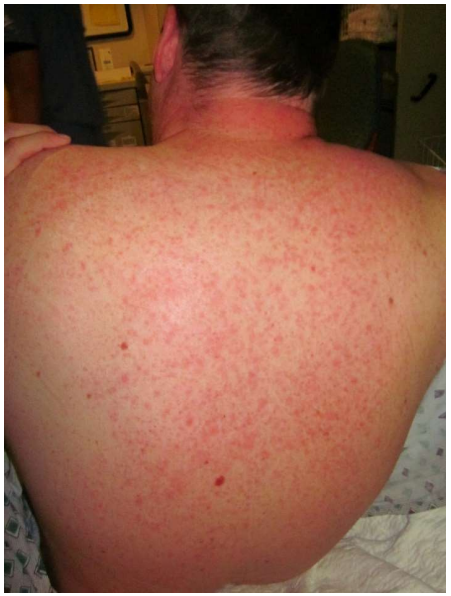
50-year-old male with urothelial carcinoma

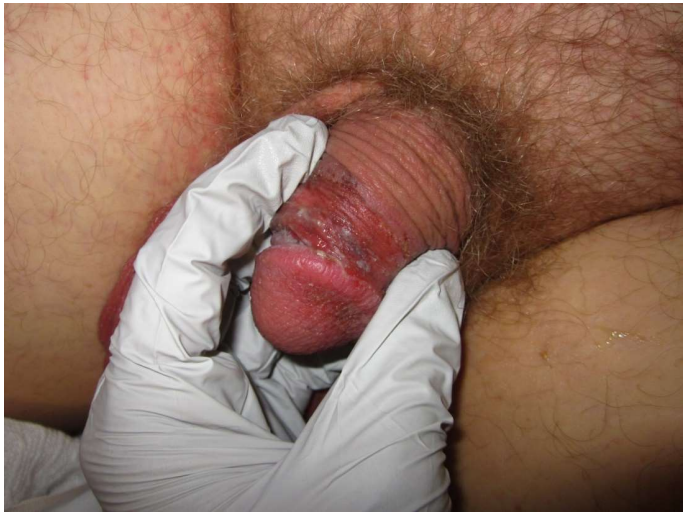
- Completed two cycles of atezolizumab monotherapy, presented acutely to clinic before 3rd cycle
- No significant past medical history
- No previous rashes
- New onset rash with mouth and eye pain
- Recent urinary tract infection treated with trimethoprim/sulfamethoxazole (TMP/SMX).

Work-up

- Clinical Evaluation
- Chemistries normal
- Febrile to 101°F. Otherwise vital signs normal

Patient Images





POLLING QUESTION

Assuming dermatology is not immediately available, what is your next immediate step of management?

1. Proceed with 3rd cycle of atezolizumab while awaiting dermatology
2. Hold therapy and evaluate for admission
3. Hold therapy, and discharge with a prednisone taper and topical corticosteroids
4. Start prednisone and change to an alternative checkpoint inhibitor

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Patient Follow-Up

- The patient was admitted to the hospital, underwent biopsy.
- Alternative etiologies for SJS/TEN were evaluated including: mycoplasma pneumonia, immunobullous disease, and cutaneous lupus were evaluated.
- After discussion, the patient was treated with high-dose corticosteroids. Ipilimumab/Nivolumab + TMP/SMX added to allergy list.
- Close discussion with oncology, dermatology, and allergy occurred to discuss
  - Etiology: Nivolumab/Ipilimumab vs Nivolumab/Ipilimumab + TMP/SMX vs TMP/SMX
  - Risk of rechallenge
  - Alternative therapy options
- Given that this patient had other options, rechallenging with avoidance of TMP/SMX was not performed. He survived the hospital and returned for outpatient follow-up.

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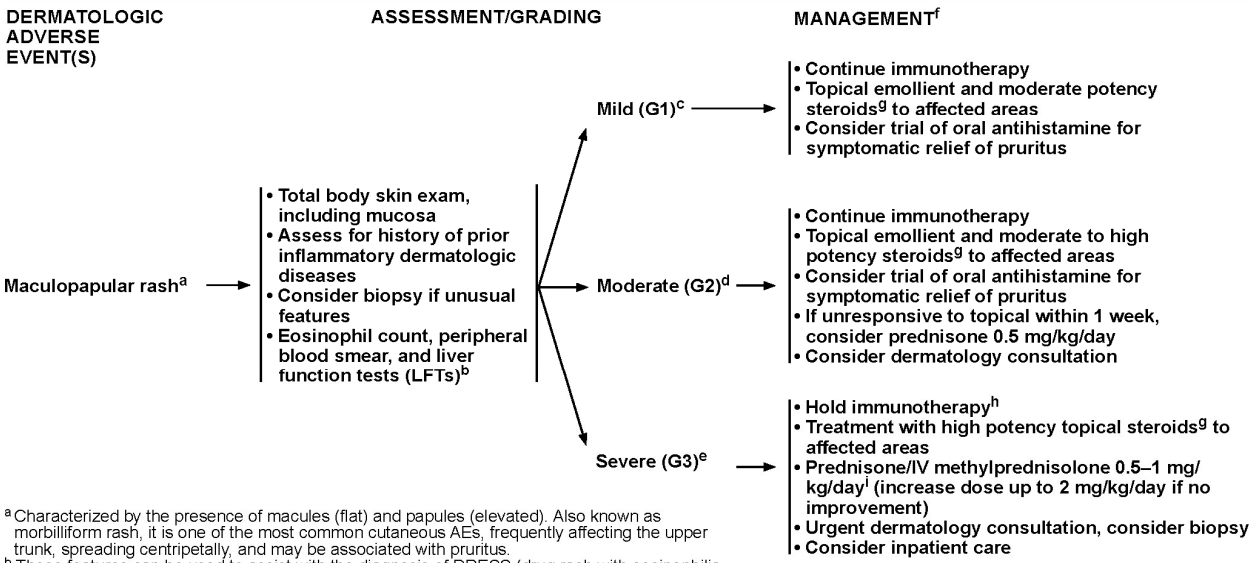

[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and may be associated with pruritus.

[b] These features can be used to assist with the diagnosis of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. This syndrome is typically characterized by a maculopapular rash that involves the face and ears and typically presents with swelling of the face and hands within 2–8 weeks after drug exposure. Note that certain classes of high-risk medications initiated in the prior few weeks may also cause maculopapular rash, including antiepileptic drugs: carbamazepine, phenytoin, lamotrigine, phenobarbital; antihyperuricemics: allopurinol, febuxostat; sulfonamides and sulphones: trimethoprim sulfamethoxazole, sulfasalazine, dapsone; and other antibiotics: vancomycin, minocycline, other beta-lactams. Kardaun SH, et al. Br J Dermatol 2013;169:1071-1080.

[c] Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness).

[d] Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting iADLs.

[e] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care activities of daily living (ADLs).

[f] Principles of Immunosuppression (IMMUNO-A).

[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).

[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).

[i] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.

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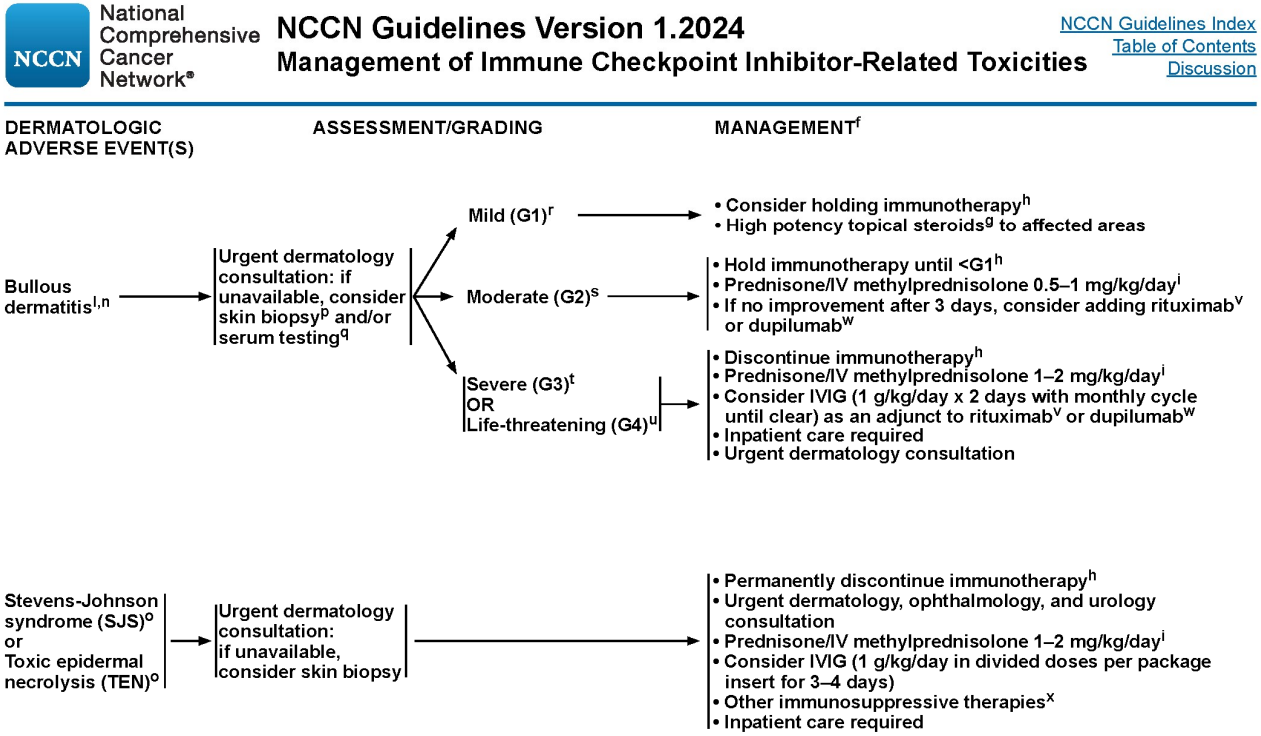

Footnotes on ICI_DERM-3A

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Rechallenge Risks:

Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN. • Psoriasis and lichen planus: Rechallenge may be considered if symptoms are controlled and extent of BSA is <30%, especially if the patient is on targeted biologic or other inhibitor of the immune response.

- Very limited data in severe cutaneous adverse reactions
- Exercise caution when considering rechallenge, as the same (or worse) reaction may occur
- However, in DRESS, 8 patients rechallenged:
  - 2 rechallenged with the same immunotherapy (atezolizumab, nivolumab) and both relapsed.
  - 1 rechallenged with single-agent PD-1 inhibitor from ipilimumab/nivolumab – and tolerated.
  - 5 patients switched PD-1 inhibitor with the addition of low-dose corticosteroids, 4 tolerated, 1 relapsed.
  - No patients died due to DRESS syndrome, even when rechallenged.
- ***Conclusion: Consider if no other options and patient consents to risks of same reaction or even greater, close supervision, and low-dose corticosteroids.***

DRESS, Drug rash with eosinophilia and systemic symptoms.

