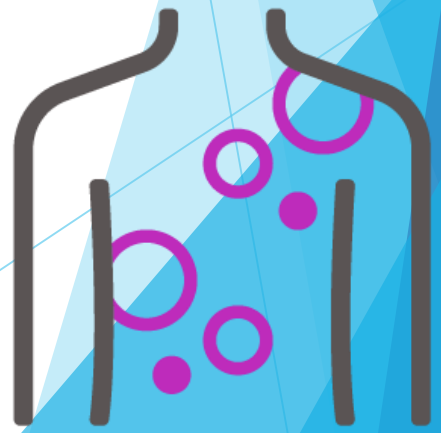
Beyond the algorithm:
The i-MPACT of optimizing MDT approach to irAE management

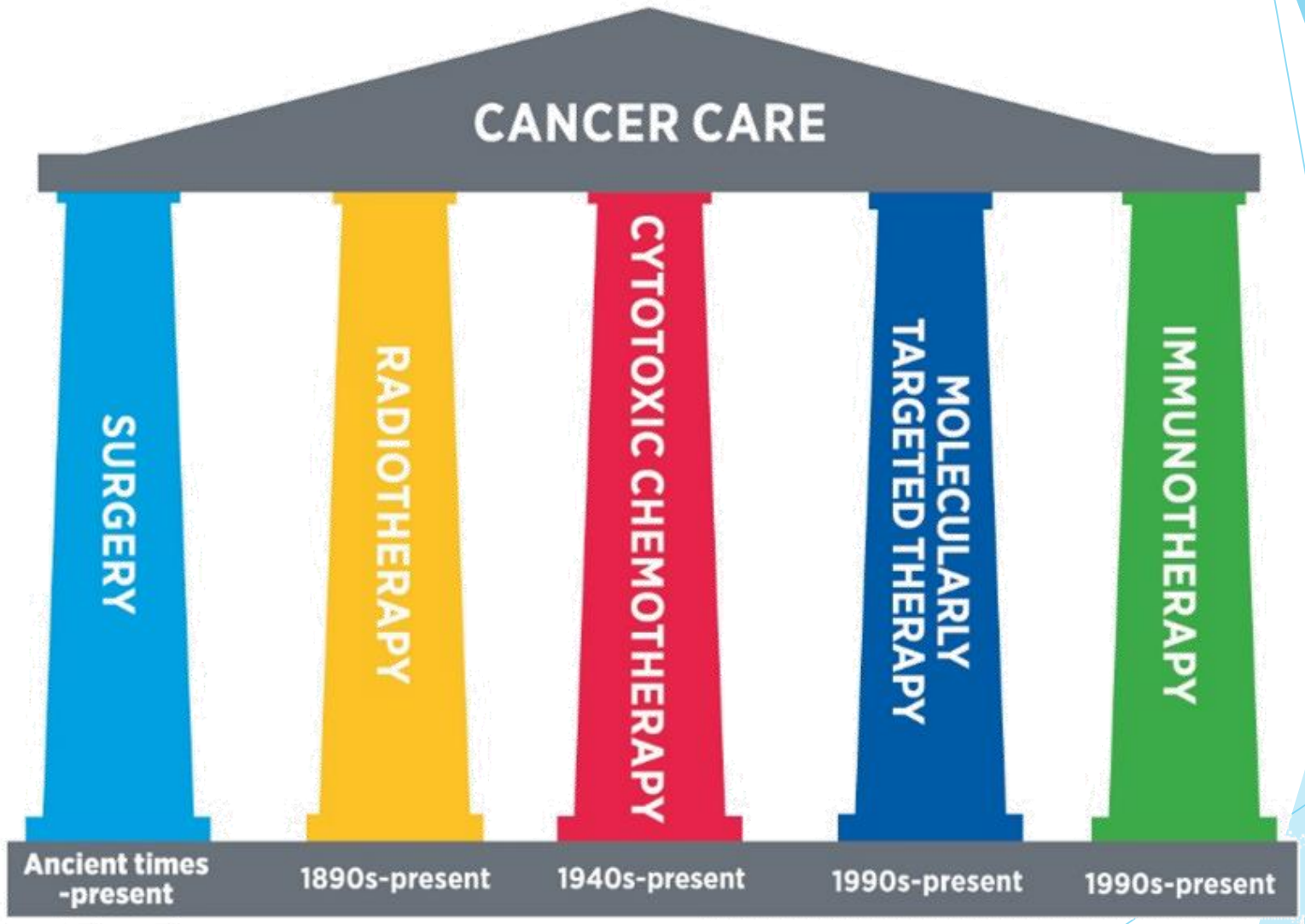
John Walker MD PhD FRCPC



Disclosures

- Research funding from BMS, Merck, EMD Serono, Pfizer
- Honoraria from BMS, Merck, EMD Serono, Pfizer, Novartis, Roche

- To mitigate bias, no specific oncologic treatment recommendations will be made during this presentation


CANCER CARE
SURGERY
RADIOTHERAPY
CYTOTOXIC CHEMOTHERAPY
MOLECULARLY TARGETED THERAPY
IMMUNOTHERAPY
Ancient times -present
1890s-present
1940s-present
1990s-present
1990s-present

2010

DECEASED

ALIVE

2019

DECEASED

ALIVE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

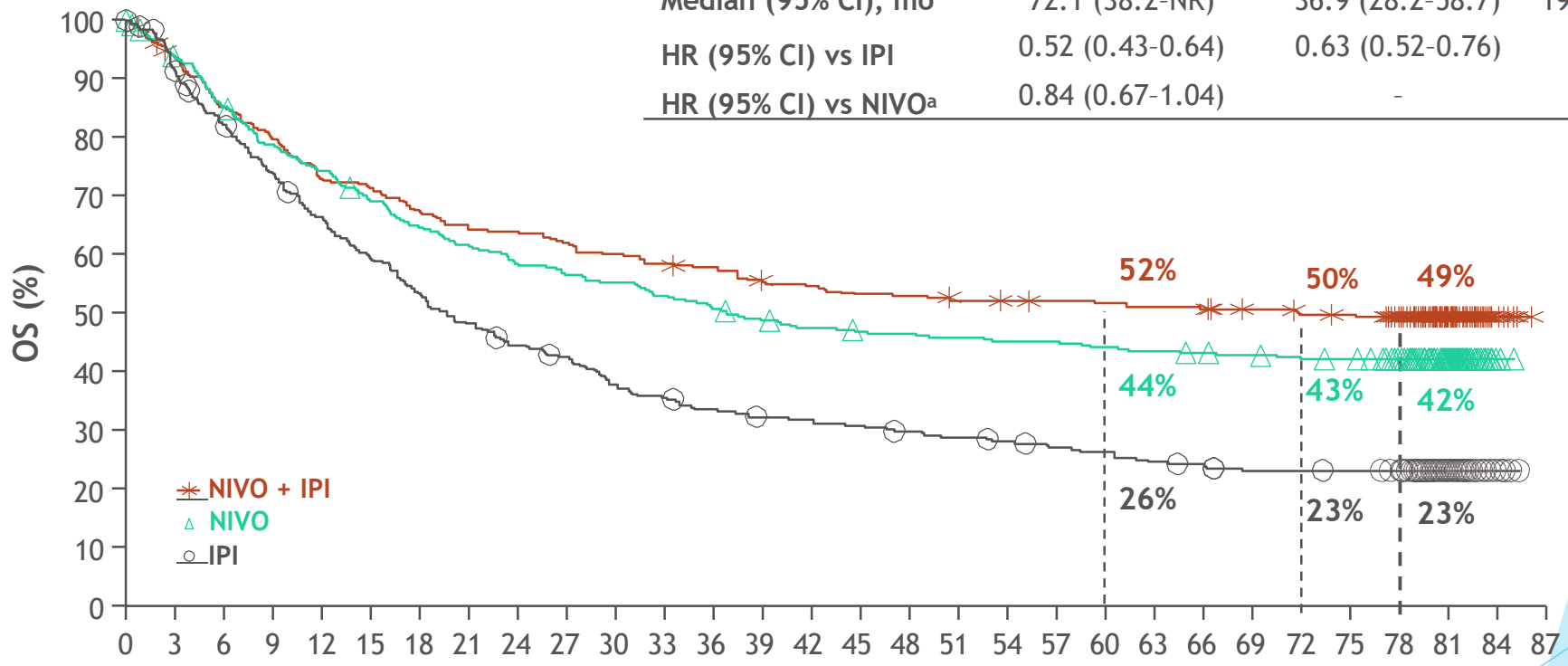
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

