Who Ya Gonna Call?

Challenges Regarding Toxicity with Immunotherapy in the Community

Presenter:
Dr. Harsahil Singh, MBBS, CCFP

May 10, 2019

Presenter Disclosure

- **Faculty / Speaker's name: Dr. Harsahil Singh**

- **Relationships with commercial interests:**
  - **Grants/Research Support: None**
  - **Speakers Bureau/Honoraria: None**
  - **Consulting Fees: None**
  - **Other: None**

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Mitigating Potential Bias

- Not Applicable

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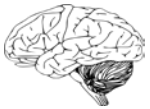
LEARNING



1: Grading of immunotherapy-related toxicities (CTCAE)

2: Discussing specific scenarios involving immunotherapy-related toxicities and their initial management

3: How to best contact Medical Oncologists when dealing with patients with immunotherapy-related toxicities?

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SOME TERMS

Immunotherapy related toxicities = Immune Related Adverse Events (irAE)

Immune checkpoint inhibitors (ICPi): PD-1, PDL-1 and CTLA-4 inhibitors

e.g. Pembrolizumab, Ipilimumab and Nivolumab

CASE DISCUSSIONS

- Actual patients
- Names changed
- Information anonymized
- Management recommendations: ASCO and ESMO guidelines

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AUDIENCE PARTICIPATION

SLI-DO POLLS

- Multiple choice questions throughout
- Responses via smartphones, tablets or PC/Mac
-  = Question!

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Sli.do

Will Dr. Singh's presentation:

- A. Edify the audience?
- B. Provide an overview of irAE grading with the CTCAE?
- C. Guide clinicians on how to communicate with Med Oncs?
- D. All of the above?

Source: Mark Kristjanson, MD

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Grading of Toxicities

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

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CTCAE Grades 1-5

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	**Moderate**	**Severe**	**Life threatening**	**Death**
• asymptomatic /mild symptoms • clinical or dx observations only • intervention not indicated	• minimal, local, noninvasive intervention • limiting age-appropriate instrumental ADL	• hospitalization / prolongation indicated • disabling • limiting self care ADL.	• urgent intervention indicated.	

Case 1: Mrs. Kelly Smith 55 y.o.

- On Pembrolizumab for Lung cancer
- Very good disease response: Immune checkpoint inhibitor therapy - CT scans
- After 6 cycles i.e. about 4 months, increased bowel movements 4 times above baseline of 1/day
- No bleeding, cramping, mucus or constant abdo. pain

Sli.do

irAE: Diarrhea

WHAT GRADE TOXICITY IS MRS. SMITH SUFFERING FROM?

A. GRADE 1
B. GRADE 2
C. GRADE 3
D. GRADE 4
E. GRADE 5

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CTCAE Diarrhea Grading

- **Grade 1**: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
- **Grade 2**: Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
- **Grade 3**: Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death

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What is the most appropriate next step in management?

A. Continue ICPi therapy
B. Permanently stop ICPi therapy
C. Hold ICPi therapy temporarily and contact Med Onc urgently, consider steroids
D. Admit patient to hospital, start IV steroids and page Med Onc on-call emergently right away

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

2018

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

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

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

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: May 2017.

ASCO Guideline Management for G2 Diarrhea

- Should hold ICPi temporarily until patient's symptoms recover to G1
- Can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less
- Concurrent immunosuppressant maintenance therapy (< 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases
- May also include supportive care with medications such as Imodium if infection has been ruled out
- Should consult with gastroenterology for G2 or higher
- Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent

Brahmer et al. (Feb 2018) American Society of Clinical Oncology: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy doi: 10.200/JCO.2017.77.6385