Ingen-Housz-Oro S, Milpied B, Bensaid B, Elshot Y, Brüggen MC, Starace M, Kaffenberger BH, Carrera C, Pham-Ledard A, Freites-Martinez A, Sanchez-Pena P, Lebrun-Vignes B, French LE, Sibaud V. Drug reactions with eosinophilia and systemic symptoms induced by immune checkpoint inhibitors: an international cohort of 13 cases. Melanoma Res. 2023 Apr 1;33(2):155-158. doi: 10.1097/CMR.0000000000000877. Epub 2023 Feb 6. PMID: 36749114.; Thompson JA, Schneider BJ, Brahmer J, Abu Zaid M, Achufusi A, Armand P, Berkenstock MK, Bermas B, Braaten T, Budde LE, Chokshi S, Davies M, Deng C, Gesthalter Y, Jain M, Jain P, Kaffenberger BH, Khalil M, Lechner MG, Li T, Marr A, McGettigan S, McPherson J, Medina T, Mohindra NA, Olszanski AJ, Oluwole O, Patel SP, Prosek J, Reddy S, Reid P, Ryan J, Ryder M, Santomasso B, Shofer S, Sosman JA, Wang Y, Zaha VG, Zucker S, Awotiwon A, Hang L. NCCN Guidelines® for Management of Immunotherapy-Related Toxicities (V.1.2024). Accessed 12/07/23. To view the most recent and complete version of the guideline, go online to www.NCCN.org/guidelines.

Differentiating Exanthems

High Risk	Low Risk
Trunk + Facial involvement	**Trunk predominant**
Facial/Hand Edema “Oblique Earlobe Crease”	Spares Face
Pustules	No Pustules
Vesicles	No Vesicles
Duskiness	Spares palms and soles
Palmar/Plantar involvement	Spares mucosal surfaces
Mucosal/Genital Involvement	

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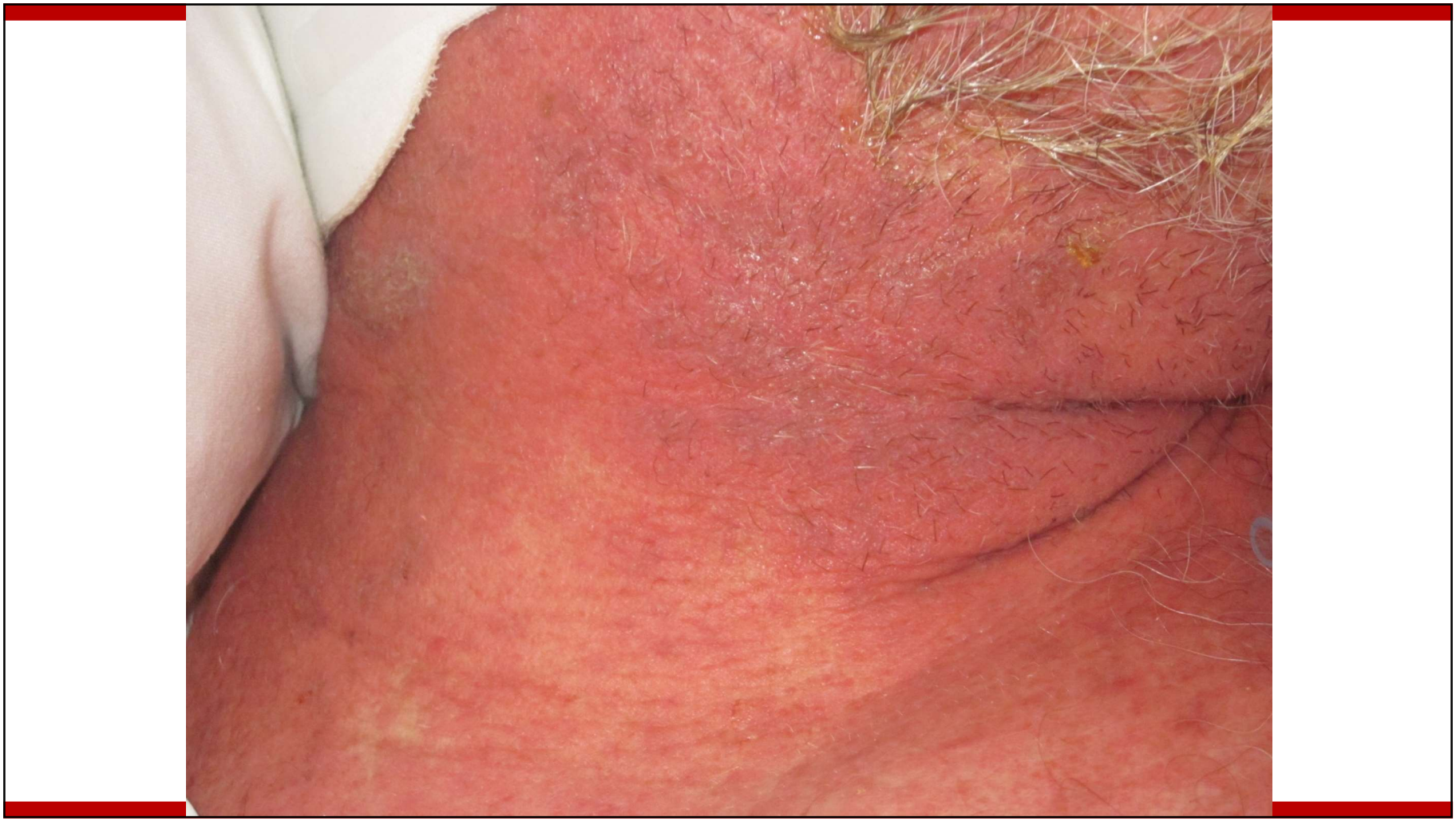
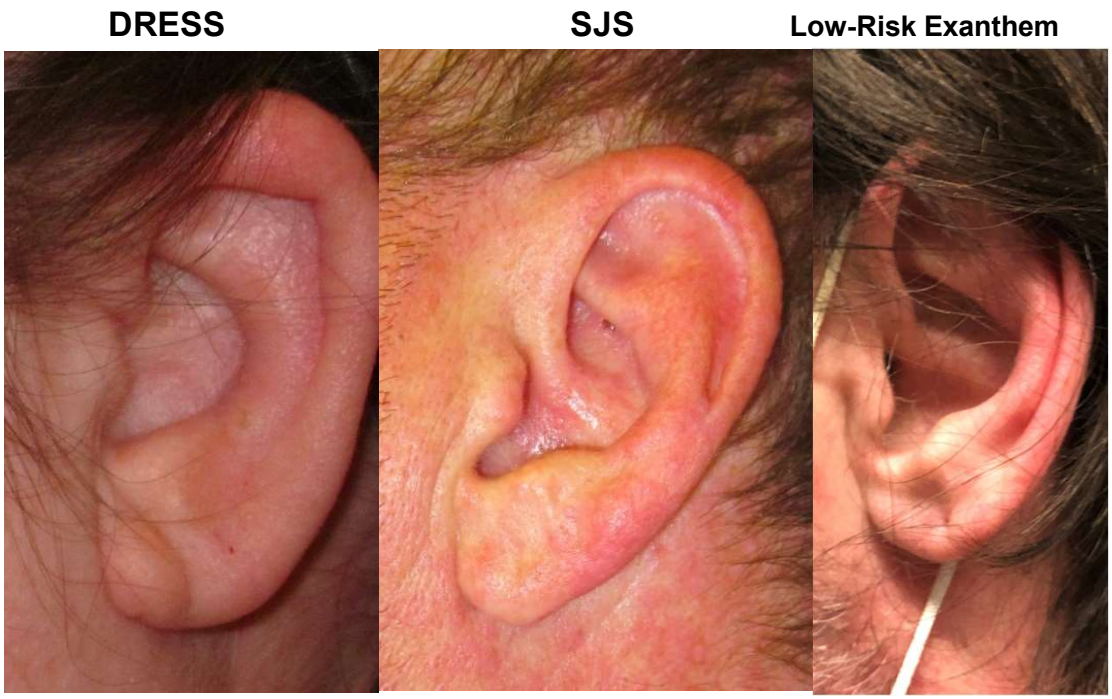


Exanthems and Facial Involvement/Swelling



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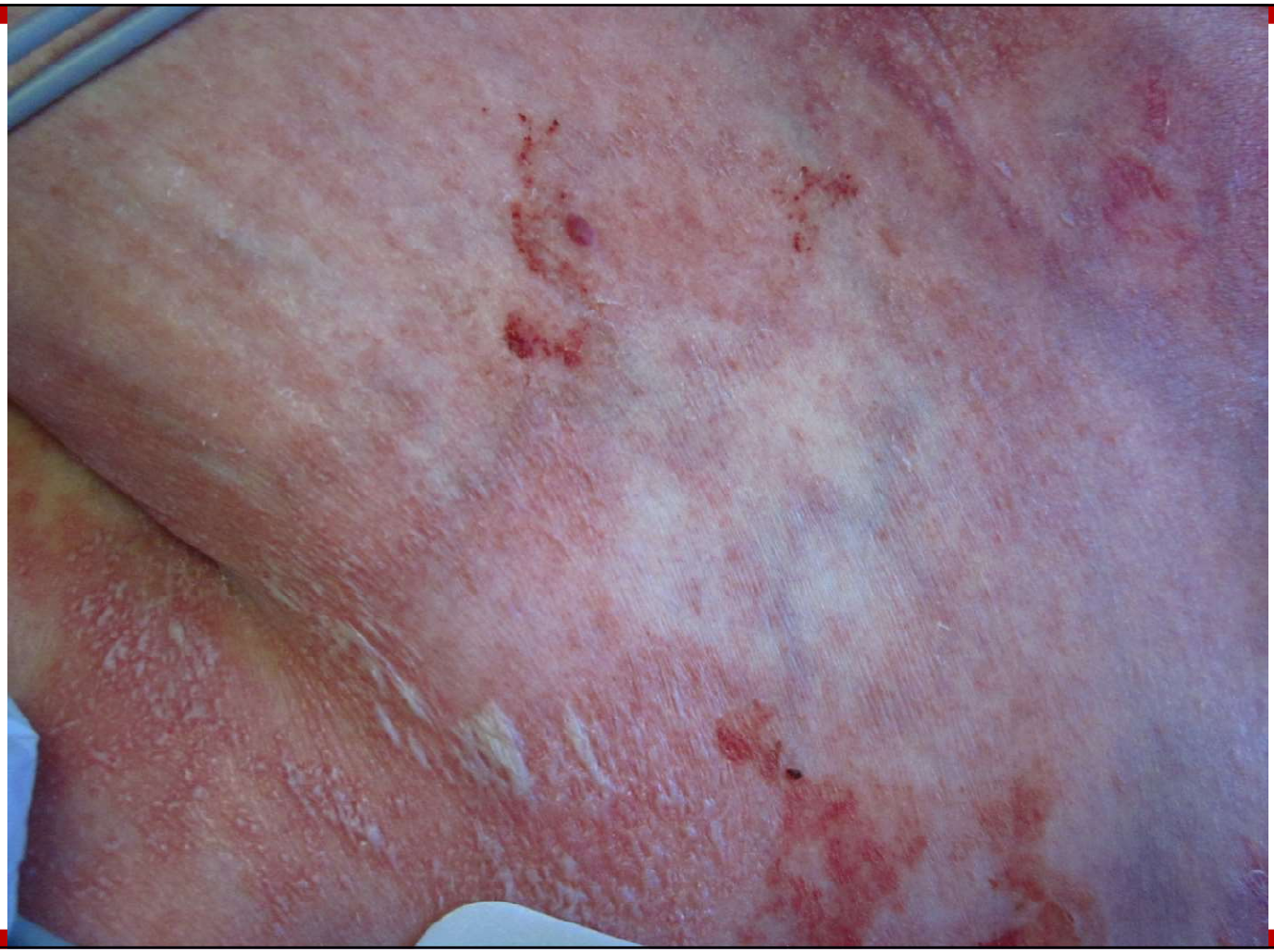

