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MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY

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Learning Objectives

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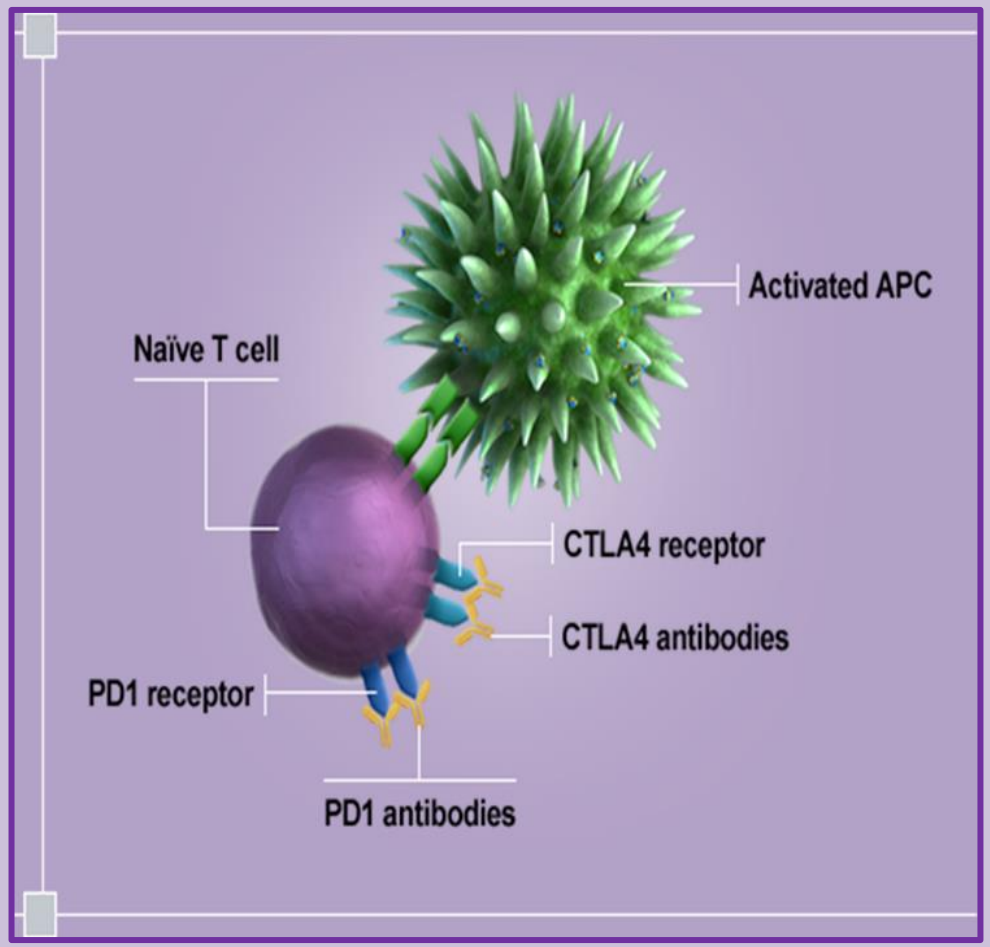
At the end of the presentation the learner will be able to:

- Discuss the toxicities and management issues associated with the immune checkpoint inhibitors
- Increase awareness of pneumonitis, colitis toxicity in the NSCLC population

Immune Checkpoints Inhibitors

Mechanism:

- Works by blocking pathways called checkpoints. These checkpoint pathways are mechanisms for the human immune system to control the immune response



ICPis Approved

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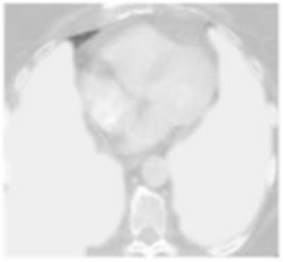
- Ipilimumab – Advance Melanoma
- Pembrolizumab and nivolumab – Advance melanoma, metastatic NSCLC, head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, and Hodgkin lymphoma.
- Nivolumab- Lung cancer, Head and Neck cancer, Hepatocellular carcinoma and renal cell carcinoma.
- Combination Ipilimumab and nivolumab- Advanced melanoma and Lung cancer
- Atezolizumab – NSCLC and urothelial cancers
- Durvalumab- Urothelial cancers
- Avelumab – Merkel cell carcinoma and urothelial cancer

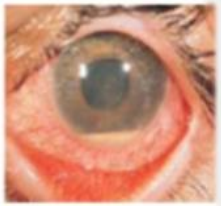
Selected Adverse Events

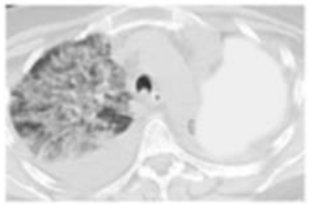


Endocrine
Thyroiditis
Hypothyroidsim
Hyperthyroidism
Hypophysitis
Hypopituitarism
Adrenal Insufficiency