5812 PubMed citations!

CheckMate 067: Overall Survival After 6.5 Years of Follow-up

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-

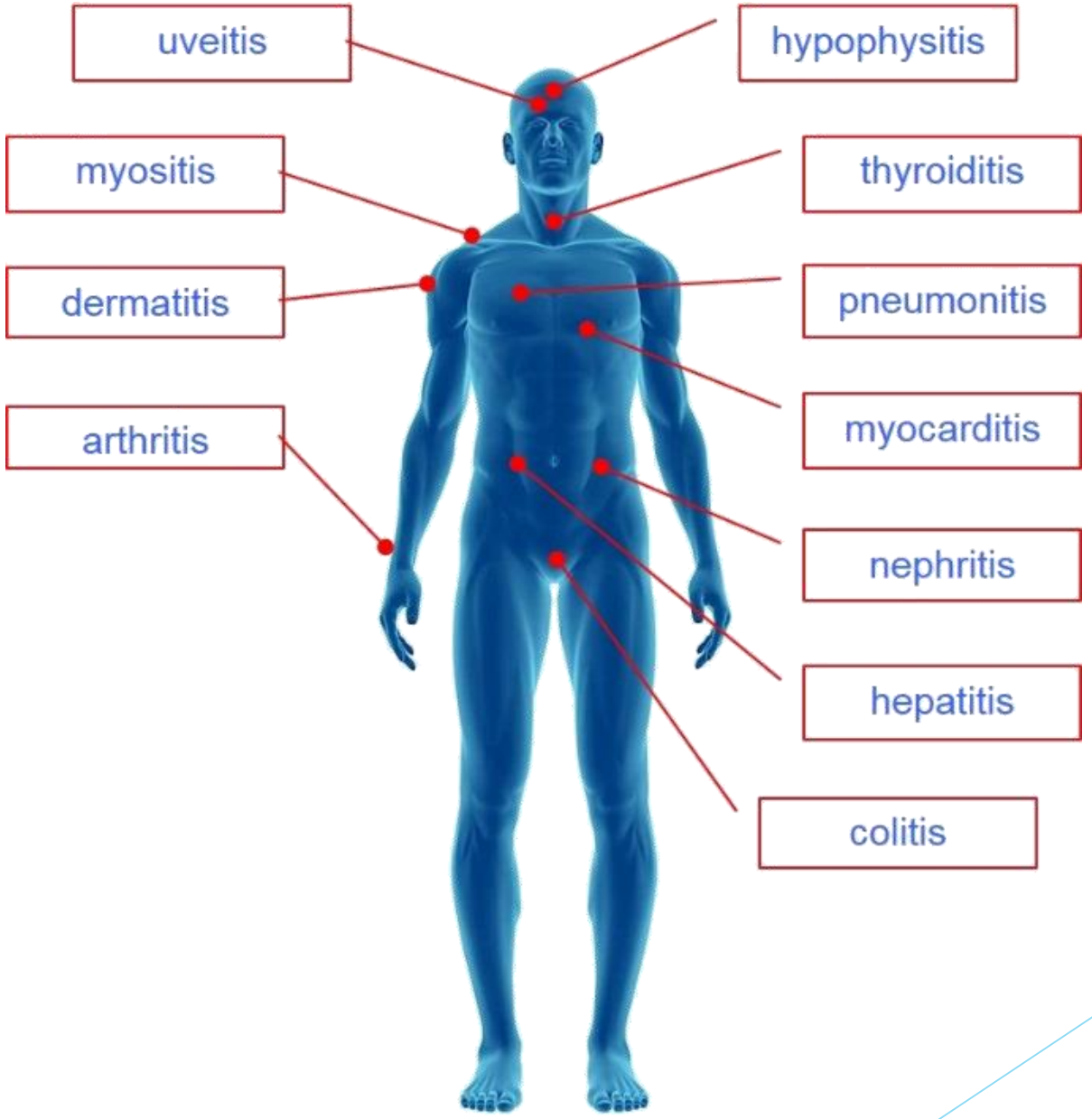


HR: Hazard Ratio

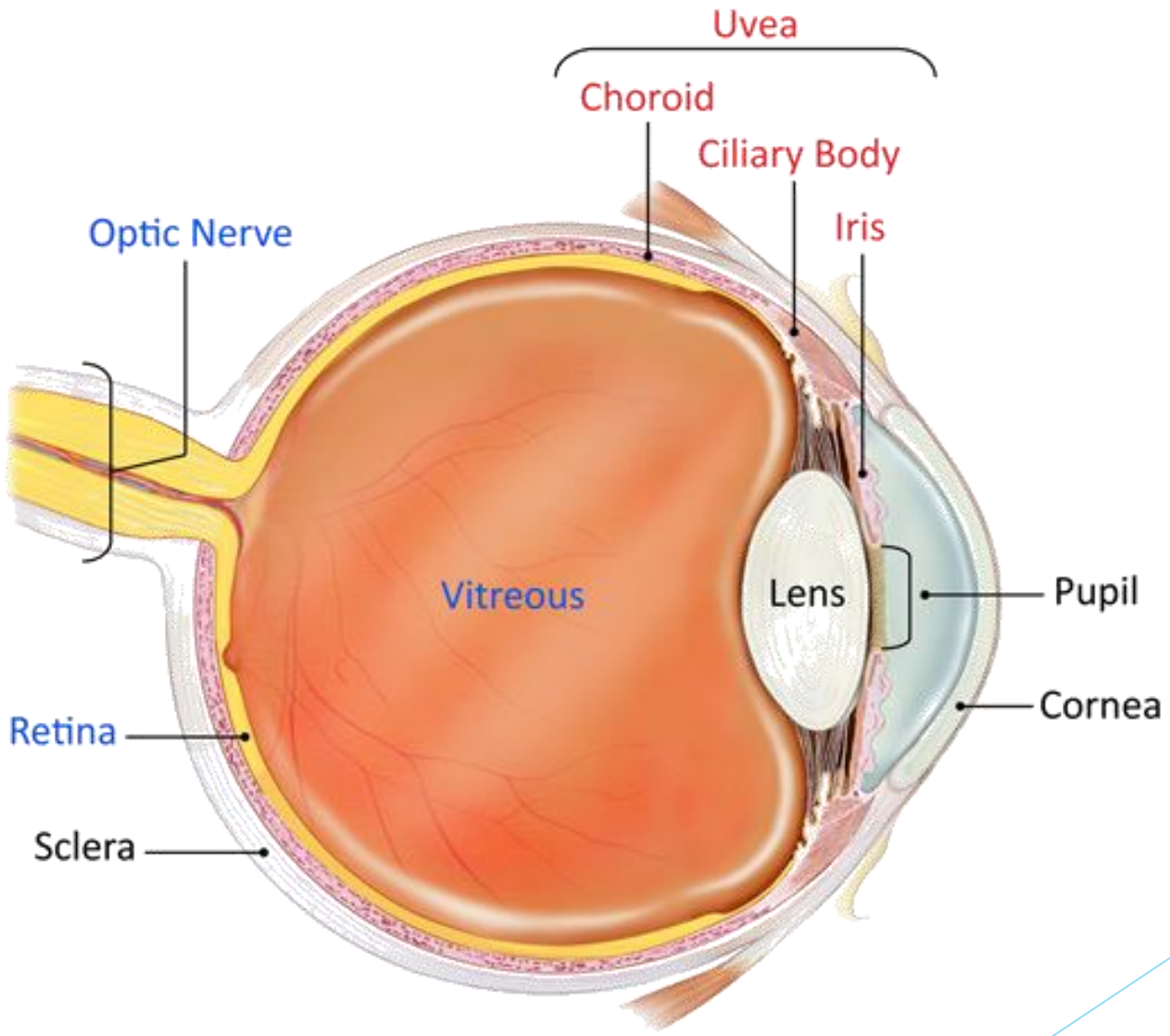
Adapted From Wolchek JD et all. Presented At ASCO June 2021.Abstract 9506

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
			number of patients with e	215 (68.7)		
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)			173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)		85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)			19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)


uveitis
hypophysitis
myositis
thyroiditis
dermatitis
pneumonitis
myocarditis
arthritis
nephritis
hepatitis
colitis

Uveitis?


Uvea
Choroid
Ciliary Body
Iris
Optic Nerve
Vitreous
Lens
Pupil
Cornea
Retina
Sclera

"If all you have is a hammer, everything looks like a nail…"

Diffuse retinal venulitis in a patient treated with pembrolizumab immunotherapy

46 M, oropharyngeal squamous cell carcinoma (PD-L1 “high”) metastatic to lung and bone

Post-cycle #3 pembrolizumab immunotherapy

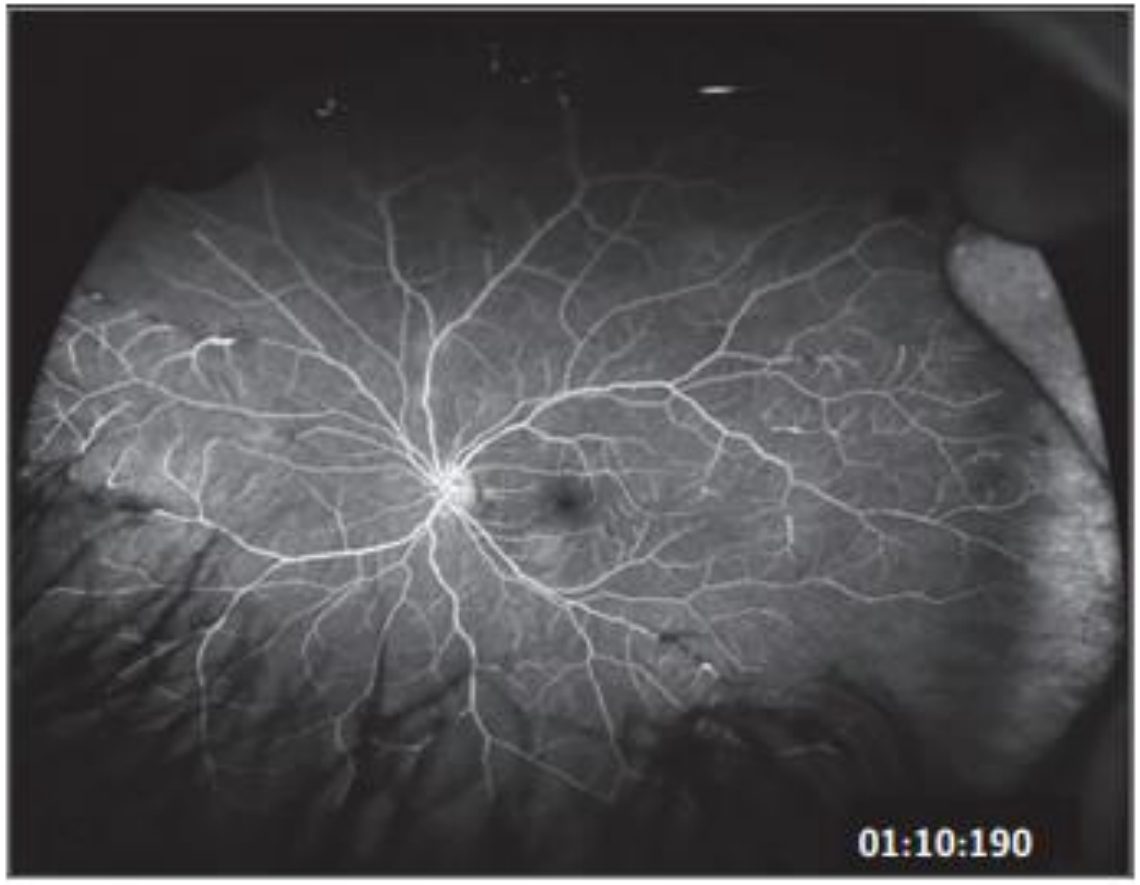
Gradual onset, bilateral “blotchy” vision (4-5 days)

Progressively worsening visual acuity and “blind spots”

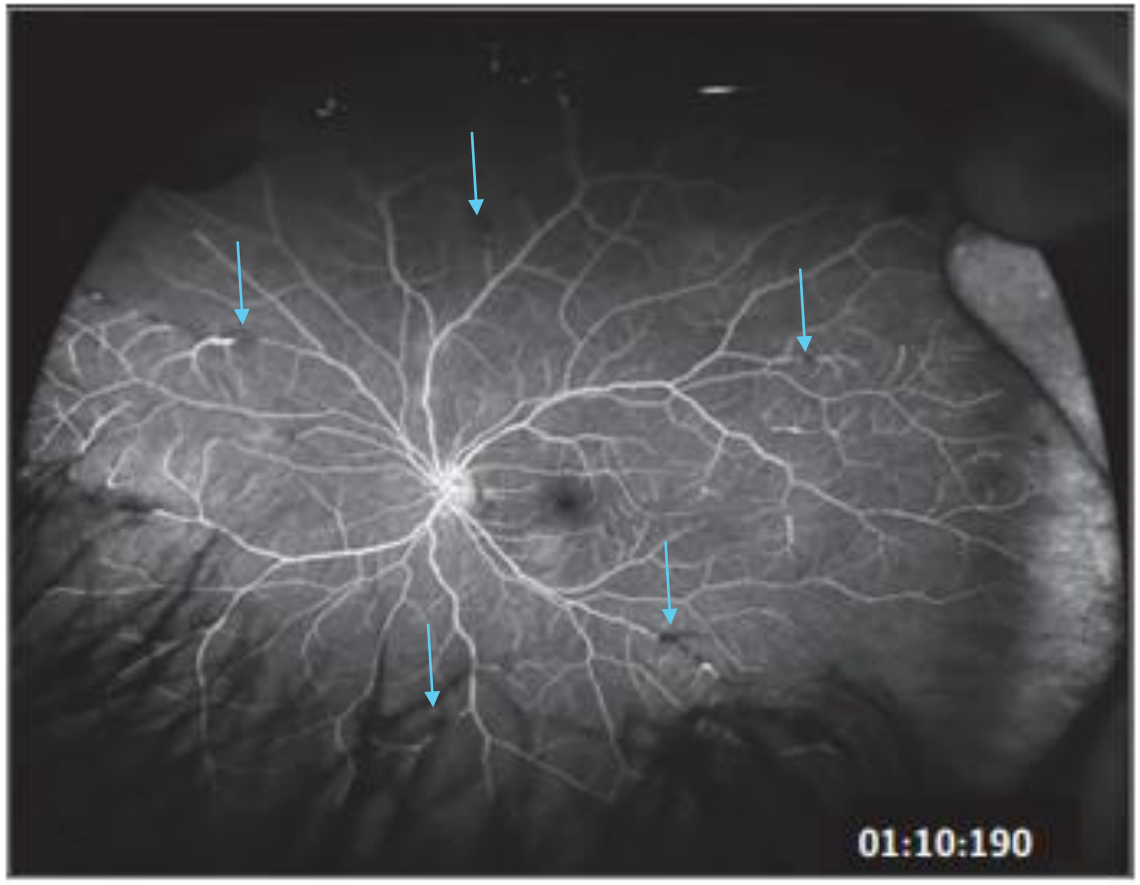
Denies ophthalmalgia, headaches or additional neurological symptoms