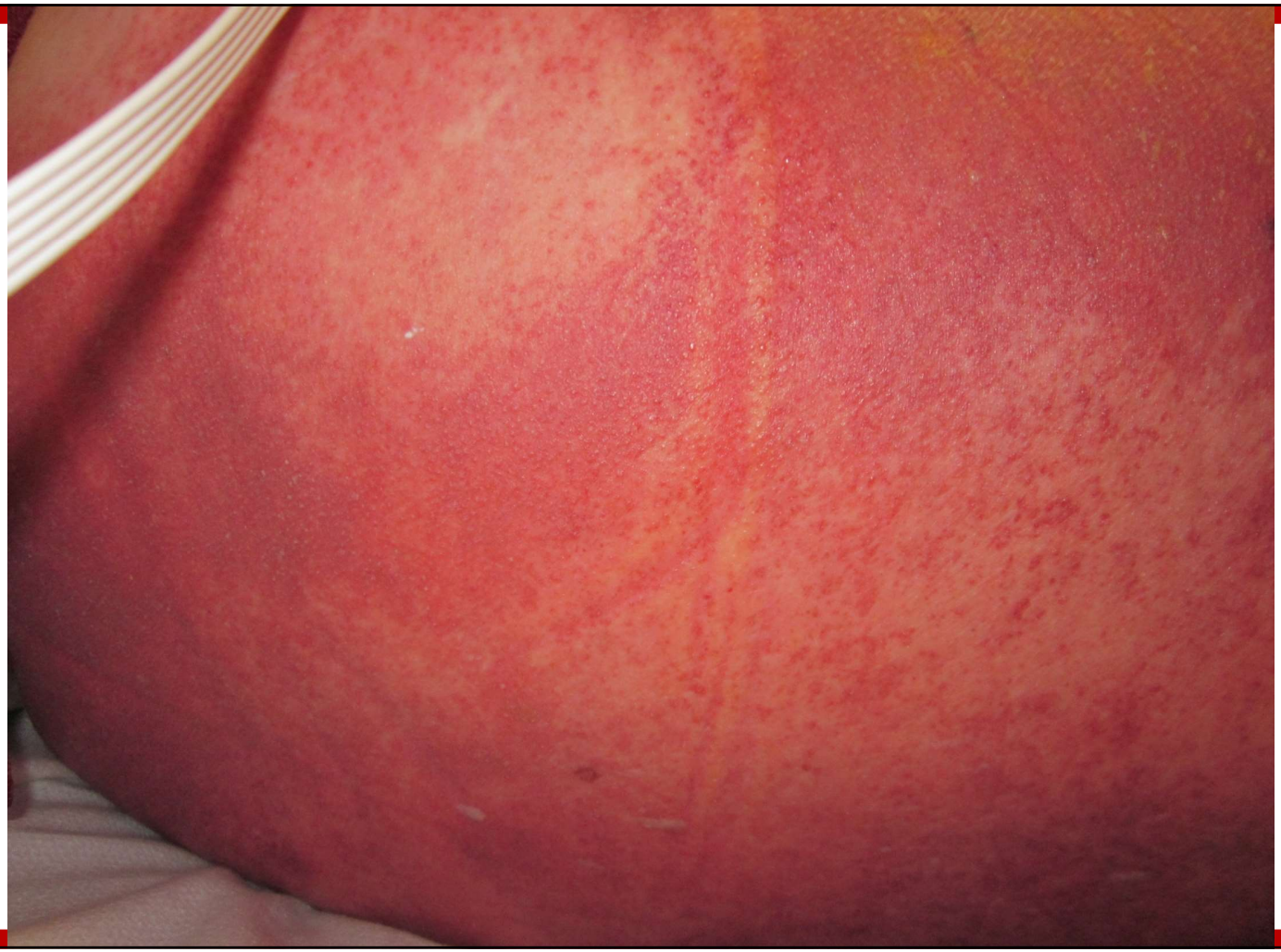

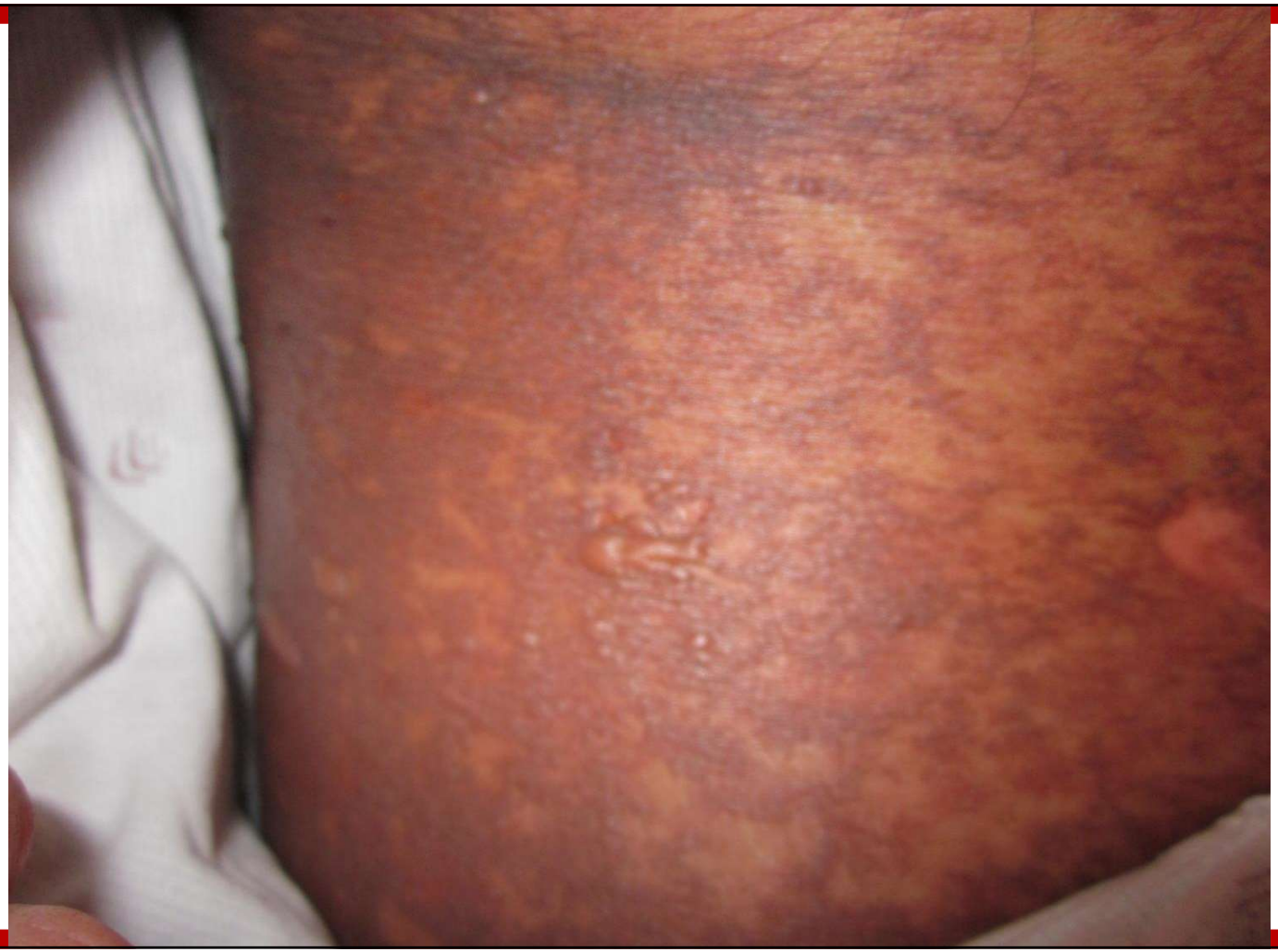

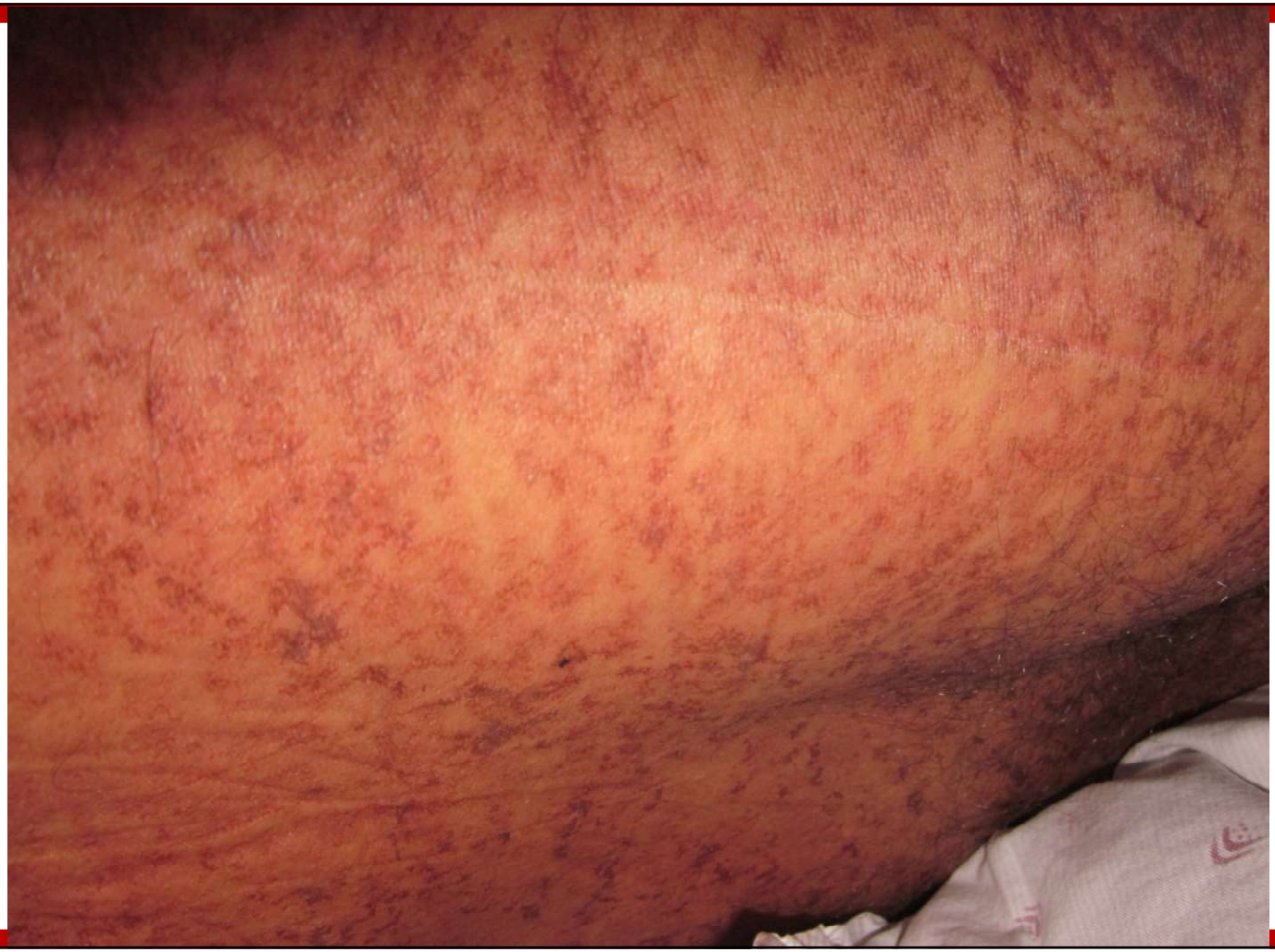

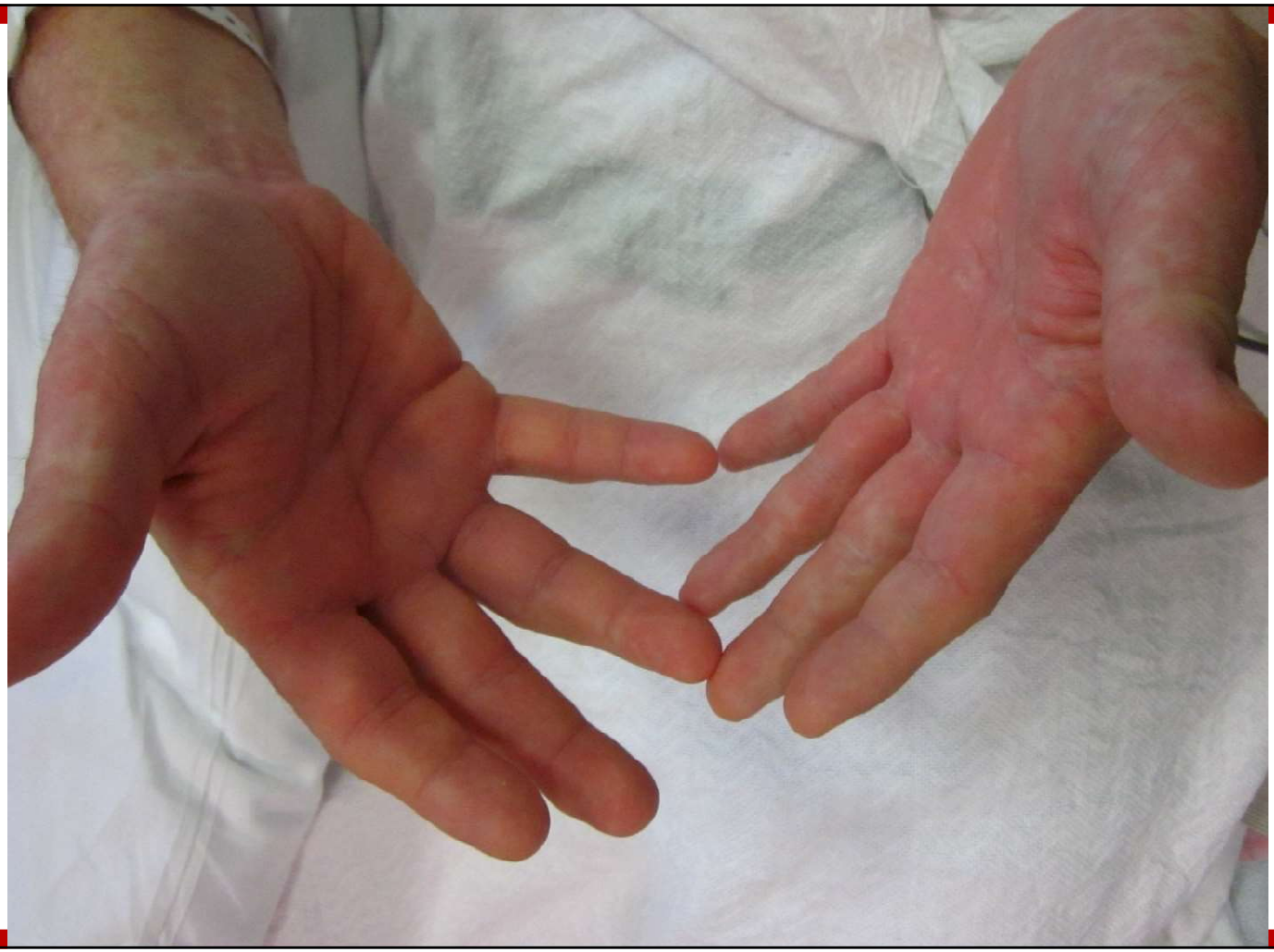

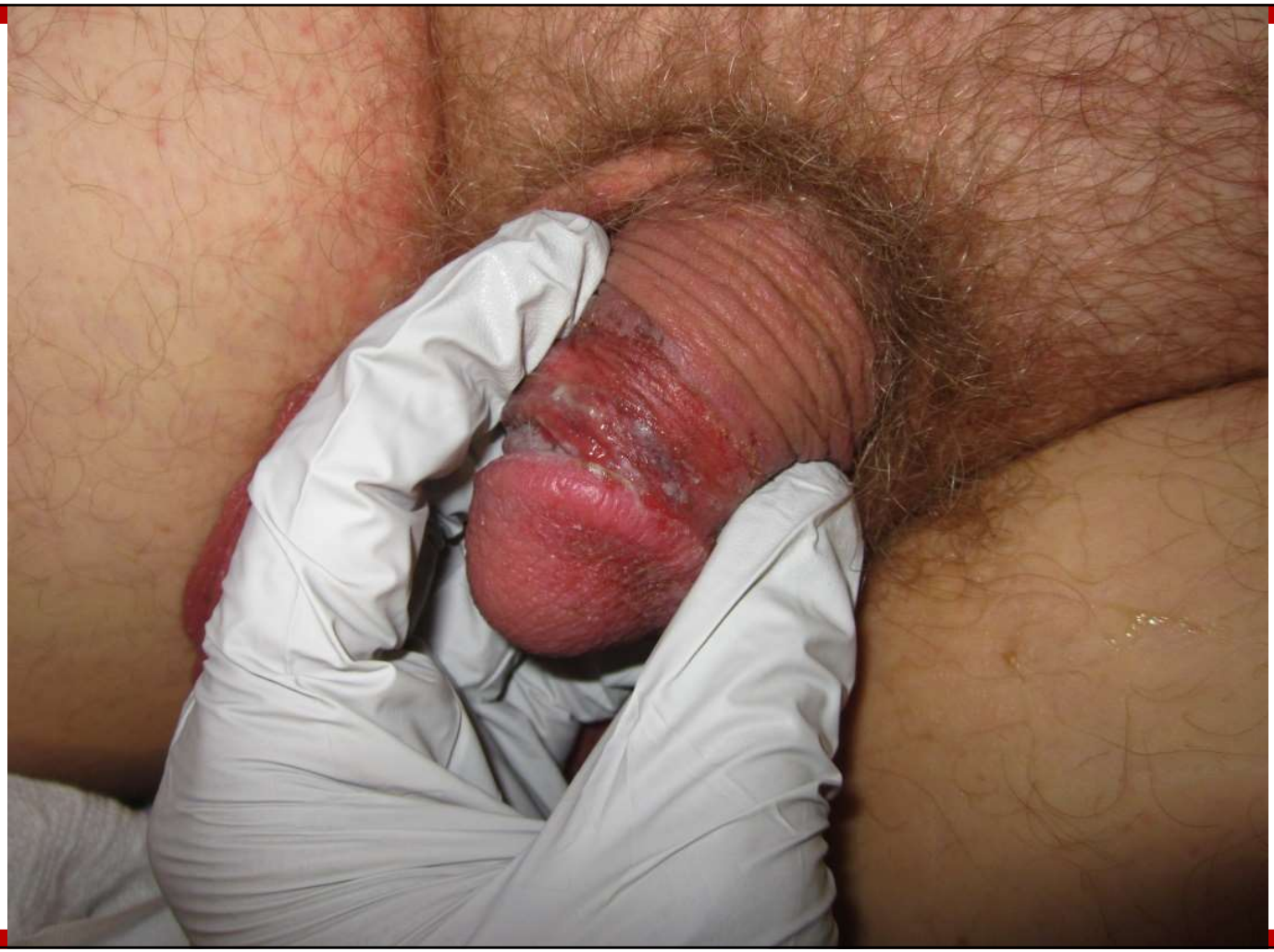

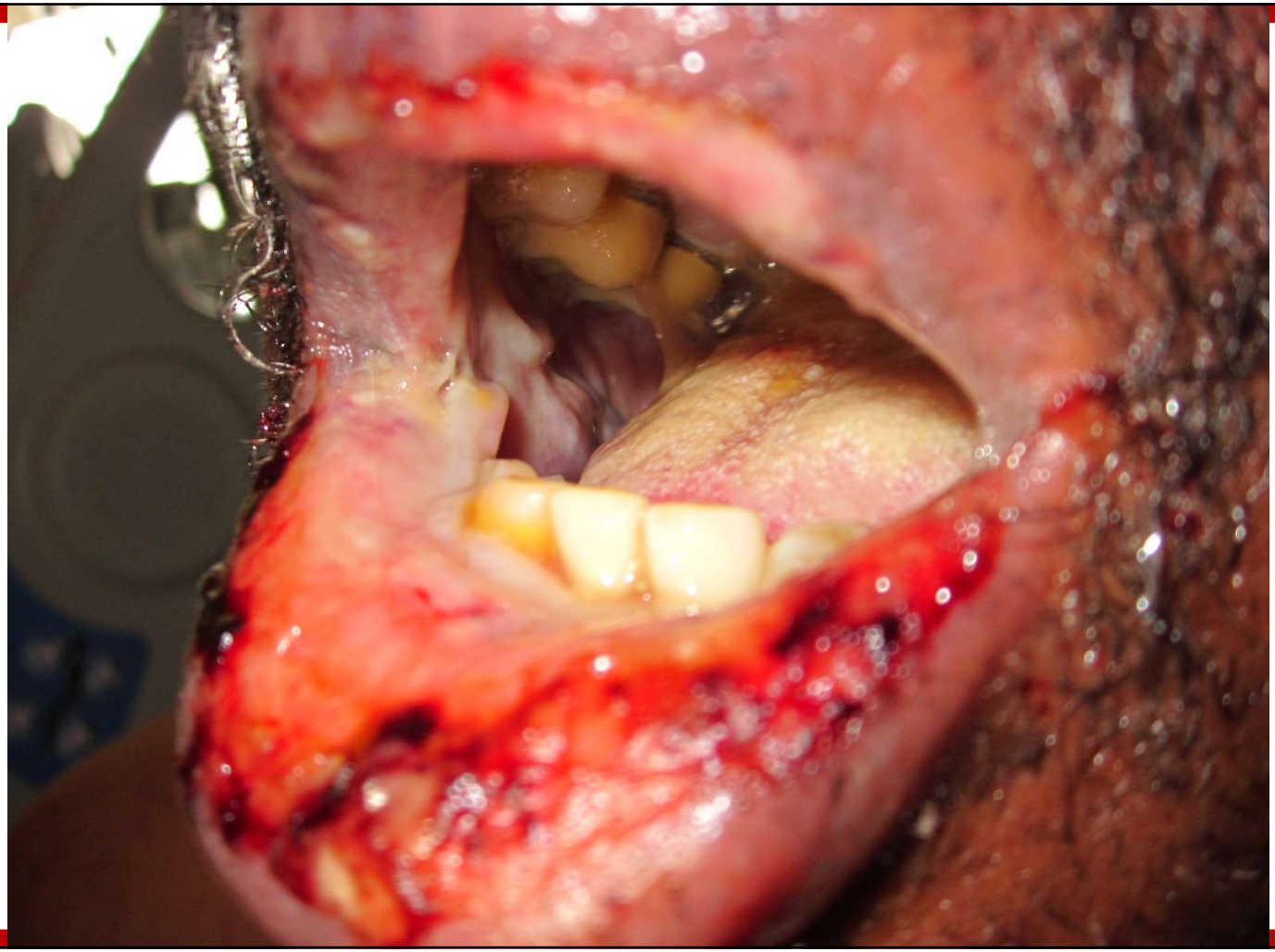

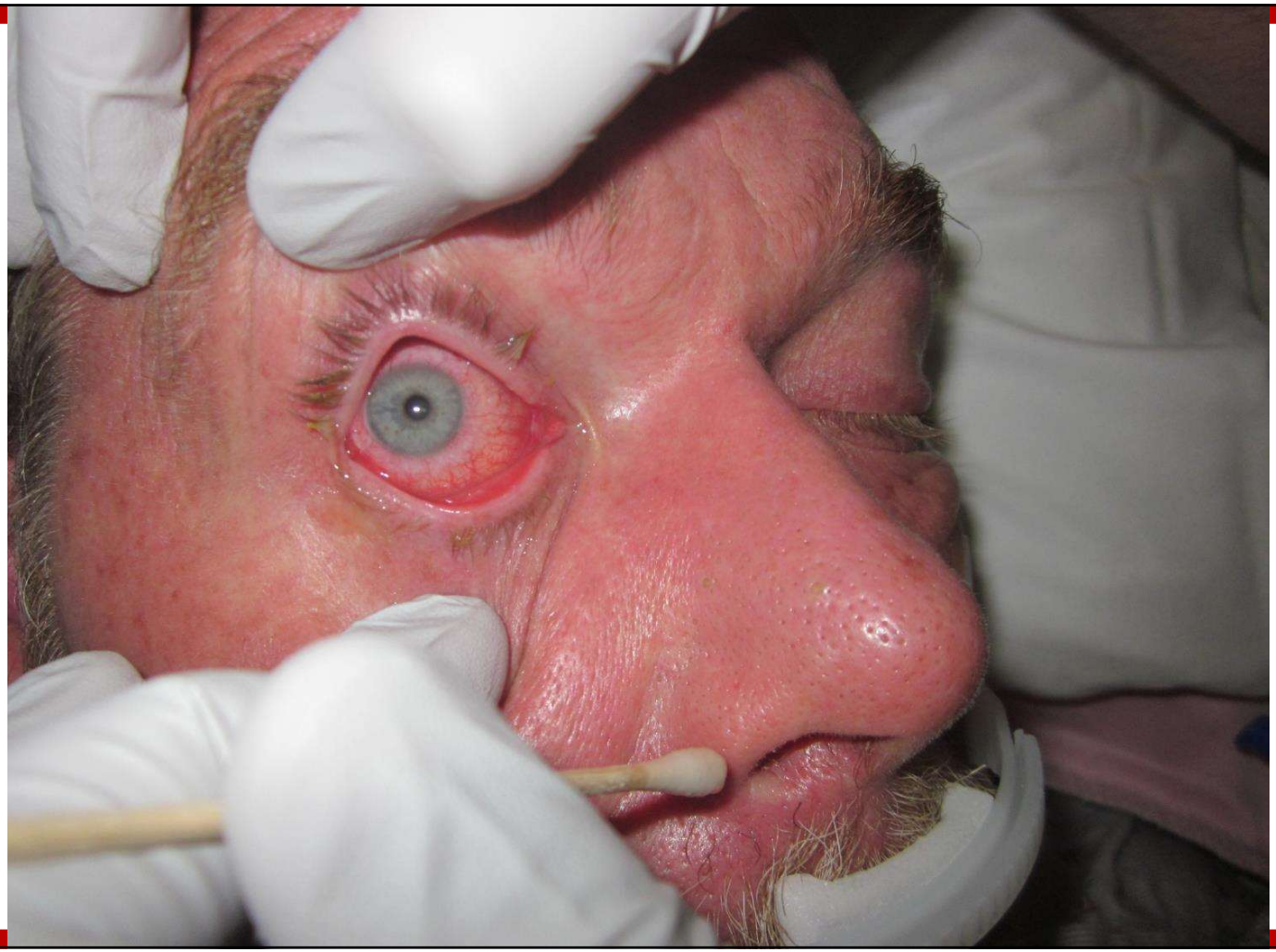

Treatment Algorithm

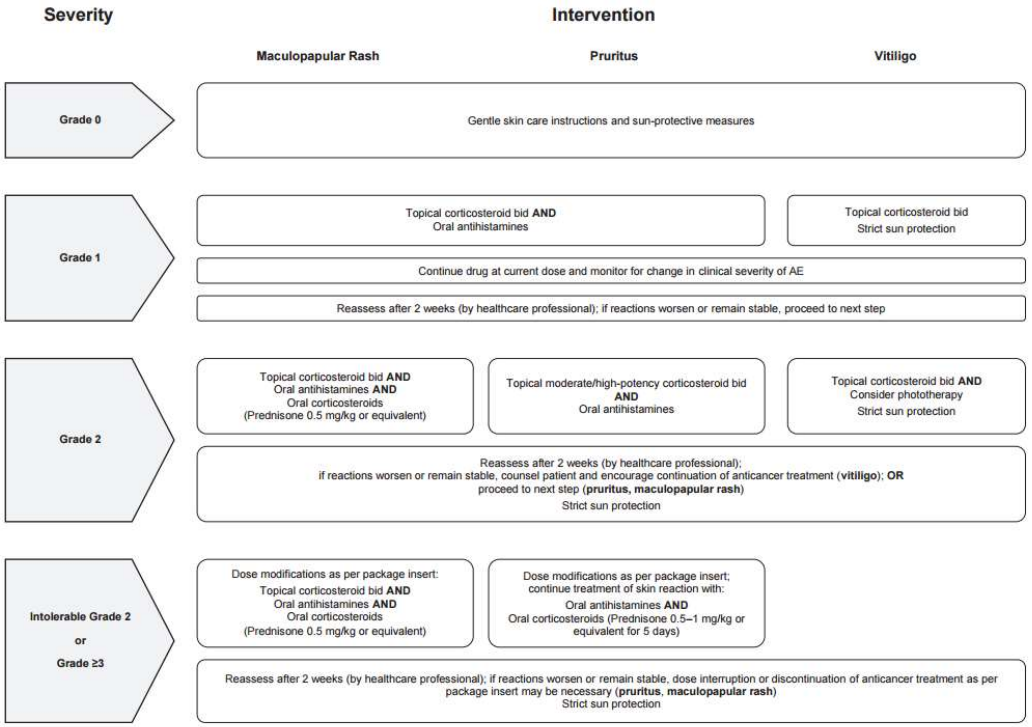