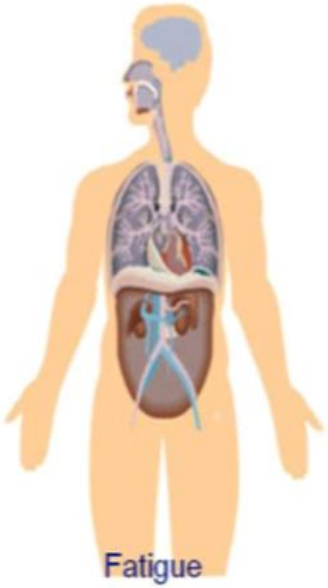
Neurologic
Neuropathy
Meningitis
Guillane-Barre Syndrome

Ocular
Iritis
Uveitis
Conjunctivitis

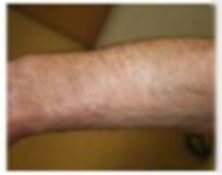




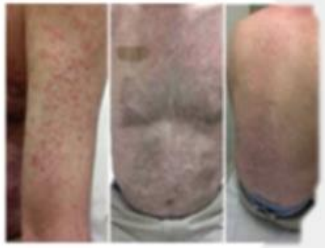
Pulmonary
Pneumonitis
Respiratory failure

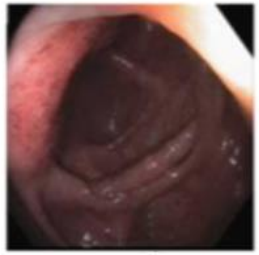


Cardiac
Pericarditis



Dermatologic
Mucositis
Rash, Vitaligo





Gastrointestinal
Nausea, Emesis
Diarrhea, Colitis,
Perforation;
Pancreatitis

Fatigue
Anorexia
Nausea

Hepatic
Transaminitis
Hepatitis

Renal
Nephritis
Renal Insufficiency

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Common Toxicities

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Common AEs in PD-(L)-1 directed agents*

Toxicities	Any Grade (%)	Grade 3-4 (%)
Fatigue	16-20	1
Decreased Appetite	10-14	1
Nausea	12	1
Rash	9-13	1
Diarrhea	8	1
Hypothyroidism	8-11	1
Pneumonitis	2-5	2

Hyperthyroidism, Myocarditis, Adrenal insufficiency, Myositis, Type I diabetes, Hepatitis. *Reviewed data from Checkmate 057, Keynote 10 and OAK

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Guidelines

- Electrolytes, TSH, LFT's and Kidney function and CBC to be evaluated before each cycle
- Educated patients and colleagues
- Consults

Guidelines Management

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Guidelines- Management

- irAEs higher with CTLA4 (exceptions- hypothyroidism, type I DM)
- Grade 1- symptomatic management, continue ICI
- Grade 2- Steroids 0.5-1.0mg prednisone, hold ICI, restart once grade 1 and prednisone at 10mg daily.
- Grade 3- Steroids 1-2mg prednisone, Infliximab. Steroid taper over 4-6 weeks. May restart PD-(L)-1 drugs with high level of caution.
- Grade 4- Steroids 1-2mg prednisone, Infliximab, other immunosuppressants, discontinue ICI (exception: endocrinopathies)
  - Brahmer, et al J Clin Oncol 2018, ASCO/NCCN guidelines on irAEs