MRI brain unremarkable

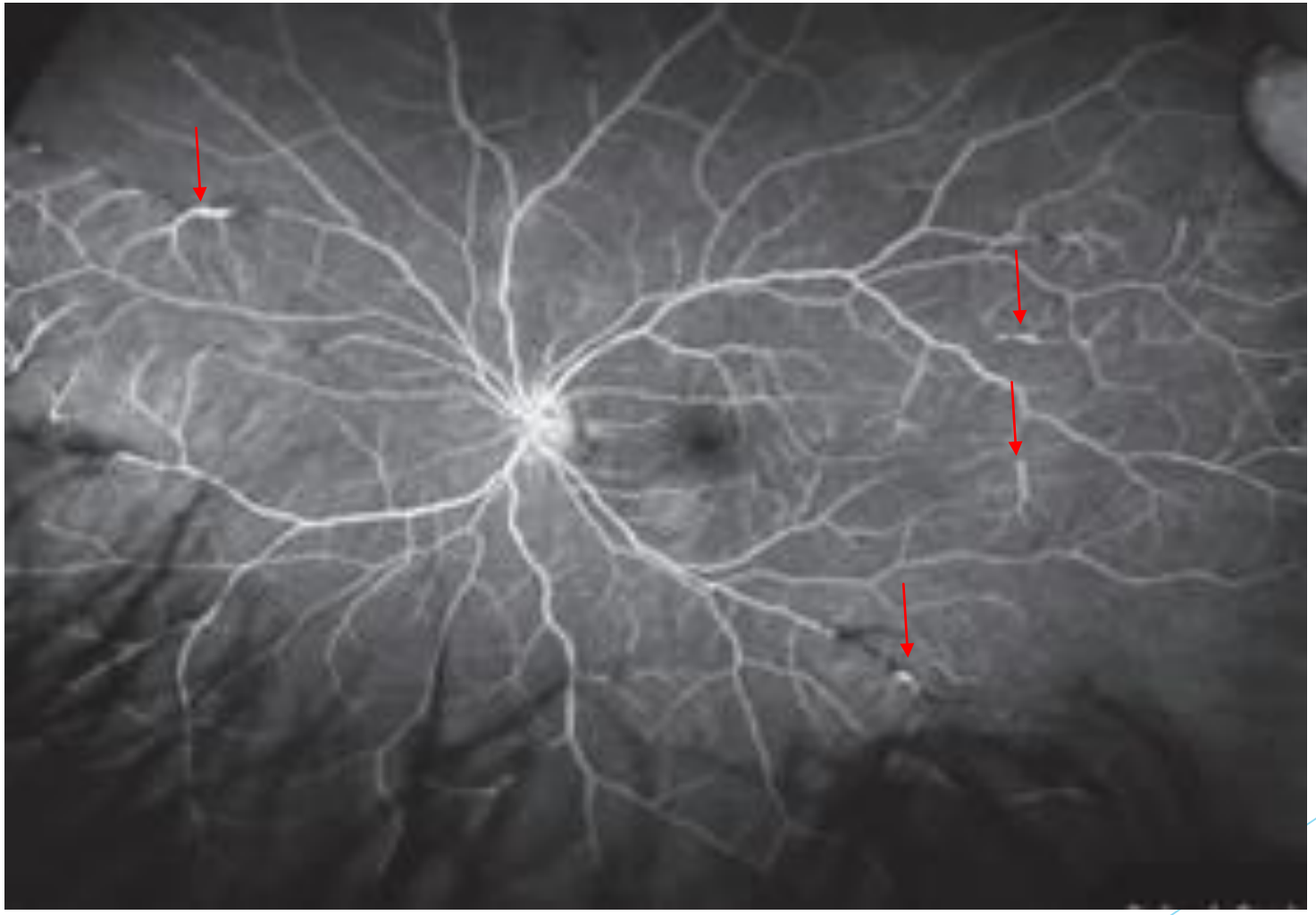
Diffuse retinal venulitis in a patient treated with pembrolizumab immunotherapy



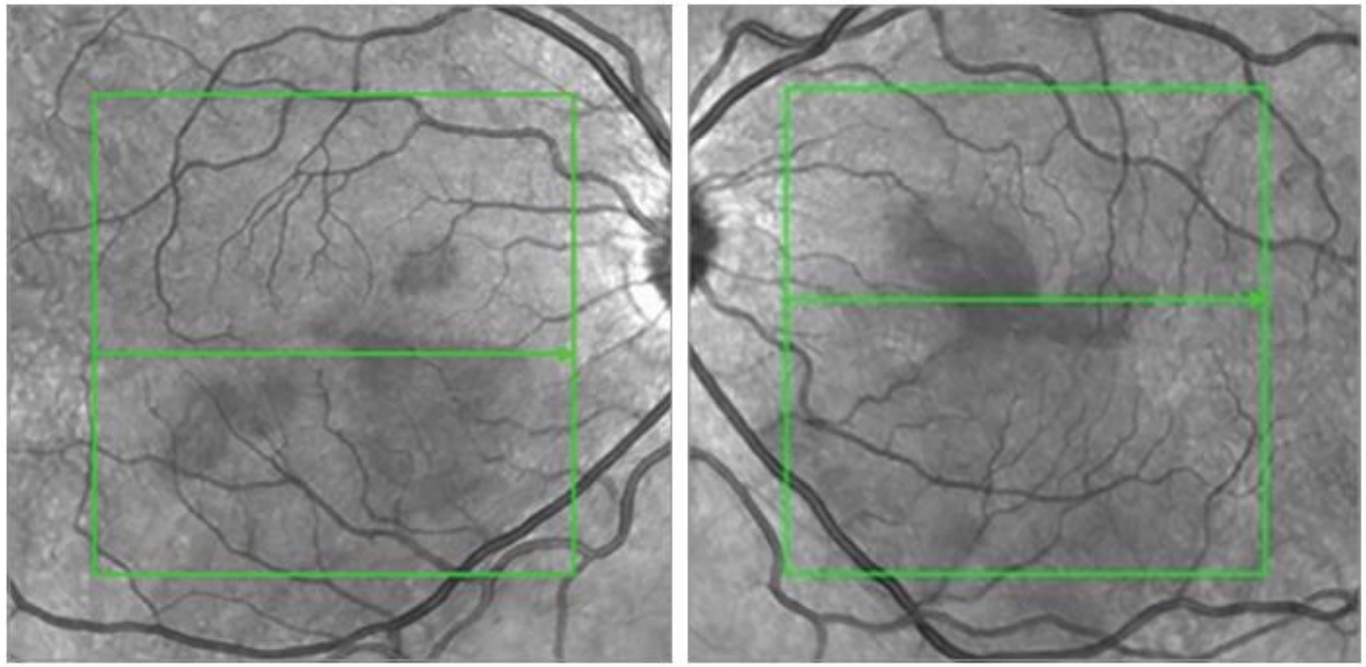
Diffuse retinal venulitis in a patient treated with pembrolizumab immunotherapy



Diffuse retinal venulitis in a patient treated with pembrolizumab immunotherapy



Diffuse retinal venulitis in a patient treated with pembrolizumab immunotherapy



Diffuse retinal venulitis in a patient treated with pembrolizumab immunotherapy

46 M, oropharyngeal squamous cell carcinoma (PD-L1 “high”) metastatic to lung and bone

Initiated on prednisone 50 mg po QD, tapered to “off” over a 6 week period

Improvement of scotomas within 72 hours, resolution by week 3

Visual acuity gradually improving

Pembrolizumab remains on hold

JAMA Ophthalmol. 2019;137(1):96-100.

Research

JAMA Ophthalmology | Brief Report

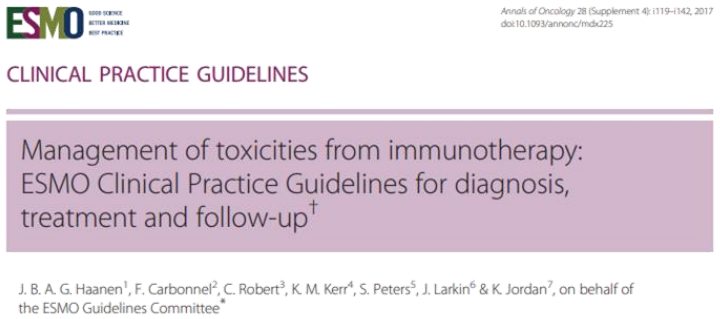
Association of Cancer Immunotherapy With Acute Macular Neuroretinopathy and Diffuse Retinal Venulitis

Leisha A. Emens, MD, PhD; S. Lindsey Davis, MD; Scott C. N. Oliver, MD; Christopher H. Lieu, MD; Ashvini Reddy, MD; Sharon Solomon, MD; Lingmin He, MD; Roland Morley, MBBS; Marcella Fassò, PhD; Andrea Pirzkall, MD; Hina Patel, PharmD; Carol O'Hear, MD, PhD; Daniela Ferrara, MD, PhD

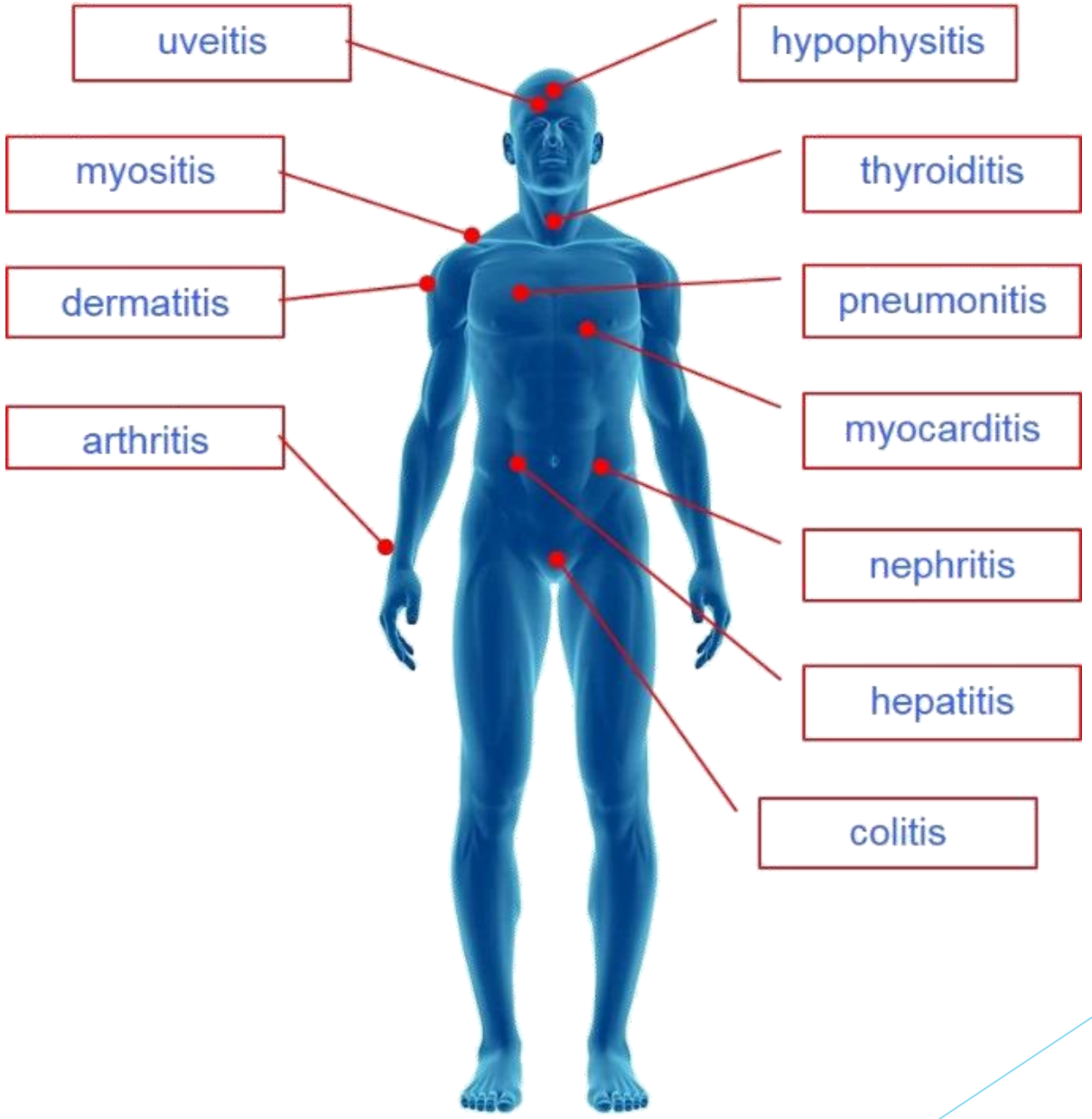
Thanks to Dr Chad Baker, Department of Ophthalmology & Visual Sciences, University of Alberta

Ocular immune-related toxicities

- irAEs of the eye are rare (<1% of treated patients)
- Include ocular inflammation, orbital inflammation and retinal and choroidal inflammation
- Treatment guided by severity: i.e., topical corticosteroids for episcleritis, systemic corticosteroids for severe ocular/orbital inflammation



www.esmo.org/content/download/151567/2718664/file/Clinical-Practice-Guidelines-Slideset-Toxicities-Immunotherapy.pdf


uveitis
hypophysitis
myositis
thyroiditis
dermatitis
pneumonitis
myocarditis
arthritis
nephritis
hepatitis
colitis

JAMA Netw Open. 2019;2(5):e192535.