Fig. 5. Treatment algorithm for the management of anti-PD-1 inhibitor–induced dermatologic AEs. PD-1, programmed death-1; AEs, adverse events.

Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer*. 2016;60:12-25. doi:10.1016/j.ejca.2016.02.010

Patient Management Question 2

75-year-old male with metastatic melanoma

- Completed six cycles of nivolumab + ipilimumab combination therapy.
- Past medical history: hypertension, hyperlipidemia, alcoholism (in remission)
- No previous rashes
- Describes extensive itch

Work-up

- Clinical evaluation
- Chemistries normal
- Vital signs normal

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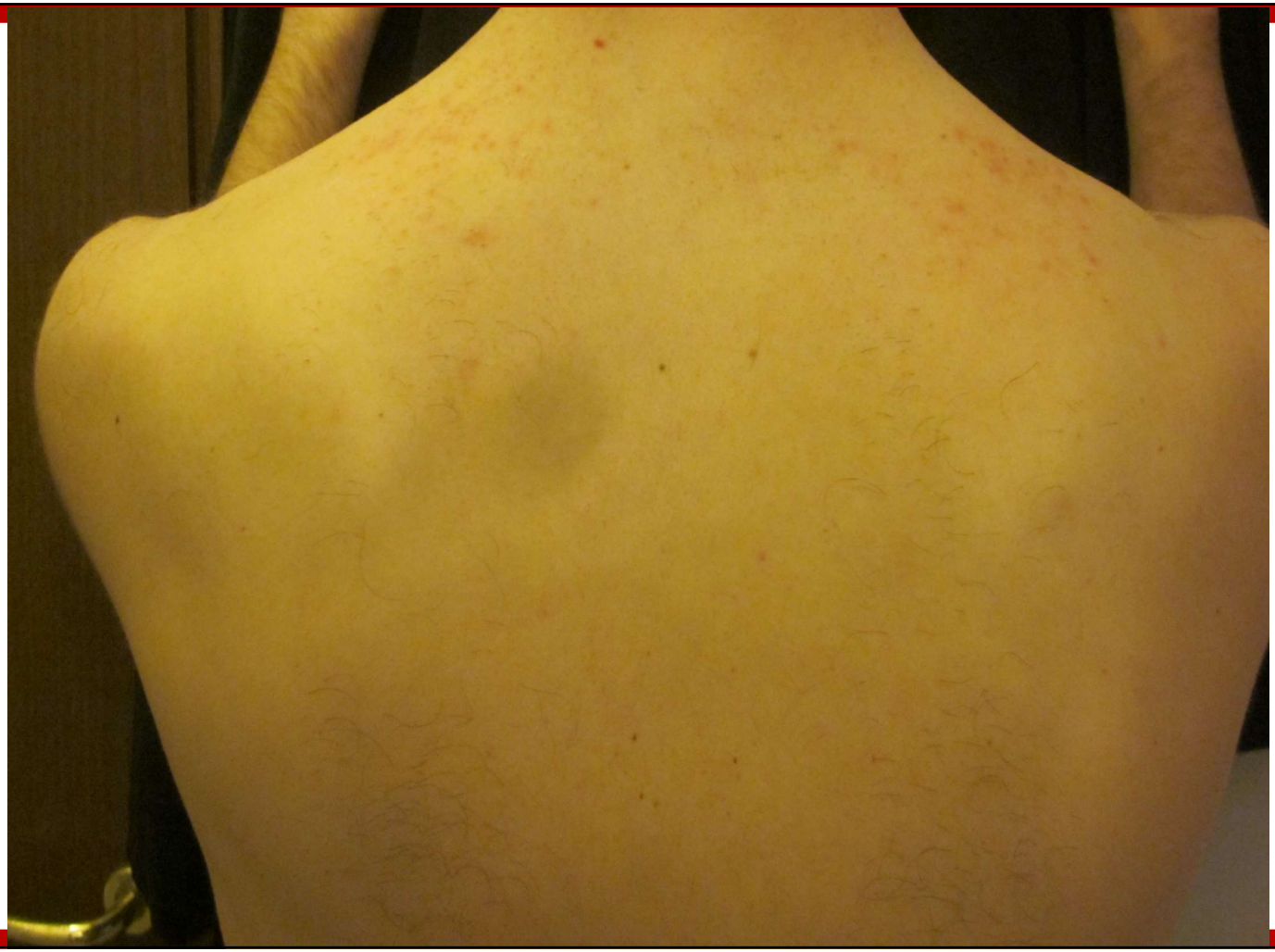

POLLING QUESTION

Which of the following skin findings would be the best reason to reference the NCCN Guidelines for pruritus treatment?