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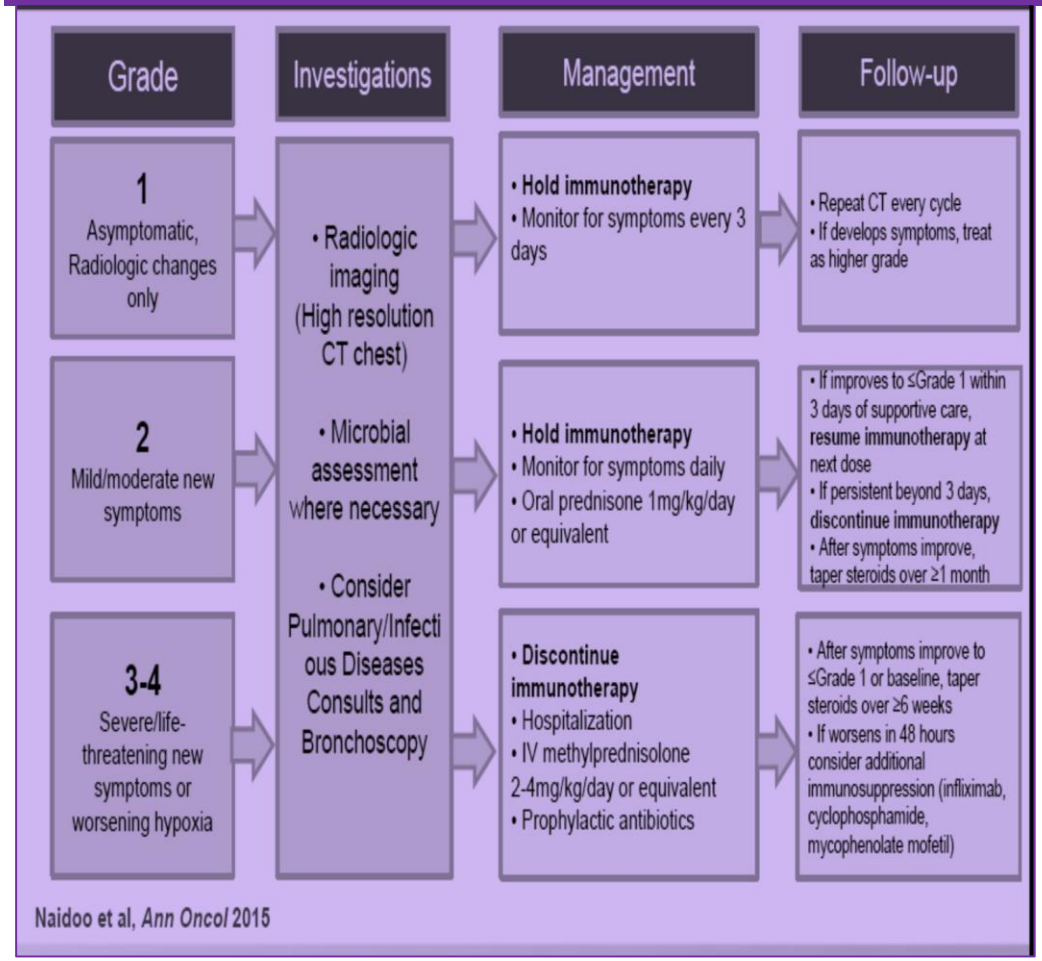
Pneumonitis

- Incidence of pneumonitis 5%: 10% with PDL-1 AND and CTLA4 combinations (higher in combinations 10% vs 3%)
- No clear association with prior chest RT.
- Median time onset: 2.8 months (9d-19.2m)
- 88% G1/G2

Pneumonitis: Management Algorithm



- G 1- No symptoms, radiographic changes only
- G 2- NO improvement in 48 hrs. with steroids→ Manage as G3
- G 3/4 – IV steroids, bronchoscopy/ empiric antibiotics/consider Ifliximab