“Dermatitis”

70 M, (resected) stage IIIB melanoma upper back, post-cycle 7 adjuvant nivolumab

Presents to OPD with a 3-day history of an evolving rash

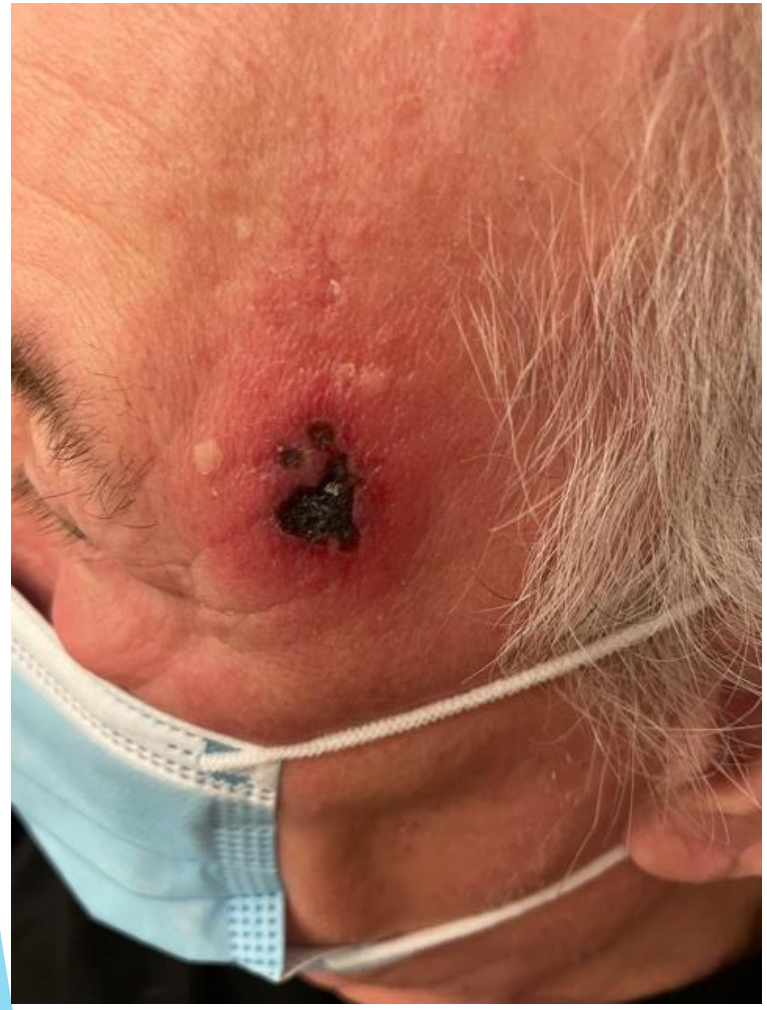
Non-pruritic (“irritating”)

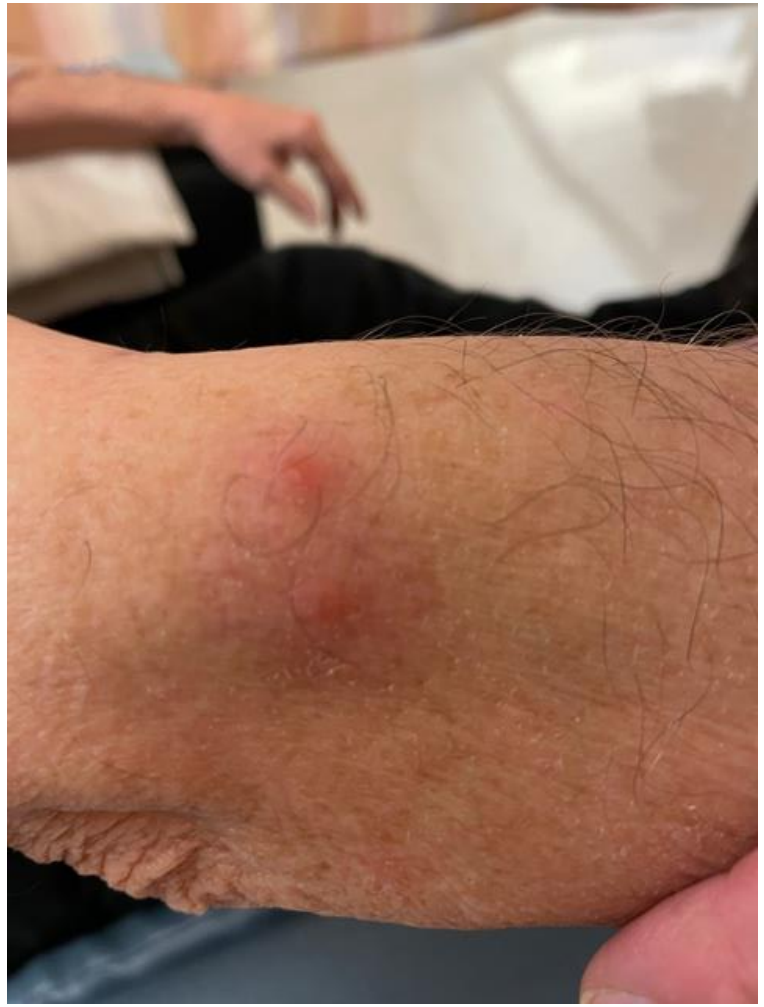
Diffusely distributed (head/scalp, trunk, upper extremities)

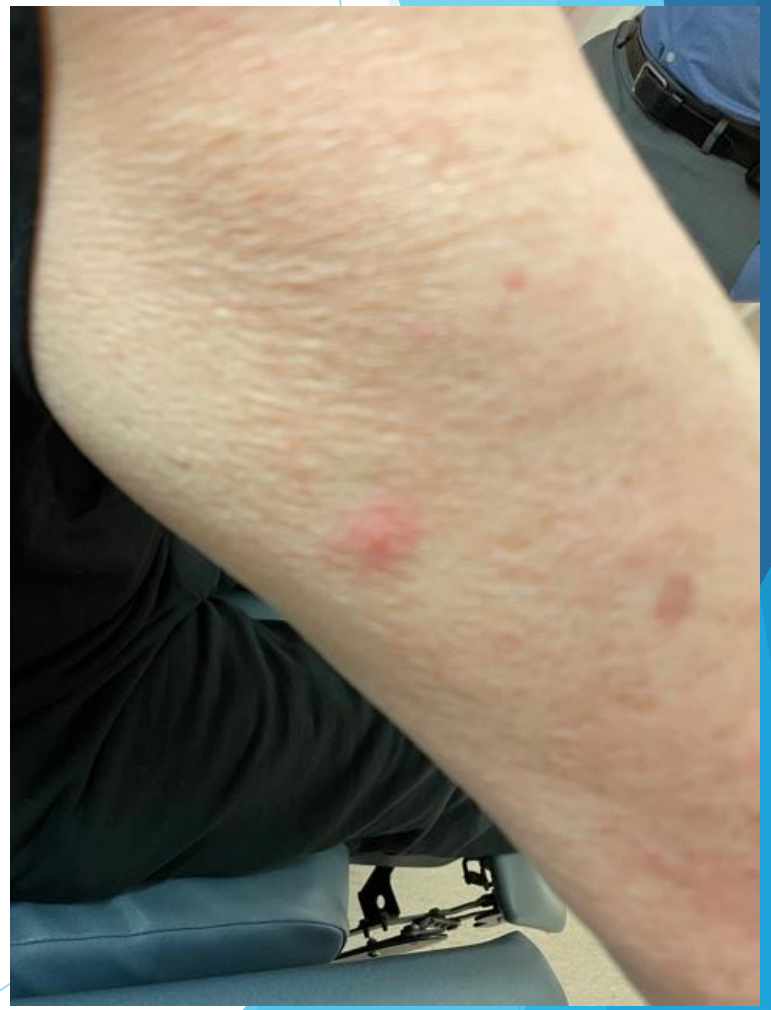
Low-grade fevers concurrent with development of rash

Decision made to proceed with cycle 8 treatment

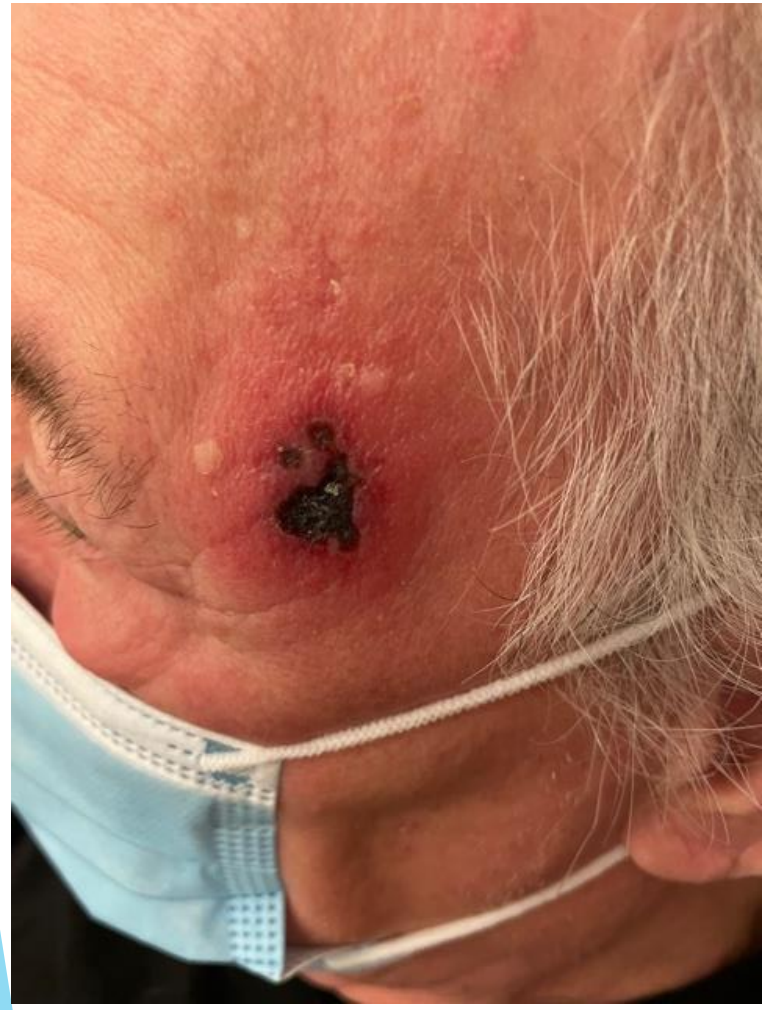
“Dermatitis”