1. A patient with prior psoriasis that has been exacerbated by nivolumab, and who complains of significant itching.
2. A patient on pembrolizumab with extensive itching and new blisters after 9 cycles of immunotherapy.
3. A patient who describes a rash, but you only see evidence of scratch marks (excoriations) on exam.
4. An abrupt new onset itchy rash that also involves the patient's mouth and groin. The patient states it itches or burns.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Management of Immune Checkpoint Inhibitor-Related Toxicities

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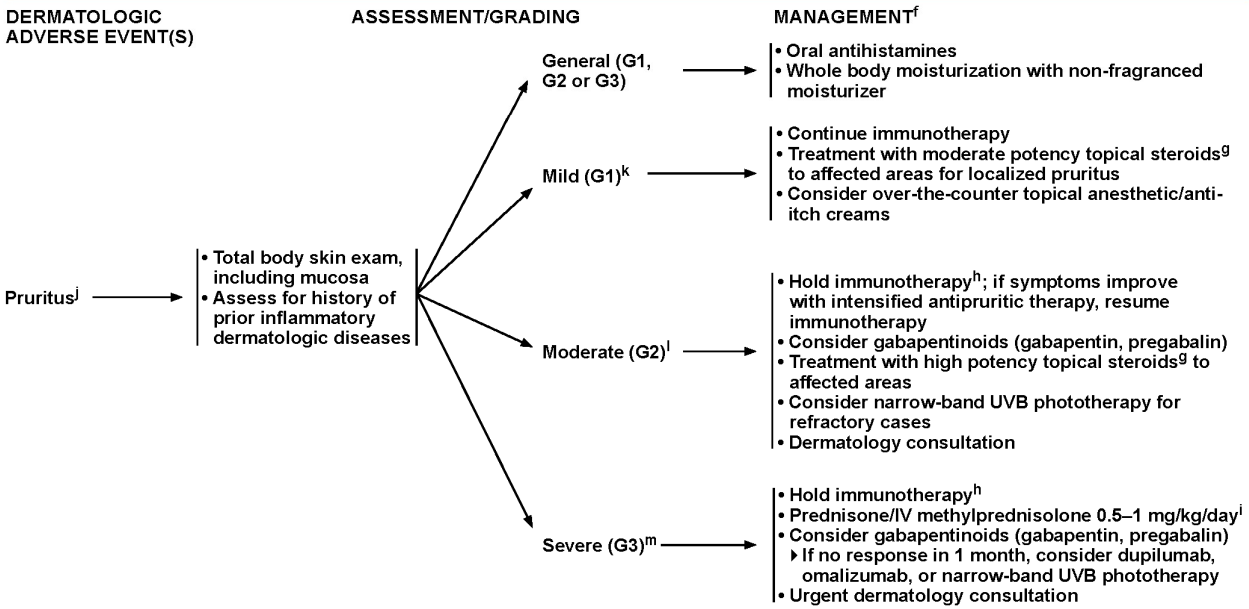


[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[j] Characterized by an intense itching sensation with or without rash.
[k] Mild or localized.
[l] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[m] Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Patient Follow-Up

The patient initially underwent therapy with hydroxyzine and topical triamcinolone 0.1% cream and immunotherapy was continued.

Consistent with NCCN Guidelines gabapentin was titrated with some effect, but the patient complained of excessive somnolence.

After inadequate improvement, he was referred to dermatology.

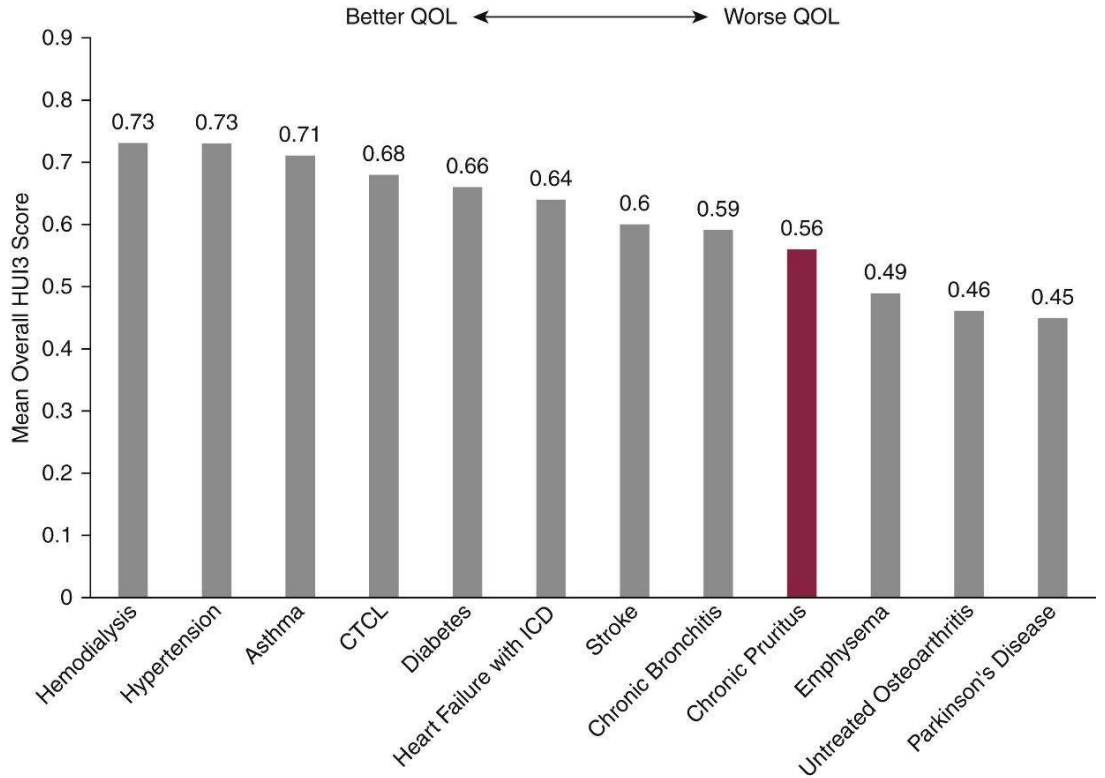
9 months later…

The patient was seen by dermatology and prescribed the same cream but 454 g tub (instead of 45 g).

With only mild improvement phototherapy vs dupilumab (an IL-4/-13 receptor inhibitor) were discussed.

Dupilumab selected resulting in dramatic decrease in pruritus and decrease from 8/10 to 1/10 pruritus within a month.

Quality-of-Life Detriment of Chronic Pruritus



Whang KA, Khanna R, Williams KA, Mahadevan V, Semenov Y, Kwatra SG. Health-Related QOL and Economic Burden of Chronic Pruritus. J Invest Dermatol. 2021 Apr;141(4):754-760.e1. doi: 10.1016/j.jid.2020.08.020. Epub 2020 Sep 14. PMID: 32941916.

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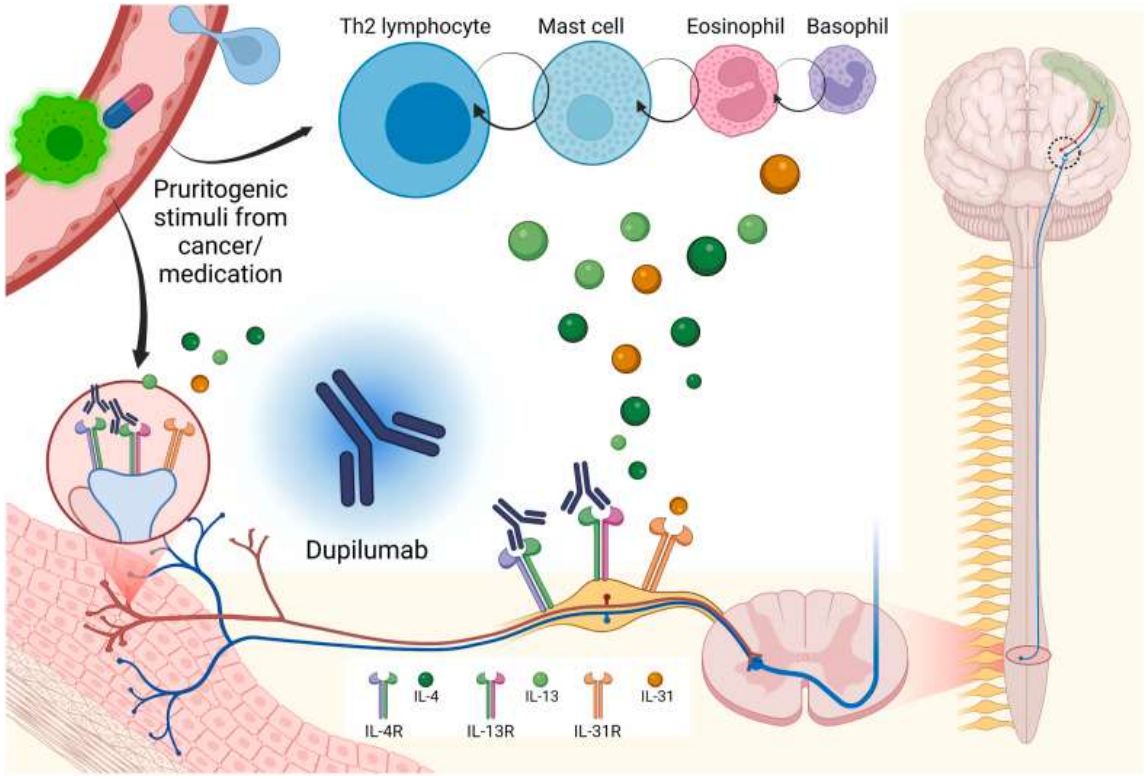
Dupilumab and Treatment Milieu



Talmon A, Elias S, Rubin L, Ribak Y, Ben Dori E, Shamriz O, Lotem M, Adini I, Tal Y. Dupilumab for cancer-associated refractory pruritus. J Allergy Clin Immunol Glob. 2023 Jun 23;2(3):100128. doi: 10.1016/j.jacig.2023.100128. PMID: 37779518; PMCID: PMC10509917.