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Clinical case

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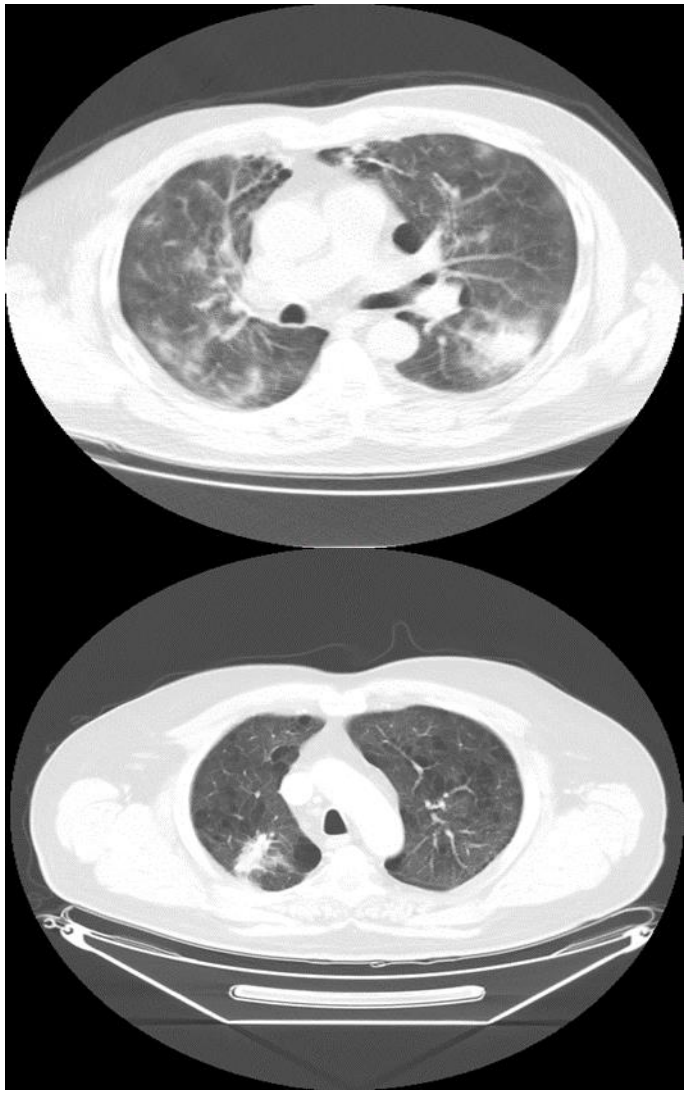
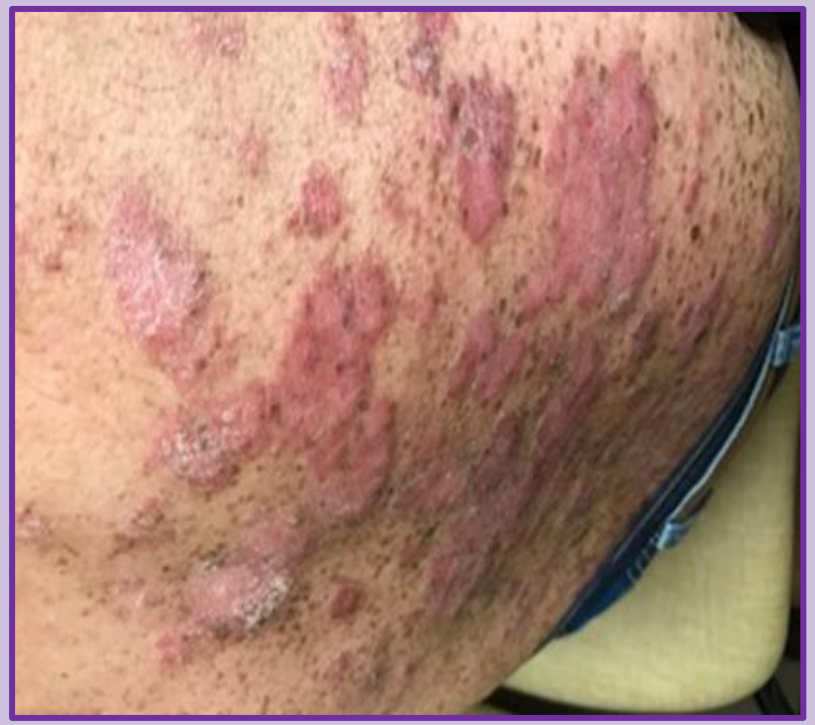
- 64 year old male
- Smoker
- PMH: emphysema, GERD, HTN, obesity
- Adenocarcinoma of the lung stage IV with left adrenal metastasis 10/2014
- Non actionable mutations
- First line: chemotherapy and maintenance until progression on 6/13/2016
- SBRT left adrenal mass 8/2016
- Second line therapy palliative immunotherapy # 4 cycles until developed bilateral pneumonitis on 11/2016
- 11/2016 worsening dyspnea. CT chest scattered areas of patchy opacity and consolidation extent bilaterally since last CT 10/2016. Negative cultures and viral panel.
- Treatment: HOLD immunotherapy. IV antibiotics for possible community acquired pneumonia + IV steroids high dose (methylprednisolone) . D/C immunotherapy.
- Patient on remission since then.