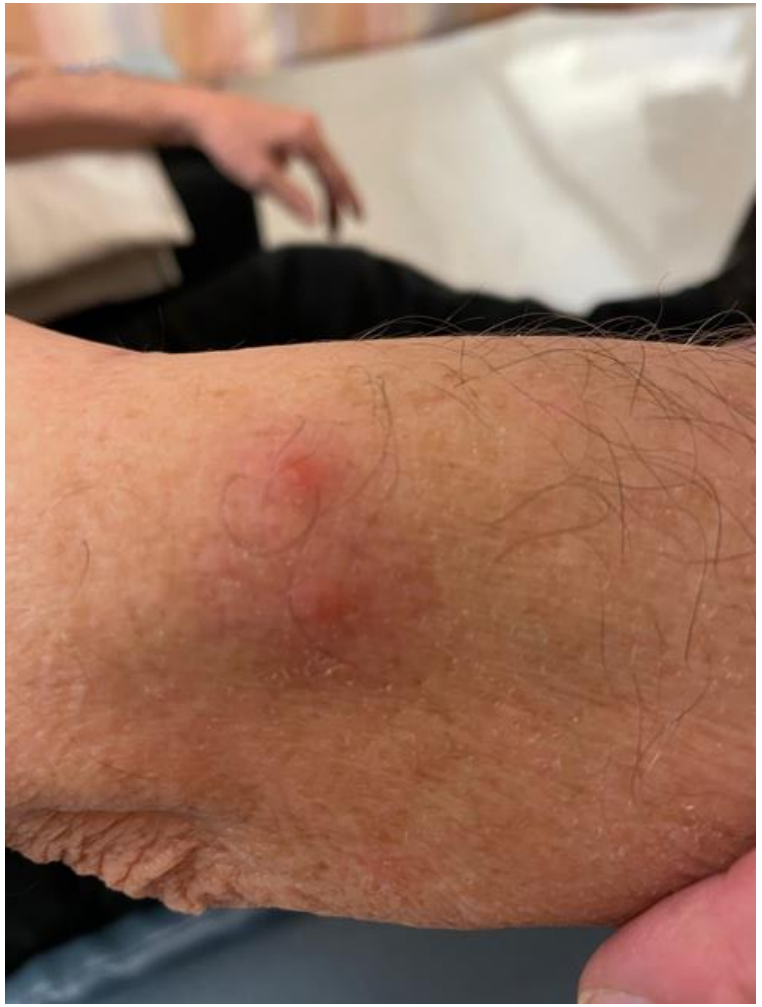


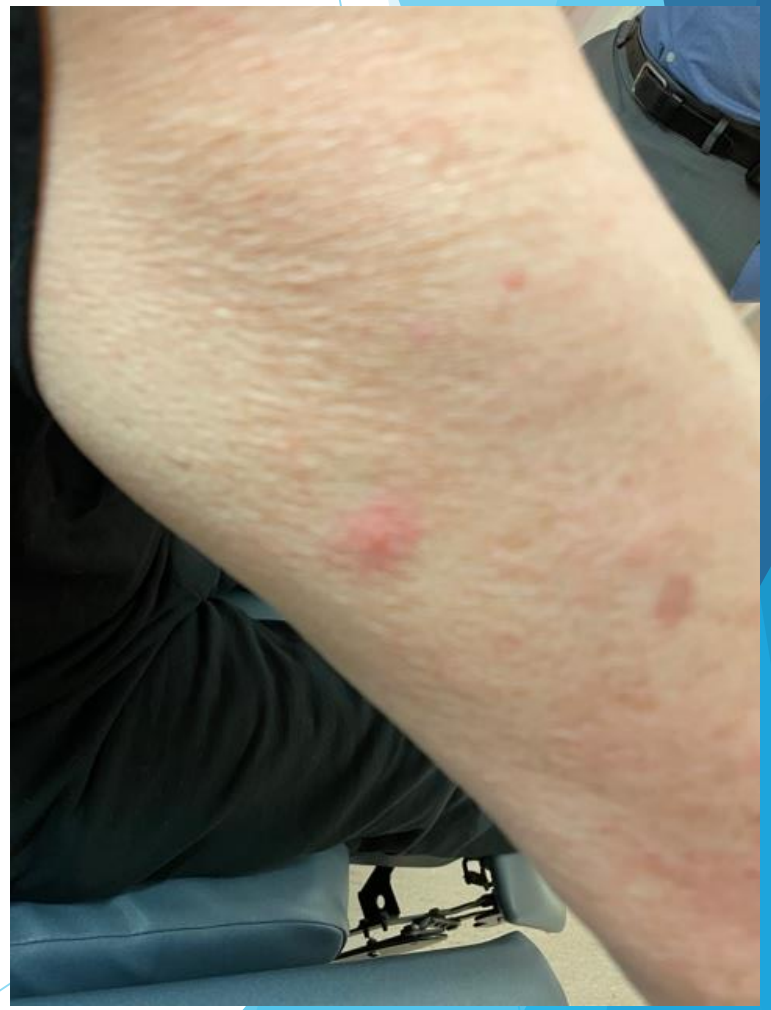




Thoughts?







Immune-related skin toxicities

- Rash/inflammatory dermatoses
- Bullous dermatoses
- Severe cutaneous adverse reactions (SCARs)

Journal of Clinical Oncology 36, no. 17 (June 10, 2018) 1714-1768.

Immune-related skin toxicities

- Rash/inflammatory dermatoses

  Erythema multiforme, lichenoid, eczematous, psoriasiform, maculopapular

- Bullous dermatoses

  Bullous pemphigoid, bullous drug reactions

- Severe cutaneous adverse reactions (SCARs)

  SJS, TEN, DRESS

Immune-related skin toxicities

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  Erythema multiforme, lichenoid, eczematous, psoriasiform, maculopapular

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  Bullous pemphigoid, bullous drug reactions

- Severe cutaneous adverse reactions (SCARs)

  SJS, TEN, DRESS

“Dermatitis”

70 M, (resected) stage IIIB melanoma upper back, post-cycle 7 adjuvant nivolumab

Reassessed on daycare unit (drug is hanging)

Persistent fevers x 48 hours

Moderate headache, anorexic

Decision made to defer infusion

Disseminated varicella zoster

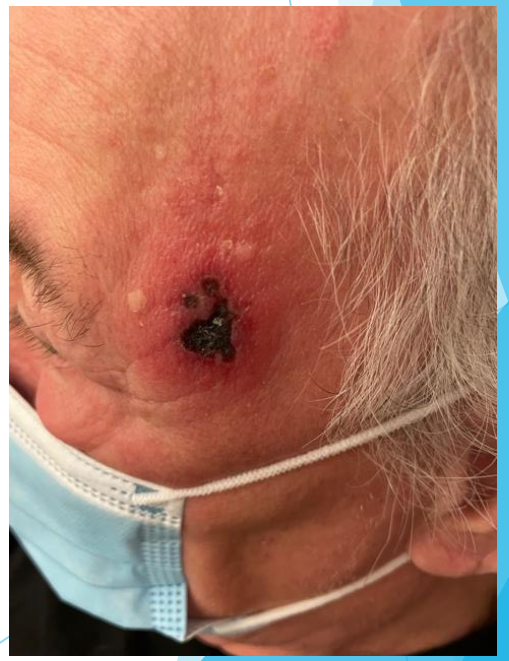
70 M, (resected) stage IIIB melanoma upper back, post-cycle 7 adjuvant nivolumab

Dermatology consulted

Lesion swabbed for viral studies (face and arm)

Patient admitted to hospital and empiric valacyclovir started

Lumbar puncture negative



Improvement of rash/symptoms over ensuing 48 hours

Management of bullous dermatoses

- G1: Asymptomatic; blistering affects <10% BSA

  May continue ICI

  Observe; local wound care (bandaging, petrolatum ointment)

- G2: Blistering affects QoL; 10-30% BSA

  Hold ICI

  Local wound care

  Topical steroids (betamethasone); regular r/a (q.3 days); low threshold to escalate to systemic corticosteroids (prednisone 0.5-1 mg/kg)

- G3: Sloughing affects >30% BSA

  Hold ICI, dermatology consultation

  IV methylprednisolone 1-2 mg/kg w/4+ week taper

  +/- Infectious Diseases consultation

  Rituximab may be considered as adjunct/alternative to steroid (Bullous pemphigus -like rxn)

- G4: BSA >30%, w/fluid and/or electrolyte abnormalities

  Management per G3, suggested permanent discontinuation of ICI

Journal of Clinical Oncology 36, no. 17 (June 10, 2018) 1714-1768.

Management of bullous dermatoses

- G1: Asymptomatic; blistering affects <10% BSA
  - *May continue ICI*
  - *Observe; local wound care (bandaging, petrolatum ointment)*
- G2: Blistering affects QoL; 10-30% BSA
  - *Hold ICI*
  - *Local wound care*
  - *Topical steroids (betamethasone); regular r/a (q.3 days); low threshold to escalate to systemic corticosteroids (prednisone 0.5-1 mg/kg)*
- G3: Sloughing affects >30% BSA
  - *Hold ICI, dermatology consultation*
  - *IV methylprednisolone 1-2 mg/kg w/4+ week taper*
  - *+/- Infectious Diseases consultation*
  - *Rituximab may be considered as adjunct/alternative to steroid (Bullous pemphigus -like rxn)*
- G4: BSA >30%, w/fluid and/or electrolyte abnormalities
  - *Management per G3, suggest permanent discontinuation of ICI*

Journal of Clinical Oncology 36, no. 17 (June 10, 2018) 1714-1768.

Management of bullous dermatoses

Thanks to Dr Tom Salopek, Professor, Faculty of Medicine and Dentistry, Department of Dermatology

Case Report

A Rare Case of Pembrolizumab-Induced Reactivation of Hepatitis B

Anita Pandey, Susan Ezemenari, Maksim Liaukovich, Ivan Richard, and Avezbakiyev Boris

Clinical Microbiology and Infection 24 (2018) 216–218

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Hot topic

Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment

CASE REPORT **Open Access**

HSV-pneumonitis in a patient with lung cancer receiving check point inhibitors – a case report

Johannes Sumer[1*], Frederike Waldeck[1], Nadja Fischer[2], Christina Appenzeller[3,4], Markus Koster[5], Martin Früh[3,4] and Werner C. Albrich[1]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 25, 2019 VOL. 380 NO. 17

Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy

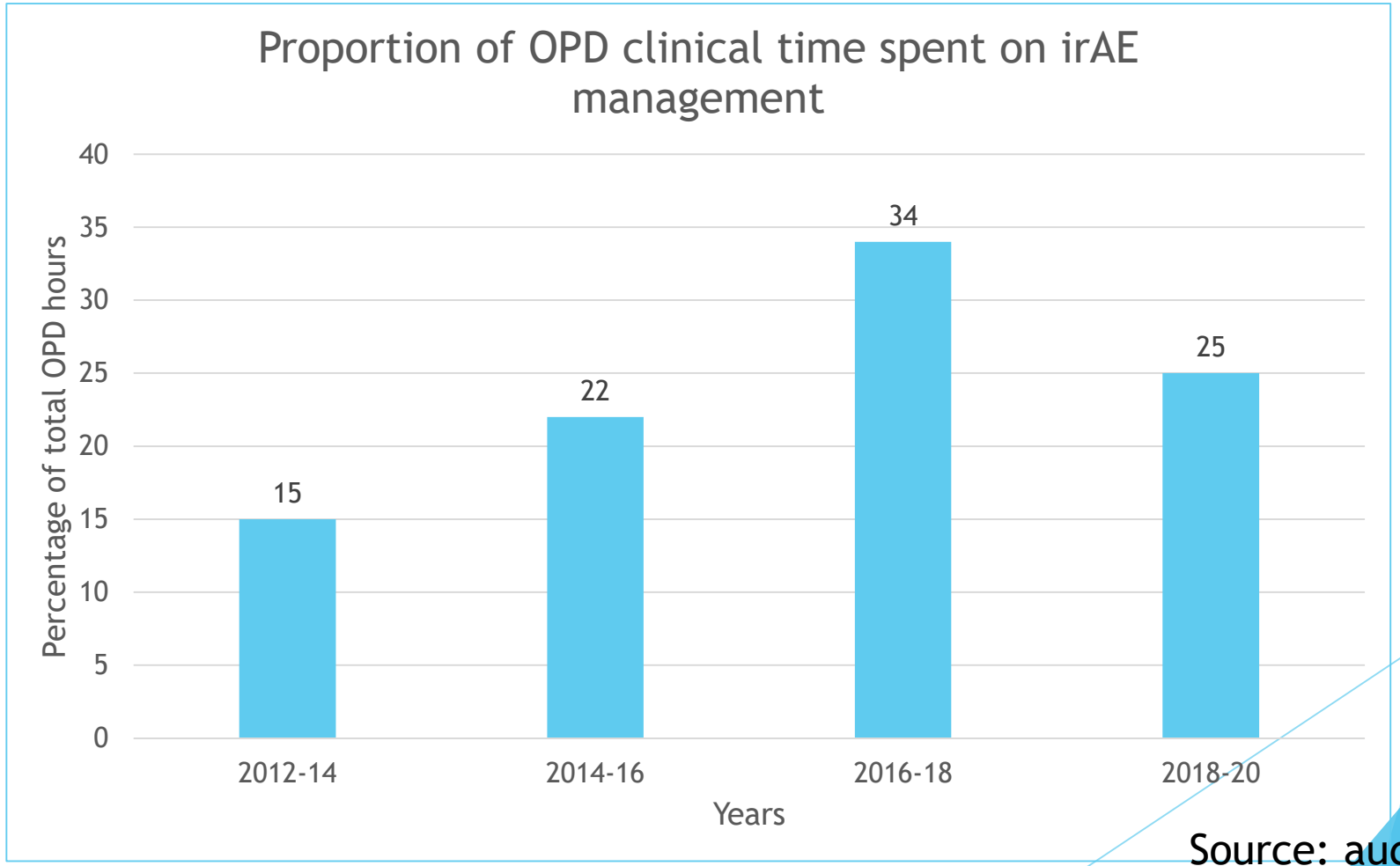
Varicella Zoster Virus Encephalitis Mimicking Nivolumab-Induced Autoimmune Neuropathy in a Patient with Lung Cancer

To the Editor:

A 70-year-old woman was admitted to our hospital in November 2018 with a 1-day history of consciousness disturbance. In 2013, the patient's condition was diagnosed as an adenocarcinoma of the right lung metastasizing to the right femoral bone. She received six cycles of carboplatin plus pemetrexed as the first-line treatment. In 2014, computed tomography revealed progressive disease, and second-line treatment with afatinib

What has been the impact of irAEs on your clinical practice?

What has been the impact of irAEs on your clinical practice?



Source: audit of CCI clinical practice

Research

JAMA Oncology | Brief Report

Chronic Immune-Related Adverse Events Following Adjuvant Anti–PD-1 Therapy for High-risk Resected Melanoma

J. Randall Patrinely Jr, BA; Rebecca Johnson, BHlthSc, MN; Aleigha R. Lawless, BS; Prachi Bhave, MD; Amelia Sawyers, BS; Maya Dimitrova, MD; Hui Ling Yeoh, MBBS, BMedSc; Marisa Palmeri, BS; Fei Ye, PhD; Run Fan, PhD; Elizabeth J. Davis, MD; Suthee Rapisuwon, MD; Georgina V. Long, MD, PhD; Andrew Haydon, MD, PhD; Iman Osman, MD; Janice M. Mehnert, MD; Matteo S. Carlino, MD, PhD; Ryan J. Sullivan, MD; Alexander M. Menzies, MBBS, PhD; Douglas B. Johnson, MD

JAMA Oncology | Brief Report

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Table 2. Incidence of Chronic Immune-Related Adverse Events (irAEs)

Chronic irAEs	Patients, No. (%)	
	With chronic irAEs	Ongoing chronic irAE at last follow-up
Total chronic irAEs	167 (100)	NA
Required steroids	55 (32.9)	NA
Symptomatic	82 (49.1)	NA
Resolved	24 (14.4)	NA
≥Grade 2	90 (53.9)	NA
Grade 3-5	6 (3.6)	NA
irAE Type[a]		
Adrenal insufficiency	12 (3.1)	12 (100)
Arthritis/arthralgias	22 (5.7)	22 (100)
Colitis/diarrhea	6 (1.6)	2 (33.3)
Dermatitis/pruritus	19 (6.6)	17 (89.5)
Xerostomia[b]	9 (2.3)	8 (88.9)
Hypophysitis	8 (2.1)	8 (100)
Neuropathy	3 (1.8)	1 (33.3)
Ocular toxic effect[c]	5 (1.3)	5 (100)
Other neurotoxicity[d]	8 (2.1)	5 (63.0)
Pneumonitis	6 (1.6)	4 (66.7)
Thyroiditis/hypothyroid	54 (14.0)	54 (100)

Research

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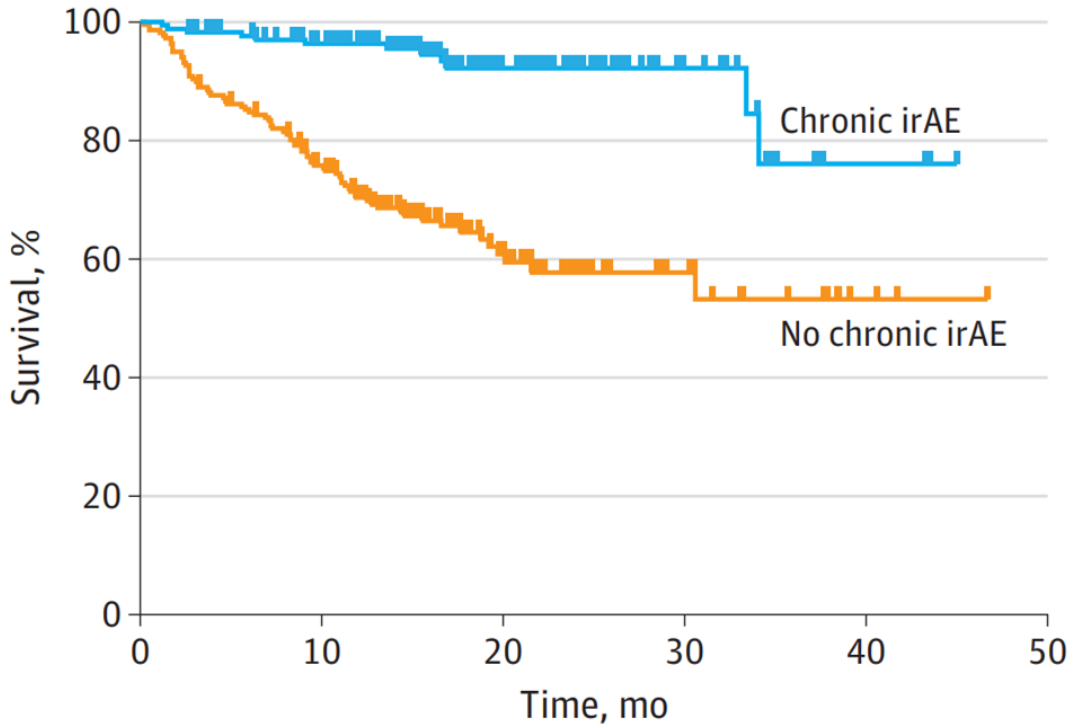
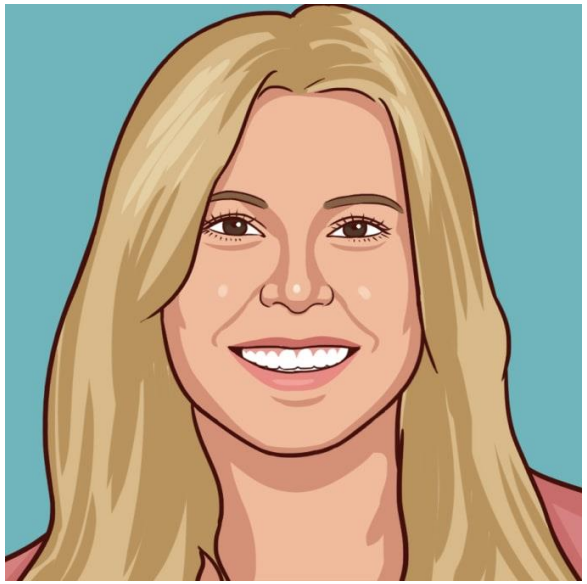
D RFS based on presence of chronic irAEs



No. at risk						
Chronic irAEs	167	144	57	18	4	0
No chronic irAEs	217	158	46	16	4	0

Asymptomatic renal insufficiency

49 F, melanoma of the anal canal, with unresectable pelvic adenopathy



BRAF-wildtype disease, exon-11 c-Kit mutation

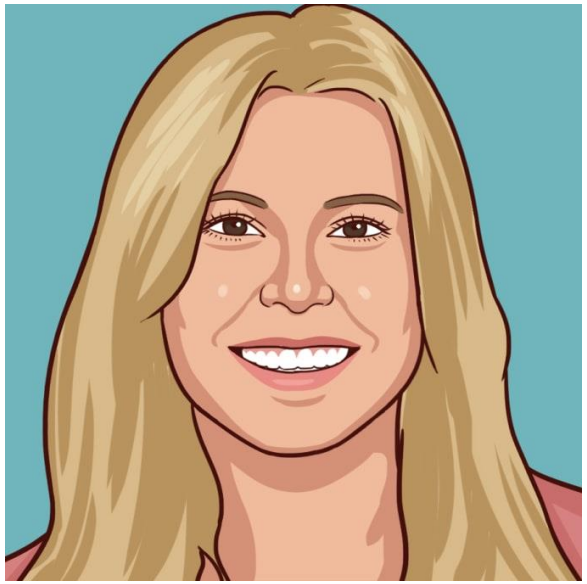
PMHx: well-controlled HTN, DM2 (A1C 7.4)

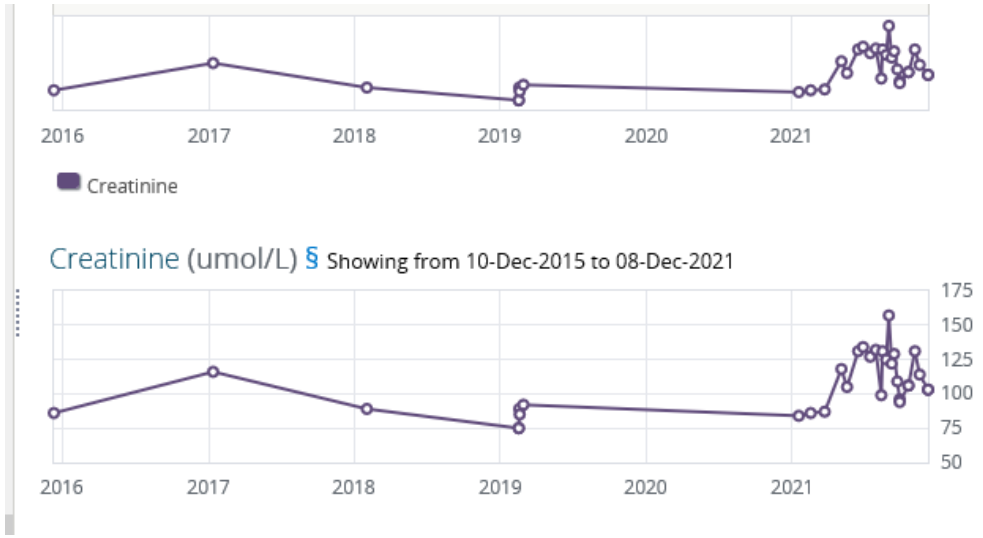
Treated with a single infusion of ipilimumab in combination with nivolumab