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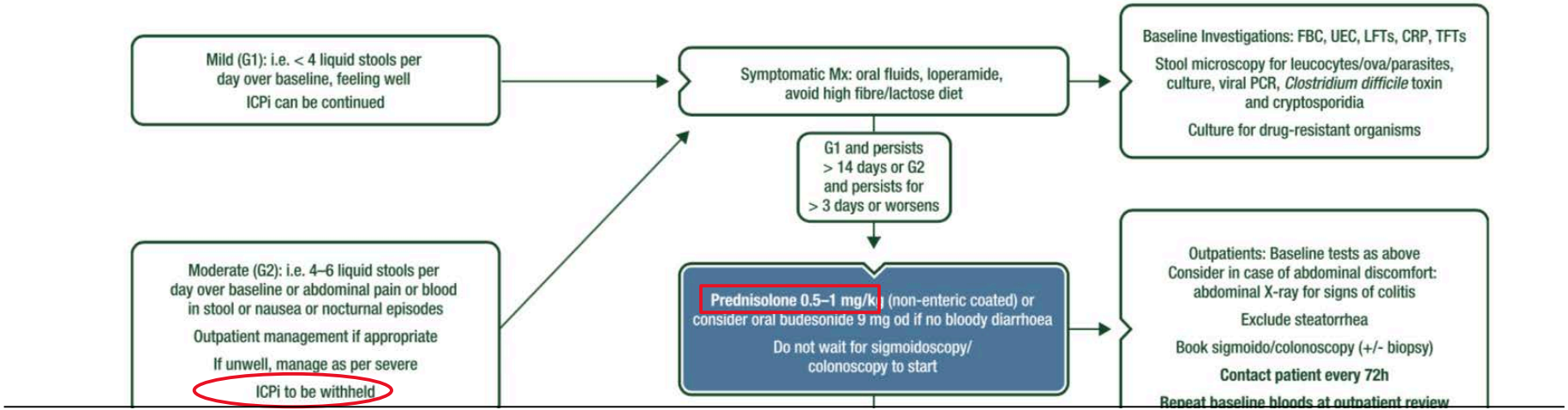
ESMO Guideline Management for G2 Diarrhea



Haanen J.B.A.G. et al. (August 2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017
DOI: 10.1093/annonc/mdx225

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HOW TO CONTACT **MEDICAL ONCOLOGIST?**

Option 1 (Preferred):

Contact the Most Responsible Medical Oncologist through paging (HSC at 204-787-2071)

Option 2: Contact Med Onc on-call (for adults) through HSC or St. B (204-237-2053) paging if:

- a.) Contacting after-hours
- b.) Unable to contact most responsible oncologist within reasonable timeframe based on clinical situation

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Back to our patient: Mrs. Smith

- BMs back to normal 1/day 4 weeks after holding ICPi and course of steroids- now on tapering
- Pembrolizumab restarted after Telehealth with Med Onc
- Warned that irAEs may reoccur
- Diarrhea same day when restarted: 2-4 BMs/day
- Med Onc call: Grade 1 toxicity- ICPi held and GI consult
- No steroids and reassessed in 4 weeks by Med Onc
- CT scan done for treatment response before appt.

Back to our patient: Mrs. Smith (contd.)

- CT Scan showed good treatment response but **evidence of colitis**
- Grade 1 diarrhea ongoing so restarted steroids- resolved
- Planned to redo CT in 2 months:

a. If disease progression, restart Pembrolizumab

b. If disease stable, observation without treatment

- GI consult- No colonoscopy required as asymptomatic
- Now- On observation as disease is stable on CT scan

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Case 2: Mr. James Miller 60 y.o.

- Stage III lung cancer- Adjuvant chemotherapy
- Developed metastatic disease
- Not surgical candidate -multiple lesions ➔ started ICPi therapy with Pembrolizumab
- After 2 cycles, developed **muscle pain in back, thighs and legs.** No fever, chills or abdo. pain
- CT Scan done to r/o spinal lytic lesions: negative
- Marked abnormalities on lab-work as follows
- On statin for 2 years

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Peak Lab Abnormalities

Test	Result	Baseline	Reference Range
AST	704 (~14X ULN)	44	16-51
ALT	306 (~6X ULN)	36	<52
LDH	2035	396	230-490
ALP	186	108	36-144
GGT	250	60	5-38
Bilirubin	Normal		
CK	6599	Not available	52-175

Sli.do

What do you suspect is going on?

A. Immunotherapy-mediated hepatitis

B. Immunotherapy-mediated myositis

C. Both of the above

D. Viral hepatitis

E. Statin-induced myopathy and hepatotoxicity

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Using CTCAE criteria and ASCO guideline, **what grade** hepatitis is Mr. Miller suffering from?

A. Grade 1

B. Grade 2

C. Grade 3

D. Grade 4

E. Grade 5

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CTCAE AND ASCO grading for hepatitis

A. G1: Asymptomatic; AST or ALT > ULN to 3.0 X ULN and/or total bilirubin > ULN to 1.5 X ULN

B. G2: Asymptomatic; AST or ALT > 3.0 to ≤ 5 X ULN and/or total bilirubin > 1.5 to ≤ 3 X ULN

C. G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis; **AST or ALT 5-20 X ULN** and/or total bilirubin 3-10 X ULN

D. G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 X ULN and/or total bilirubin > 10 X ULN)

Brahmer et al. (Feb 2018) American Society of Clinical Oncology: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy doi: 10.200/JCO.2017.77.6385

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What is the next best step in management?