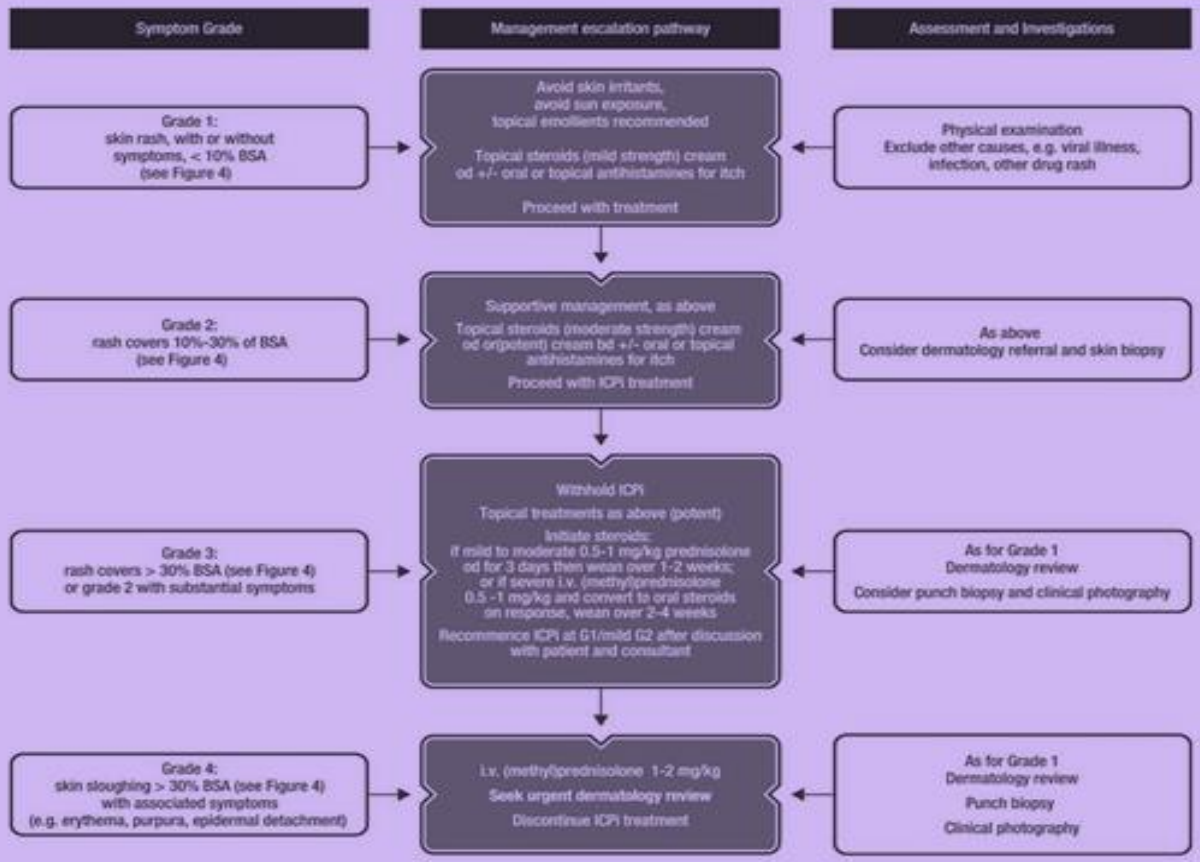


Rash

Types of rash:
Dermatitis, dermatitis acneiform, dermatitis bullous, erythema, pruritus allergic, rash erythematous, rash generalized, rash macular, rash popular and rash pruritic



Skin Rash Management



Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treat and follow-up† Ann Oncol. 2017

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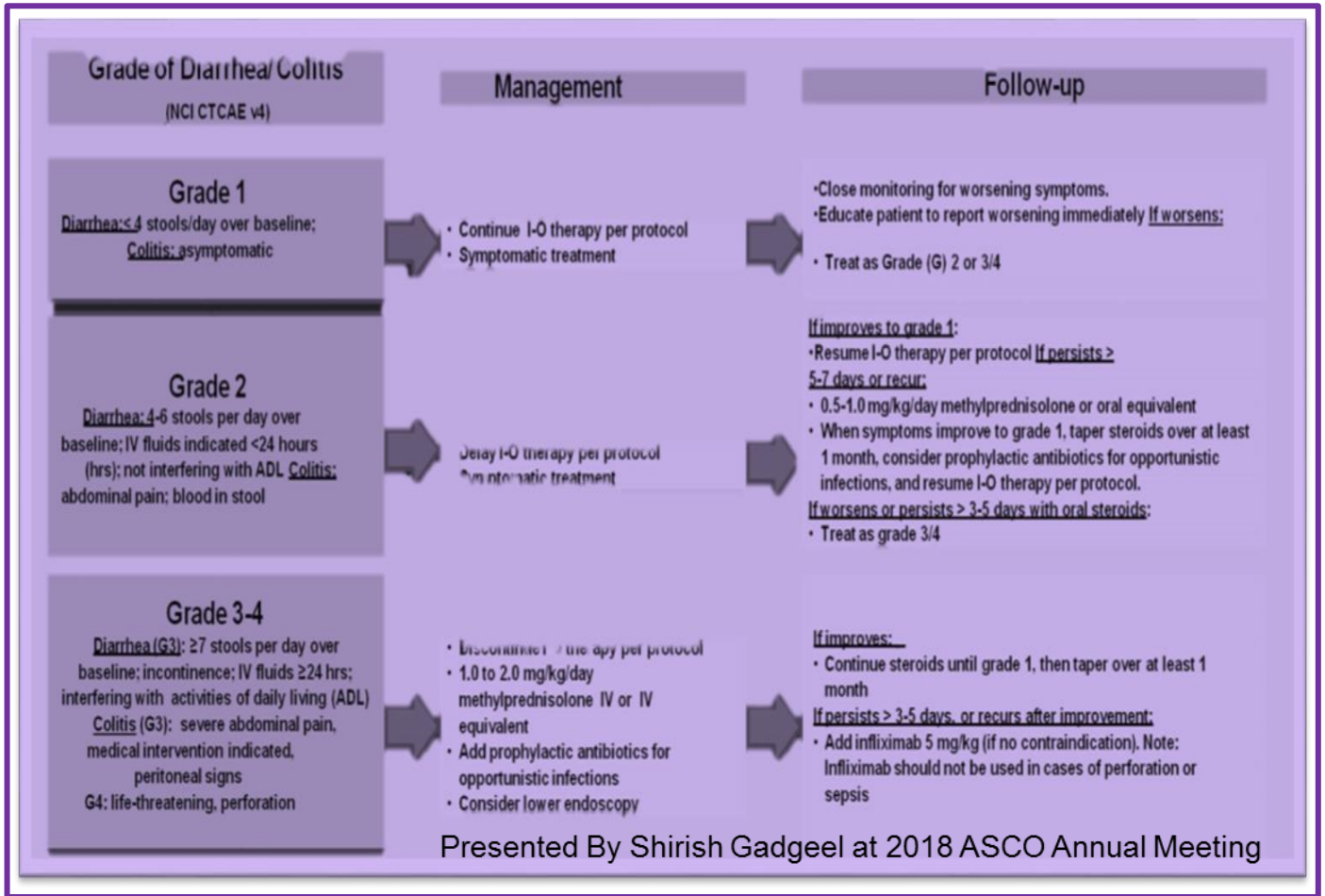
- Incidence: PD-1 20%/ CTLA4 40%
- G3-4/ 1-3%
- Pruritus without rash may occur
- OS longer in patients with rash
- Bullous /Dermatology consult/bx