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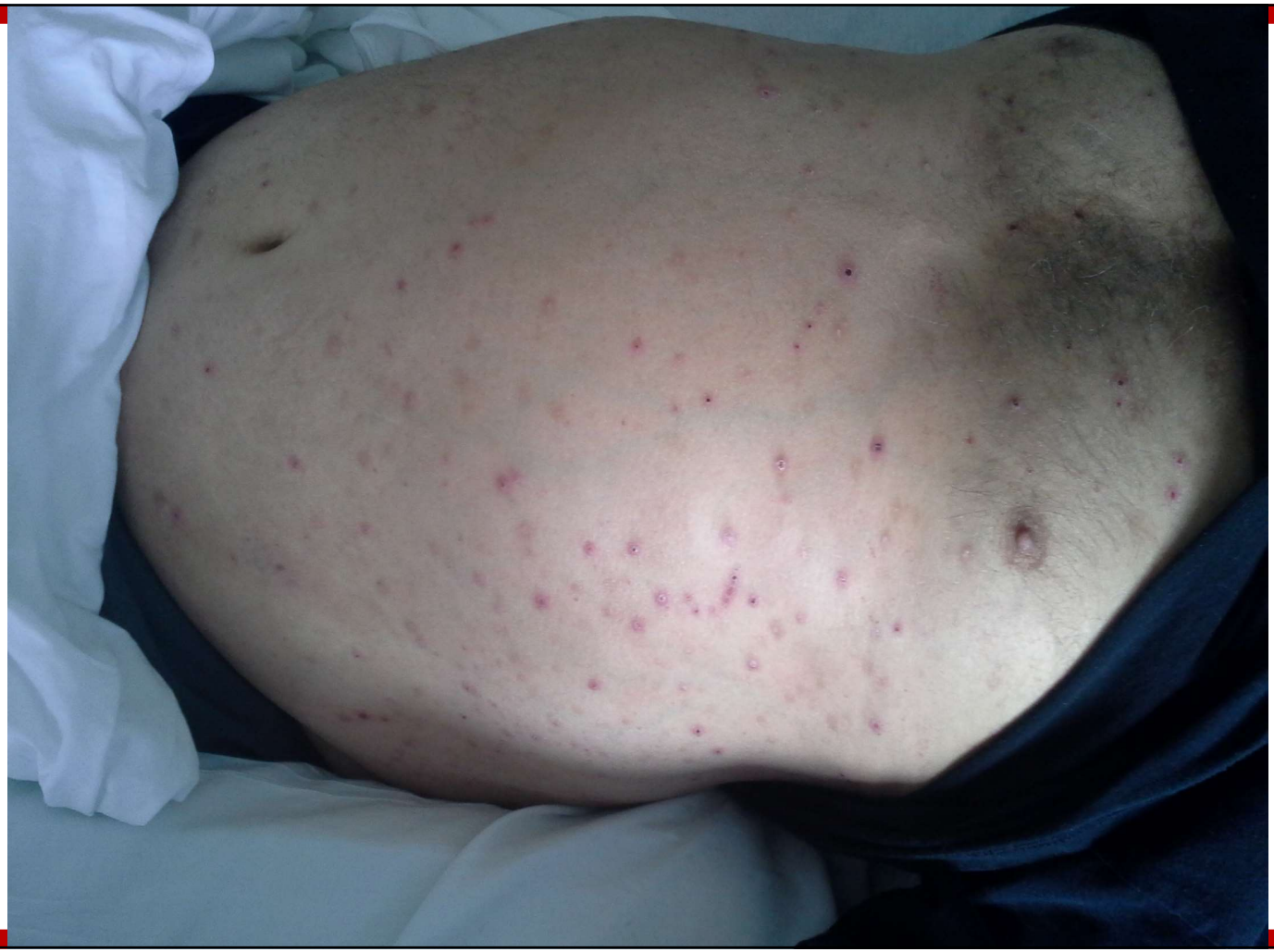
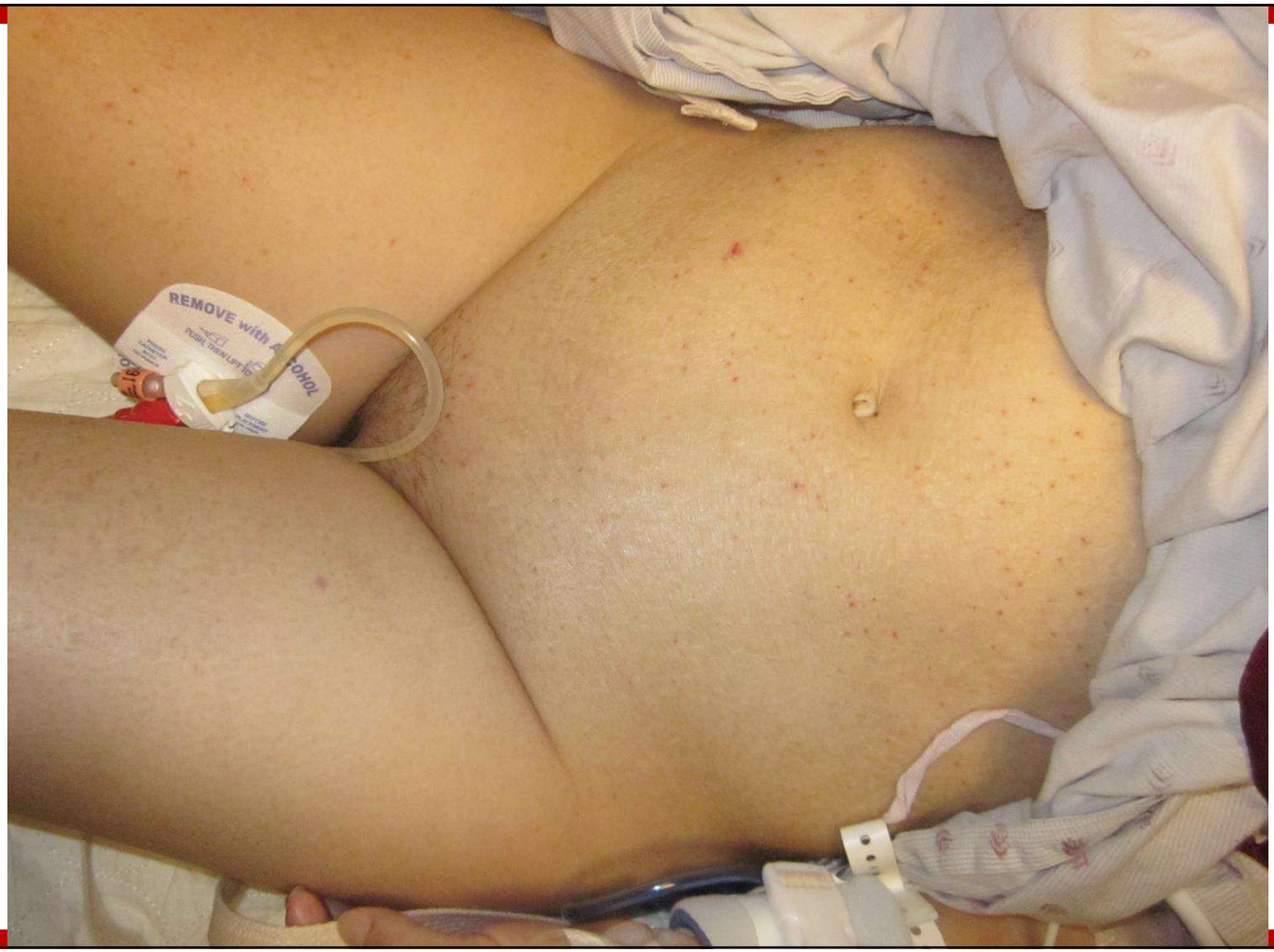
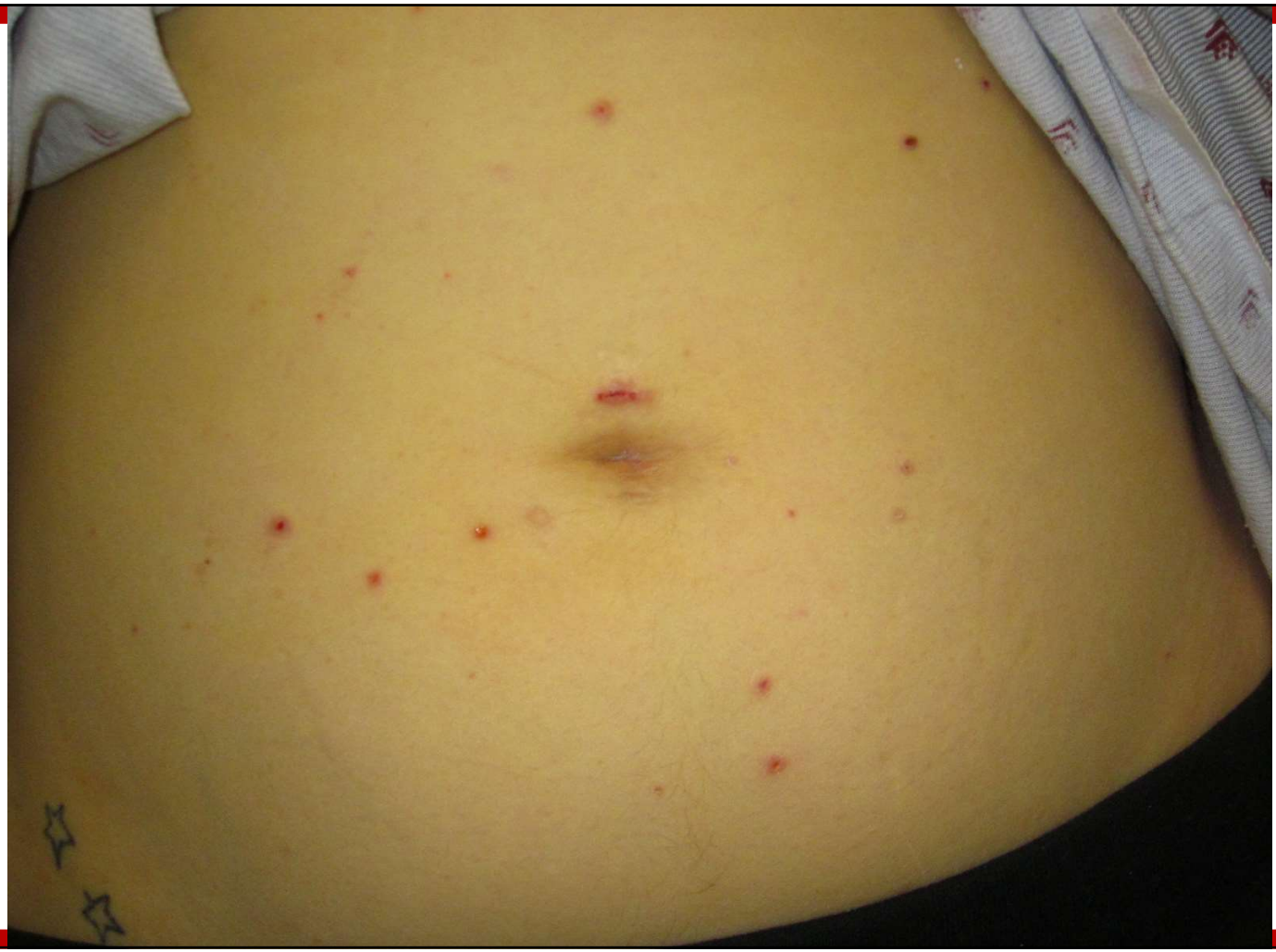
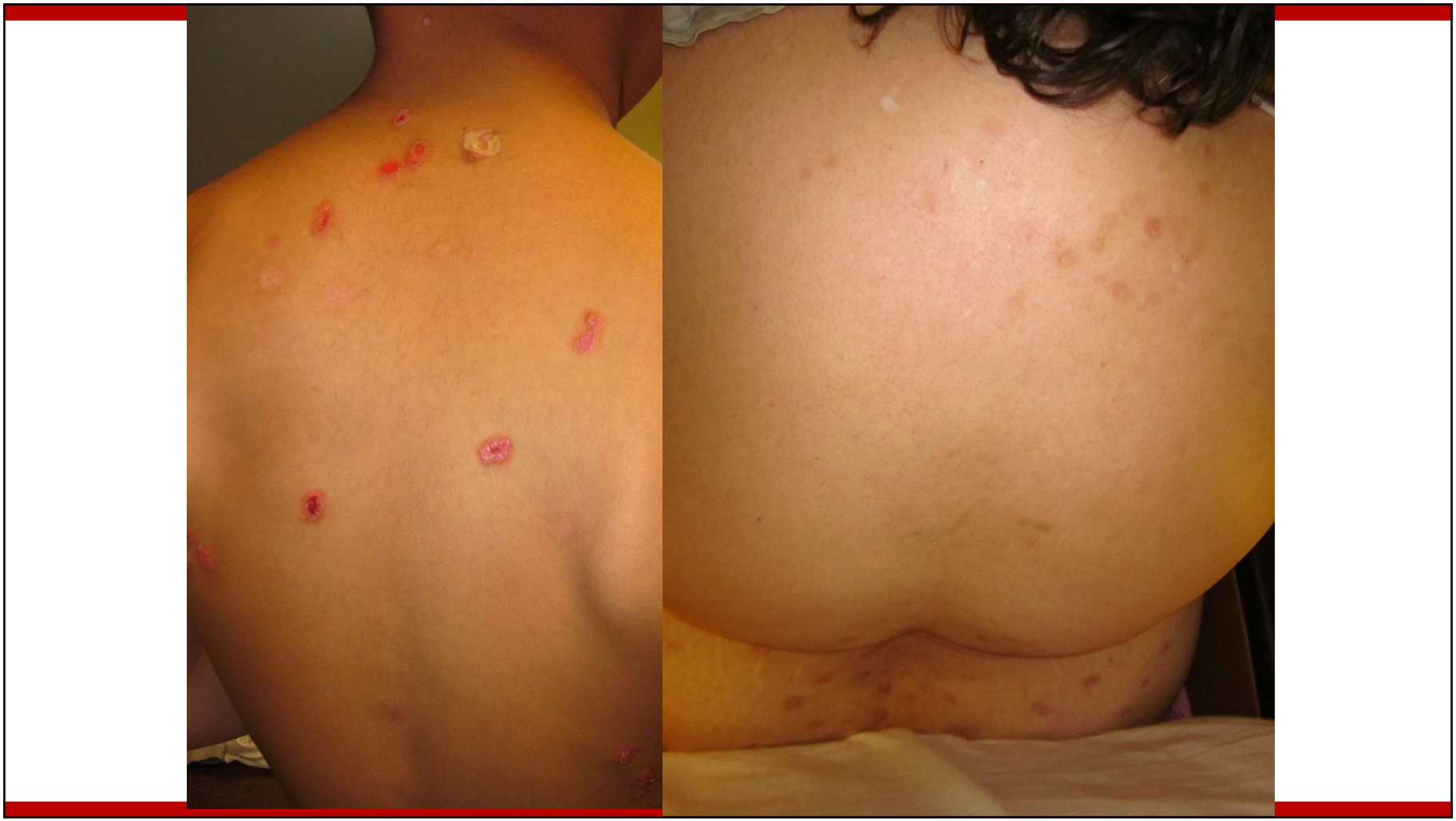
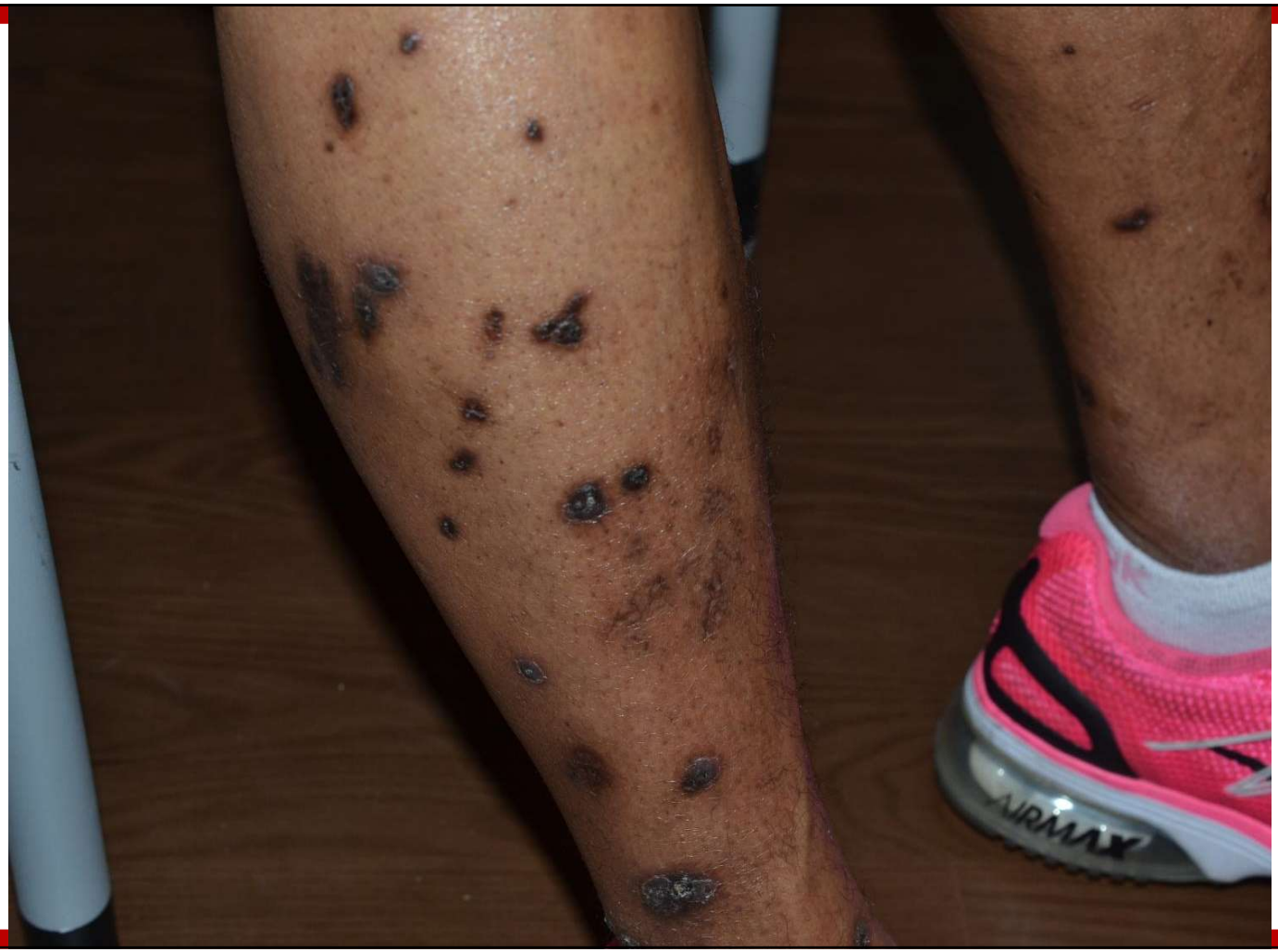