A. Continue pembrolizumab

B. Permanently discontinue pembrolizumab, immediately start steroids and contact Med Onc emergently

C. Hold pembrolizumab, contact Med Onc urgently and consider steroids

D. Permanently discontinue pembrolizumab and start mycophenolate

E. Permanently discontinue pembrolizumab and start infliximab

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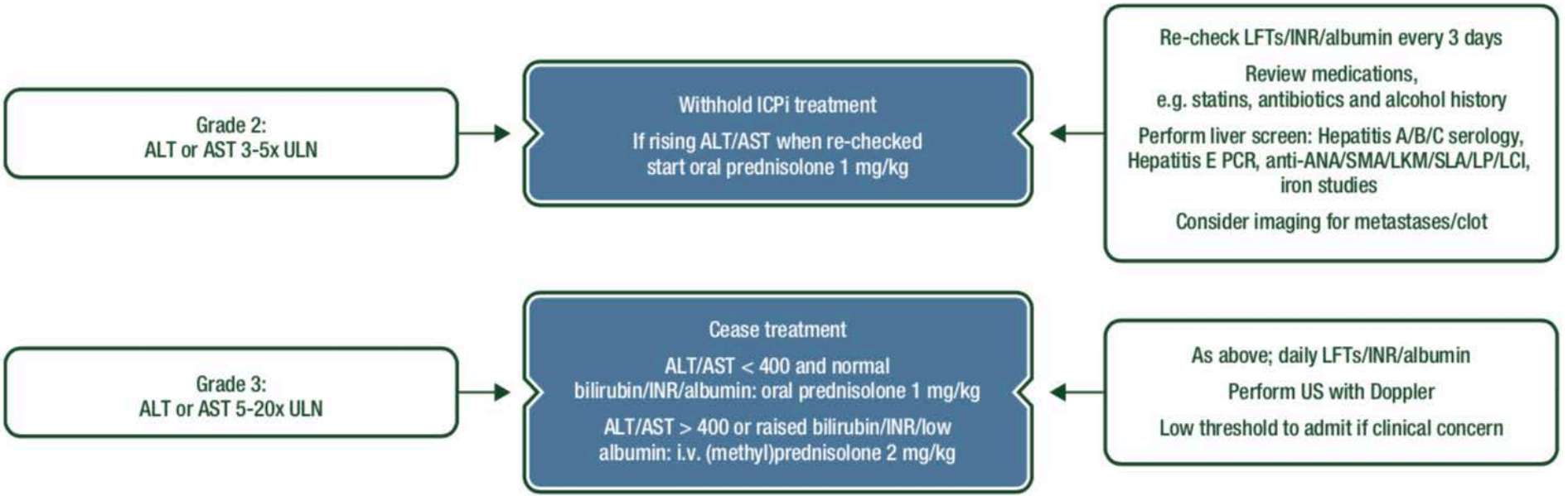
ASCO MANAGEMENT OF ICPi related GRADE 3 HEPATITIS

G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated TB 3 × ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-α agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear

Brahmer et al. (Feb 2018) American Society of Clinical Oncology: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy doi: 10.200/JCO.2017.77.6385



ESMO Management of ICPi related Grade 3 Hepatitis

Haanen J.B.A.G. et al. (August 2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017

Sli.do

Using CTCAE criteria and ASCO guideline, **what grade** myositis is Mr. Miller suffering from?

A. Grade 1

B. Grade 2

C. Grade 3

D. Grade 4

E. Grade 5

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MYOSITIS DEFINITION

- Definition (ASCO):

- Disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK).
- Muscle pain can be present in severe cases.
- Can be life threatening if respiratory muscles or myocardium are involved

Brahmer et al. (Feb 2018) American Society of Clinical Oncology: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy doi: 10.200/JCO.2017.77.6385

CTCAE GRADING FOR MYOSITIS

- Grade 1: Mild Pain
- Grade 2: Moderate pain (weakness); pain limiting instrumental ADL
- Grade 3: Pain associated (severe weakness); limiting self care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated

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What is the next best step in management?

A. Permanently discontinue ICPi

B. Permanently discontinue ICPi and start IV steroids; contact Med Onc emergently

C. Continue ICPi therapy and start IV fluids

D. Hold ICPi temporarily, consider NSAIDs and start steroids if not improved; contact Med Onc urgently

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ASCO Management of Grade 2 myositis

- Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose <10 mg; if worsens, treat as per G3
- NSAIDs as needed
- Referral to rheumatologist or neurologist
- If CK is elevated three times or more: prednisone or equivalent at 0.5-1 mg/kg
- May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)

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Back to our patient: Mr. Miller

- ER visit- oral hydration, no IV fluids given
- Creatinine: 112 (Baseline of 83) eGFR- 59
- Pembrolizumab held
- CCP next day- given 1 litre IV normal saline
- Renal dysfunction resolved quickly
- Med Onc contacted- patient was improving ➔ no steroids were started

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Back to our patient: Mr. Miller (contd.)