Diarrhea Management



- Incidence: PD-1 10%- CTLA4 40%
- Routine evaluation diarrhea (C. diff)
- If starting steroids/ CT scans and Colonoscopy

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Clinical case

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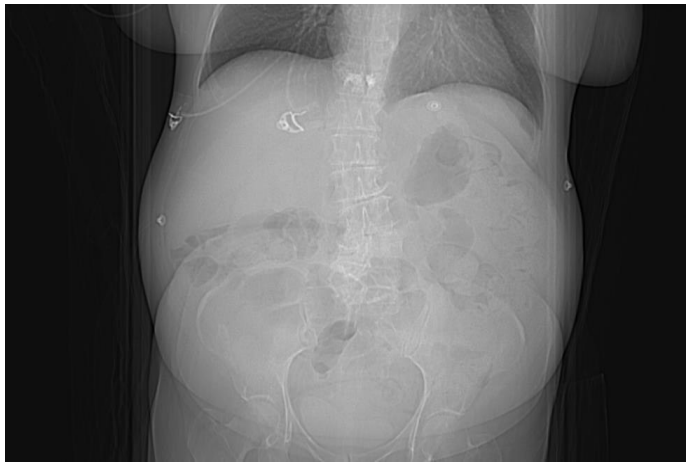
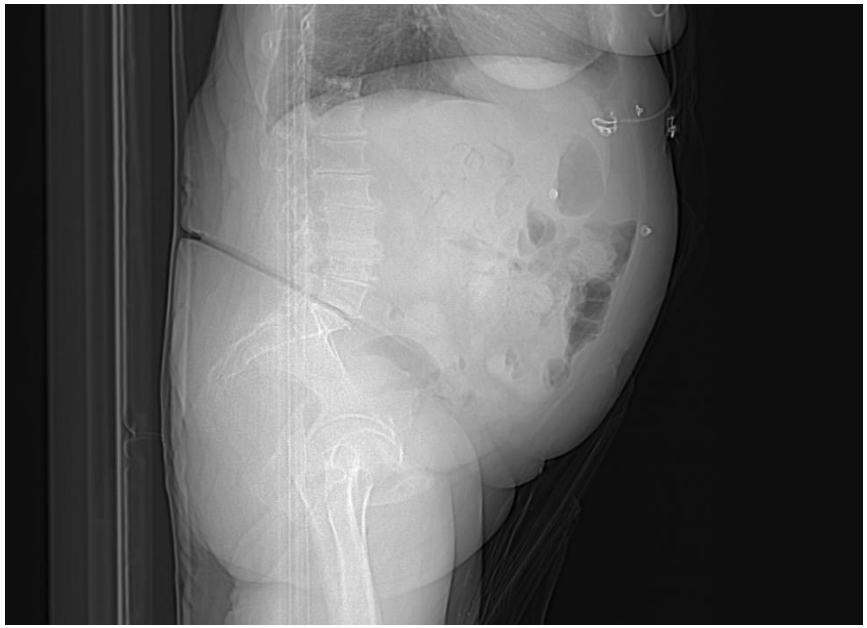
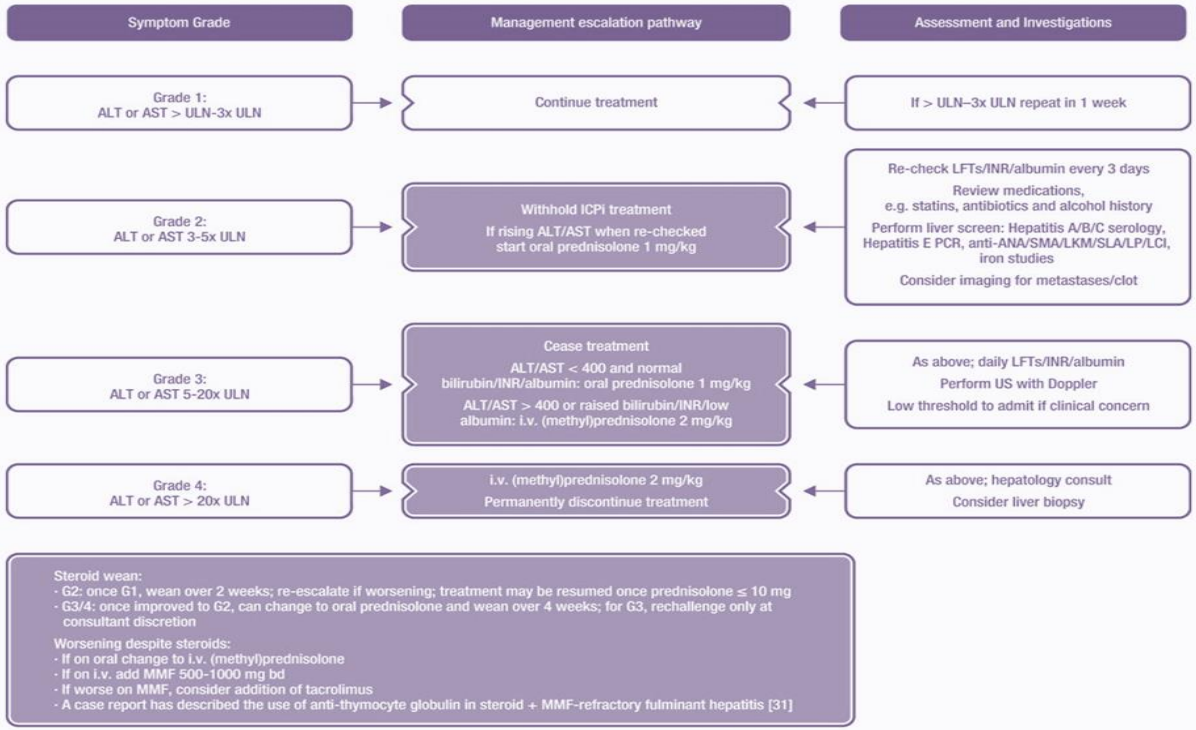
- 71 y/o female former smoker
- Adenocarcinoma of the lung stage IV 10/2018 with bone metastases
- Non actionable mutations
- First line chemotherapy +immunotherapy
- Sx: Nausea, diarrhea more than 6 for 3 days and no appetite and fever on 2/2019. Imodium at home without improvement.
- C. diff negative. CT abdomen: Inflammation involving the rectosigmoid. Sigmoidoscopy: Active colitis.
- Treatment: Hold immunotherapy. Loperamide + high dose steroid + electrolyte replacement. D/C immunotherapy.