Presents for re-assessment pre-cycle #2: fatigue, subjective fevers

Asymptomatic renal insufficiency

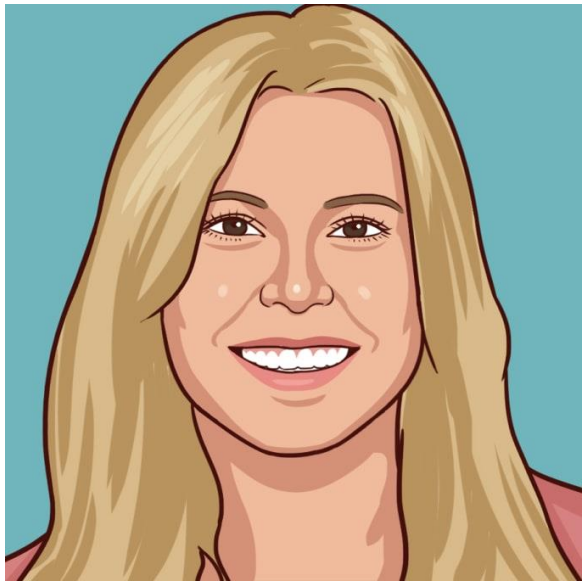
49 F, melanoma of the anal canal, with unresectable pelvic adenopathy

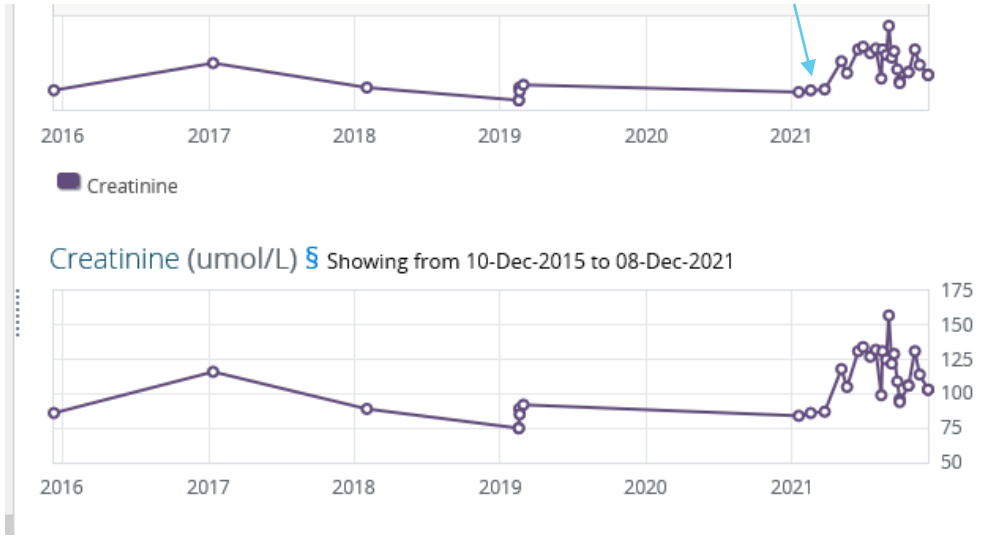




Asymptomatic renal insufficiency

49 F, melanoma of the anal canal, with unresectable pelvic adenopathy





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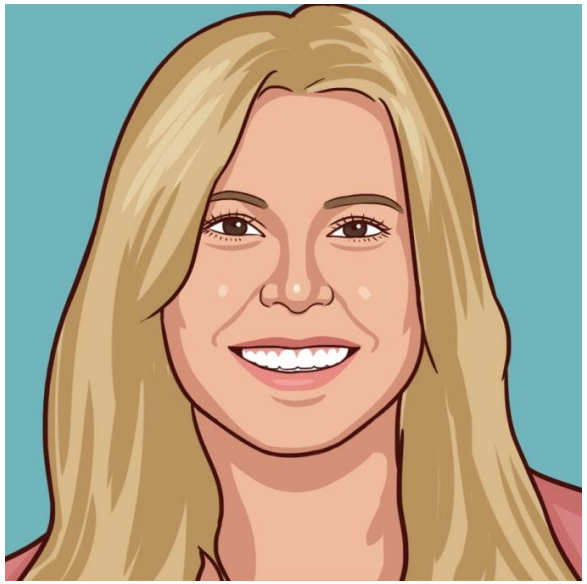
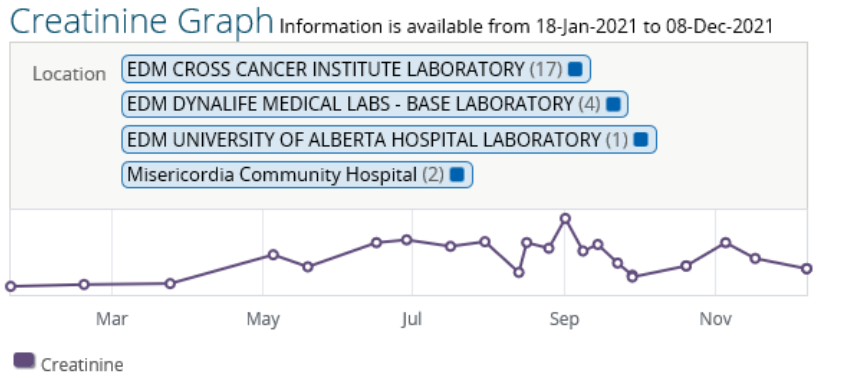
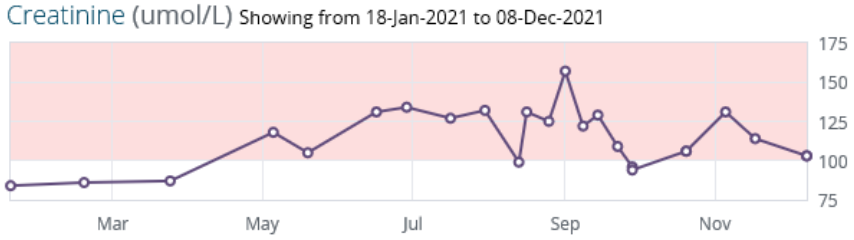
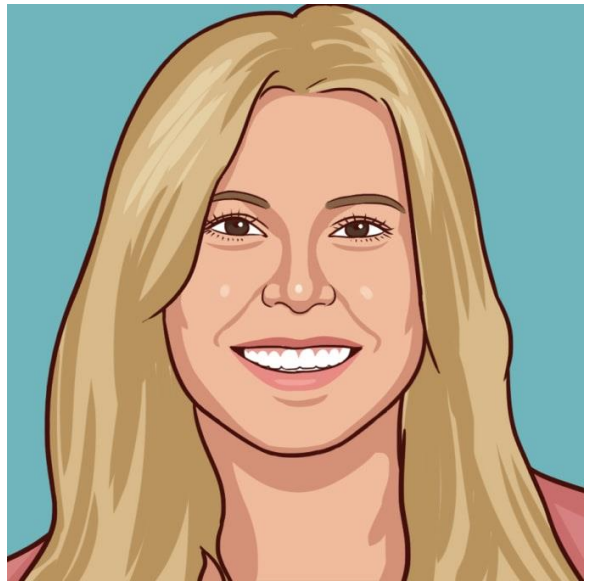


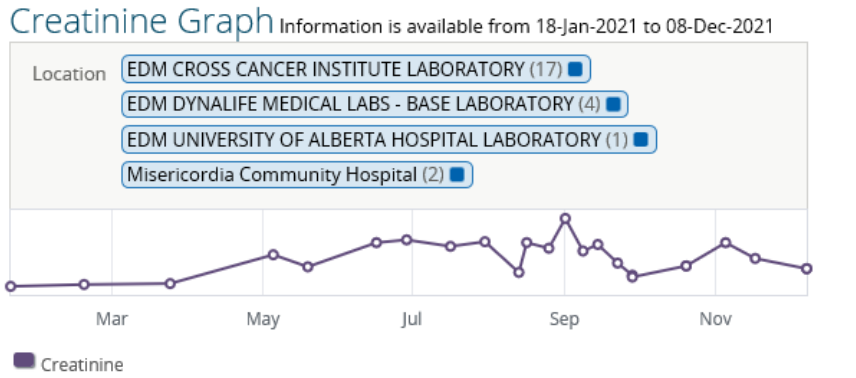


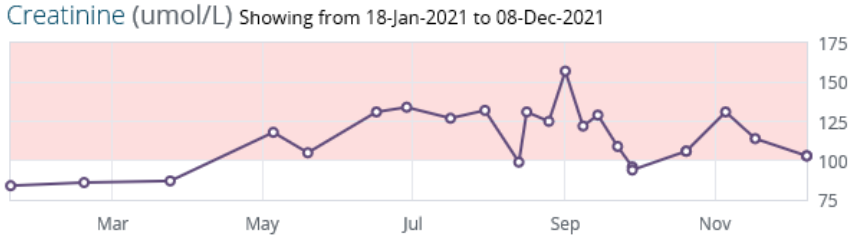


Thoughts?

49 F, melanoma of the anal canal, with unresectable pelvic adenopathy

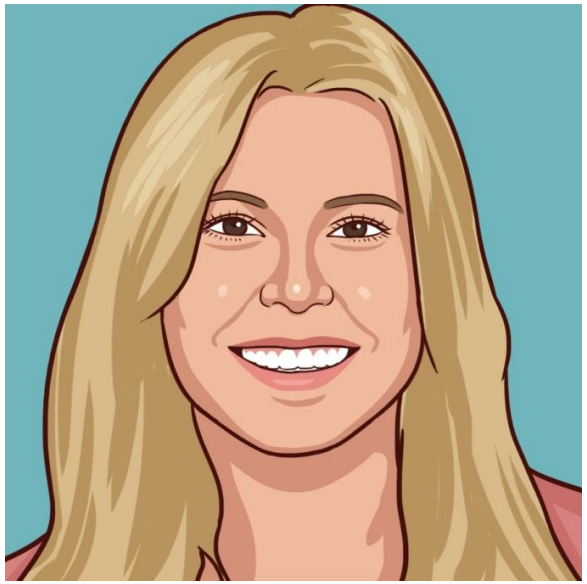






Acute interstitial nephritis

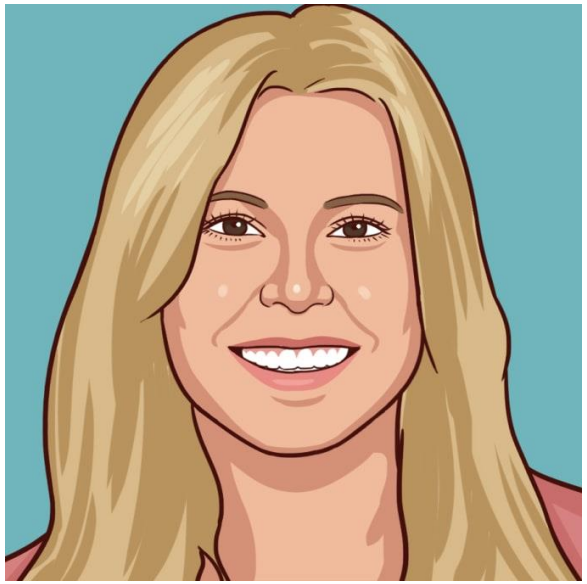
49 F, melanoma of the anal canal, with unresectable pelvic adenopathy