- Considered myositis induced by Pembrolizumab - a rare AE (happens in ≤1% patients) *Source: UpToDate*
- After discussing with FPOs, CCP RN and Thoracic DSG members- Med Onc decided to permanently discontinue treatment due to myositis and hepatitis.
- Patient switched to chemotherapy
- Unfortunately, CT scans show disease progression

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Sli.do

Spectrum of toxicity of immune checkpoint blockade agents

HOW MANY ORGAN SYSTEMS ARE KNOWN TO BE AFFECTED BY ICPi THERAPY IN LITERATURE?

A. 5
B. 6
C. 7
D. Almost all of them

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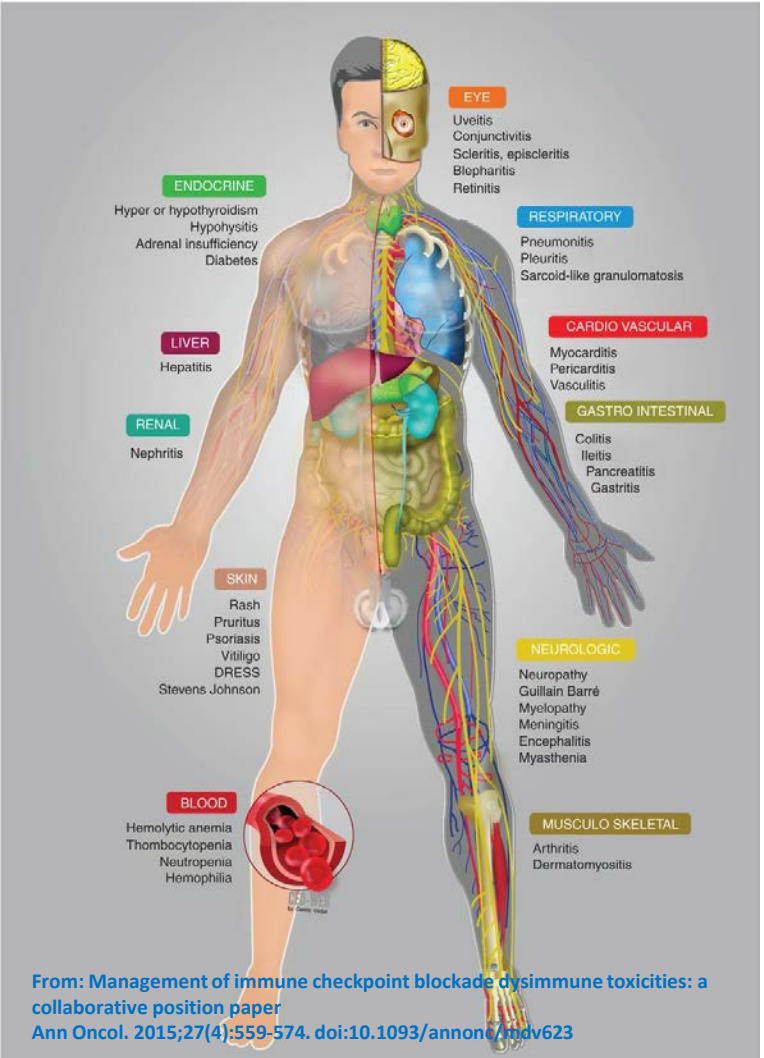

From: Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper
Ann Oncol. 2015;27(4):559-574. doi:10.1093/annonc/mdv623

- Eye
- Endocrine
- Respiratory
- Cardiovascular
- Liver
- Gastrointestinal
- Renal
- Skin
- Neurologic
- Blood
- Musculoskeletal

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References

- American Society of Clinical Oncology: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy Published online ahead of print February 14, 2018, doi: 10.200/JCO.2017.77.6385, Brahmer et al.
- (All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate)
- Management of Toxicities from Immunotherapy: ESMO Clinical Practice Guidelines Published in 2017 – Ann Oncol (2017) 28 (suppl 4): iv119–iv142. Authors: J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan
- UpToDate: https://www.uptodate.com
- Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017 U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, National Cancer Institute
- Immunotherapy and its complications- A module of the Early Cancer Diagnosis Workshop Series, November 2018, M. Kristjanson et al.

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Thank
You
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