Hepatic Toxicities Management

Management of Hepatic Toxicities



1. Incidence- 5-10%
2. Asymptomatic rising liver enzymes- start steroids
3. Infliximab not used
4. Steroid refractory- Mycophenolate mofetil, tacrolimus

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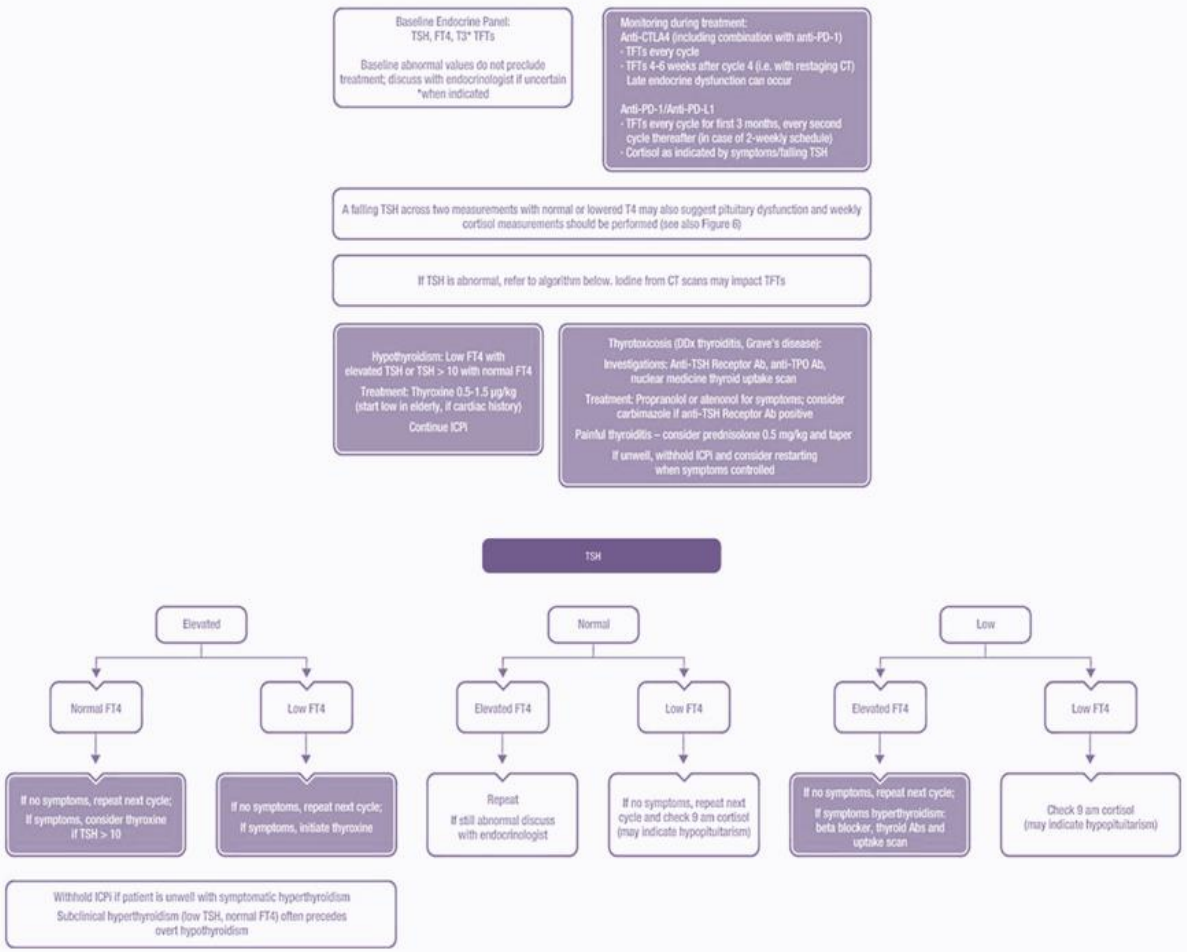
Management of Thyroid Dysfunction