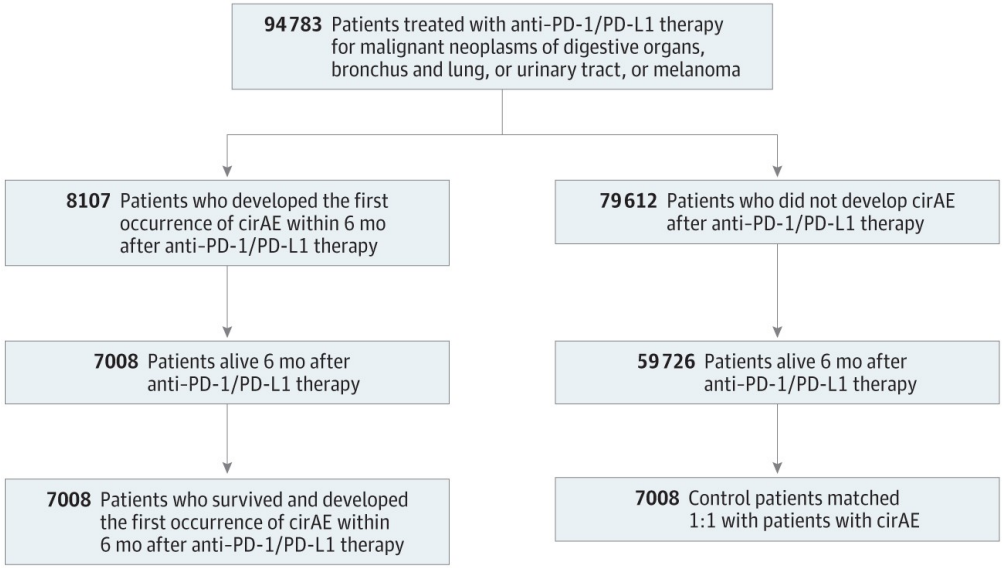








The Glass IS Half-Full



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The Glass IS Half-Full

Table 2. Association Between Cutaneous Eruptions and Survival Among Patients Treated With Anti–PD-1 or Anti–PD-L1 Therapy

Cutaneous diagnosis[a]	No.	Hazard ratio	*P* value[b]
Hyperhidrosis	281	1.381	.08
Mucositis	563	1.161	.21
Dermatomyositis	105	0.93	.79
Maculopapular eruption	230	0.845	.36
Erythroderma	247	0.769	.17
Drug eruption and nonspecific drug reaction	1075	0.755	.001
Hyperkeratosis	39	0.707	.49
Rash and other nonspecific eruption	3163	0.704	<.001
Psoriasis	299	0.703	.05
Pruritus	1694	0.695	<.001
Xerostomia	163	0.671	.13
Xerosis	441	0.626	.001
Eczema and atopic dermatitis	72	0.612	.15
Vitiligo	100	0.534	.09
Bullous pemphigoid	32	0.524	.33
Lichen planus	97	0.511	.03
Grover disease	18	0.468	.28
Any cutaneous diagnosis	7008	0.778	<.001

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The Glass IS Half-Full

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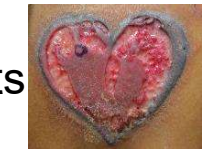
Take Home Points

1. Differentiate high-risk features as your first step in new-onset exanthems including facial involvement, facial swelling, palm involvement, mucosal involvement, pustules, and/or vesicles.
2. Utilize multidisciplinary guidance to determine risks vs benefits of immunotherapy rechallenges.
3. While Quality-of-Life effects of cutaneous immune-related adverse events may be profound, the largest studies and systematic reviews are consistent in a survival advantage across indications and drugs.

Dermatologists  Helping

Oncodermatology Society. Oncodermatologist Member Database. https://www.oncodermatologysociety.org/?page_id=3658.

Questions: Benjamin.Kaffenberger@osumc.edu

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An alliance of leading cancer centers devoted to patient care, research, and education

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To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision
To define and advance high-quality, high-value, patient-centered cancer care globally

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