2-week treatment delay, but then proceeded with second cycle I/N

Acute interstitial nephritis

49 F, melanoma of the anal canal, with unresectable pelvic adenopathy

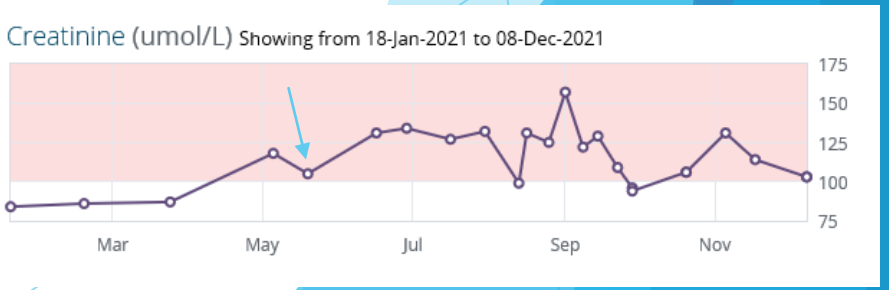


2-week treatment delay, but then proceeded with second cycle I/N

Further elevation of the serum creatinine

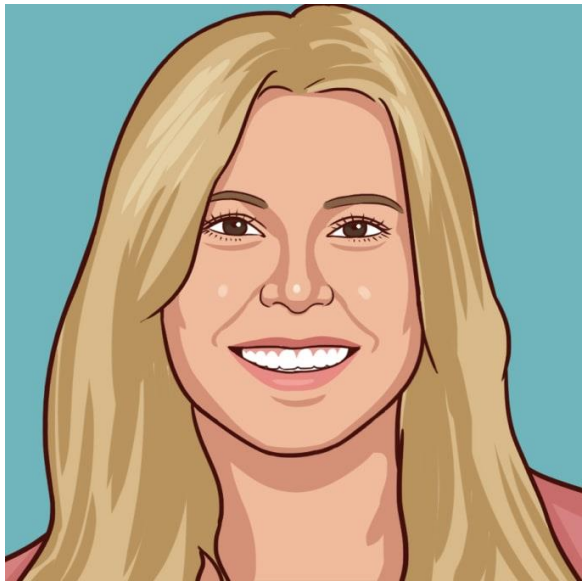
Test	Result	Ref. Range (Units)
Color, Urine	Yellow	
	Reference Range Comment:Colorless, Yellow	
Clarity, Urine	Clear	Clear
Specific Gravity, Urine	1.015	1.005 - 1.030
pH, Urine	5.0	5.0-8.0
Leukocytes, Urine	* 25	Negative (Leu/uL)
Nitrite, Urine	Negative	Negative
Protein, Urine	Negative	Negative (g/L)
Glucose, Urine	Negative	Negative (mmol/L)
Ketones, Urine	Negative	Negative (mmol/L)
Blood, Urine	Negative	Negative (Ery/uL)

MICROSCOPIC		
WBC, Urine	0-5	0-5 (/HPF)
RBC, Urine	0-2	0-2 (/HPF)
Bacteria, Urine	0-20	0-20 (/HPF)
Squamous/Transitional Epithelial Cells, Urine	0-5	0-5 (/HPF)



“Phone a friend”

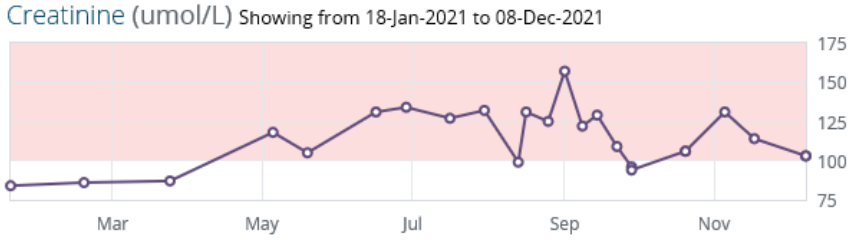
49 F, melanoma of the anal canal, with unresectable pelvic adenopathy



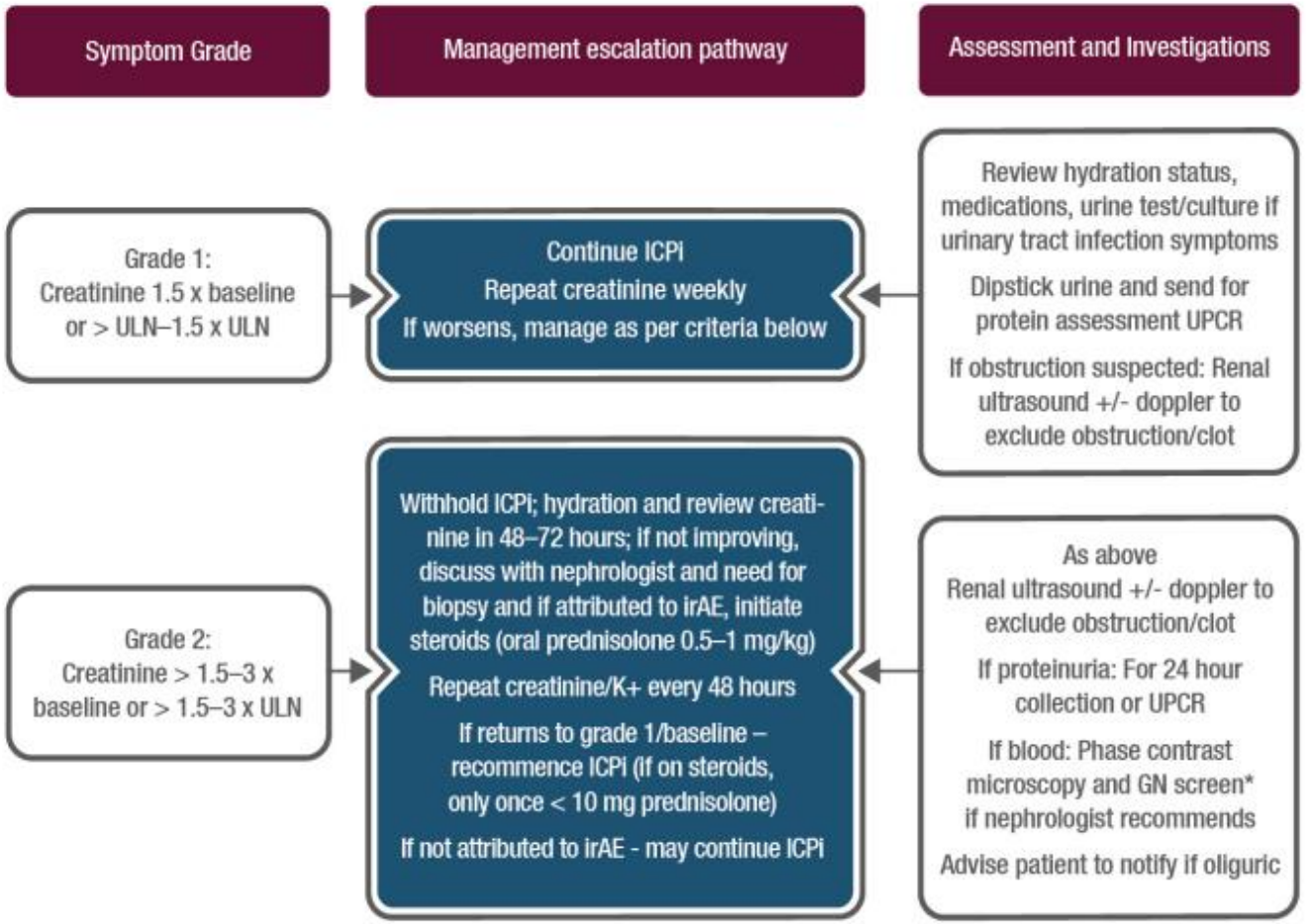
Nephrology referral (thank you, Dr Kevin Wen)

Same-day kidney biopsy revealed acute, interstitial nephritis

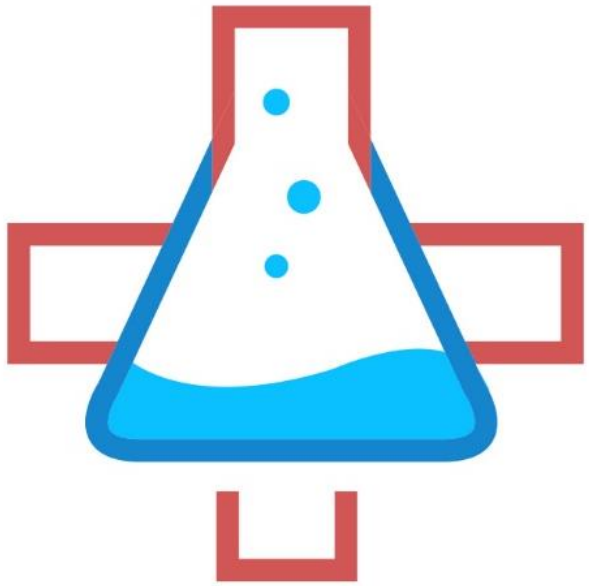
Started on prednisone 1 mg/kg



Management of nephritis



www.esmo.org/content/download/151567/2718664/file/Clinical-Practice-Guidelines-Slideset-Toxicities-Immunotherapy.pdf



i-MPACT™

Immune-Mediated Pathophysiology
And Clinical Triage

What is i-MPACT?

- **i-MPACT is a novel, patient-centered clinical/research program** which optimizes management of immune-related toxicity.
- Optimizing patient-care pathways reduces down-stream healthcare resource utilization while improving patient satisfaction and clinical outcomes.
- An integrated clinical/research platform fosters the development of innovative programs to improve care while establishing the Cross Cancer Institute as an international leader in immunotherapy research.

Program Goals

- **Optimization of care** for patients who develop immune-related toxicities
- **Exploration of the pathophysiology** of immune-related toxicity
- **Implementation and evaluation of novel treatment strategies** and algorithms for the management of immune-related toxicity
- **Prospective collection of data** to facilitate outcomes-based clinical research
- **Design and Conduct of interventional clinical trials** which will explore the efficacy and safety of immunotherapies within novel patient populations

i-MPACT program highlights

- **Educational resources**

  i-MPACT podcast series

- **The i-MPACT clinic**

  Initiated November 2021

  First in Canada

  Dedicated, twice-weekly outpatient clinic offering supportive care and management for patients with immune-related toxicities (tumor agnostic), run by a qualified general internist (i-MPACT fellow)

  Aligned with dedicated i-MPACT partners

i-MPACT
Immune-Mediated Pathophysiology And Clinical Triage

i-MPACT program highlights

- **The i-MPACT team**

  Neurology (Dr Cecile Phan)

  Ophthalmology (Dr Chad Baker)

  Endocrinology (Dr Miriam Shahidi)

  Dermatology (Dr Tom Salopek)

  Pulmonology (Dr Alia Daoud)

  Gastroenterology (Dr Jan-Erick Nilsson)

  Nephrology (Dr Kevin Wen)

  Rheumatology (Dr Carrie Ye – www.canrio.ca)

  i-MPACT fellow (Dr Daniel Van Zanten)

i-MPACT
Immune-Mediated Pathophysiology And Clinical Triage

i-MPACT program highlights

- **i-MPACT clinical trials**

  i-MPACT 1.0: prophylactic mesalamine for ipi/nivo treated patients

  i-MPACT 2.0: HCQ as a steroid-sparing agent

  i-MPACT 2.1: MTX as a steroid-sparing agent

  i-MPACT 3.0: Prednisone vs dexamethasone for the control of neurological symptoms in ICI-treated patients with brain metastases

  i-MPACT 5.0: skeletal health in ICI-treated patients

  i-MPACT 6.0: the LADDER study (Layered, ADaptive immunotherapy Dependent on Early Re-staging)

  i-MPACT 7.0: expectant management versus early intervention for patients with ir-hepatitis

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Thank you for your attention

jwwalker@ualberta.ca


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