1. Incidence- 10%
2. Hyperthyroidism- 2%
3. Regular TFT testing
4. TSH > 10mIU/L start thyroid hormone therapy.

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Musculoskeletal Toxicities Management

Most common musculoskeletal toxicities:

- Inflammatory arthritis, Myositis and Polymyalgia like syndrome.
- Incidence: 40% more frequent with PD1/PD-L1 antagonist
- NSAIDs alone are not sufficient add corticosteroids (Prednisone 1-2 mg /kg /daily and synthetic DMARDs might be required
- Myositis may be lethal / Cardiac muscle/ referral rheumatologist or neurologist.

Case # 1

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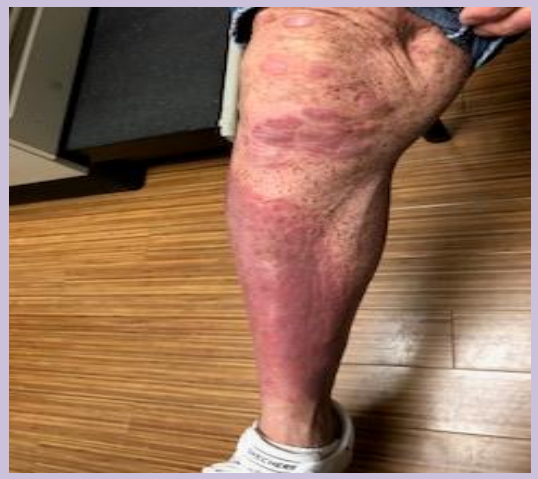
Case Scenario

A 62 year old male patient diagnosed with poorly differentiated adenocarcinoma of the neck (base of the tongue) treated with cisplatin high dose and radiation therapy on 4/2017. On 1/2018 PET scan showed lung metastases biopsy proven. Case was presented on tumor board and it was agreed to treat him with Cyber knife on the lung lesion and immunotherapy. Patient has a history of Psoriasis under treatment with Apremilast, well controlled. After given him cycle # 2 immunotherapy patient developed an exacerbation of his psoriatic lesions.



Question

What will be your next step on treatment?

a) Permanently discontinue ICPi
b) Continue ICPi + steroids
c) Hold ICPi + reevaluate to decided further treatment

Re-Challenge With PDL1

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Re-challenge with PD-(L)-1 after irAEs

- 482 lung cancer patients at MSKCC; 15% (70) patients developed irAE
- 38 (54%) were re-challenged
- 24% developed same irAE; 26% developed new irAE
- 16 were treated successfully; 2 (5%) deaths
- Among patients who had response before irAE no difference whether ICP therapy re-started or not.

Santini, et al ASCO 2017, abstract 9012.

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Conclusion

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- ICPi agents may cause immune related side effects\
- Close monitoring is very important
- Referral…Referral… Referral
- Side effects respond to steroids

References

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- Brahmer, Julie R., et al. "Management of Immune-Related Adverse Events in Ptients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline." Journal of Clinical Oncology, doi:https://doi.org/1.12oo/JCO2017.776385. Accessed 12 Mar. 2018

- Naido J, Page DB,li BT et al: Toxcities of the anti-PD-1 and anti-PD-L1 immune checkpoints antibodies. Ann Oncol 26:2375-91,2015 Erratum in: Ann Oncol 27:2362,2016

- Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632,2017

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