

Immunotherapy Related Adverse Events (IRAEs)

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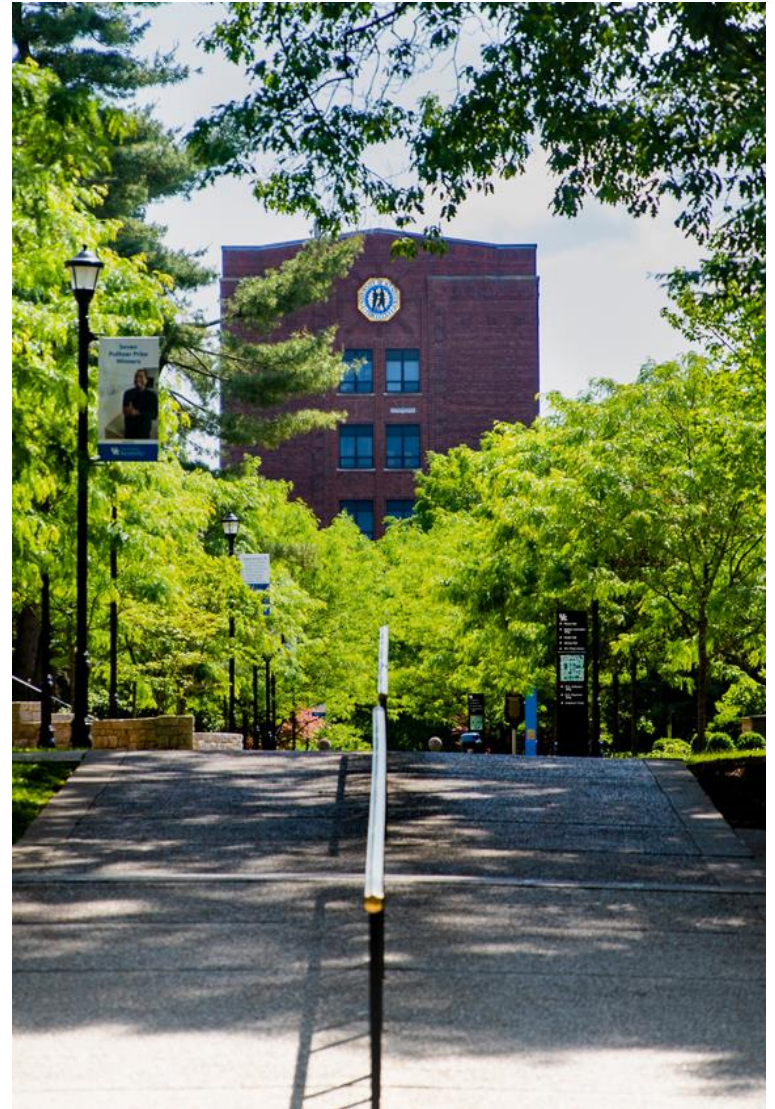
University of Kentucky



Objectives



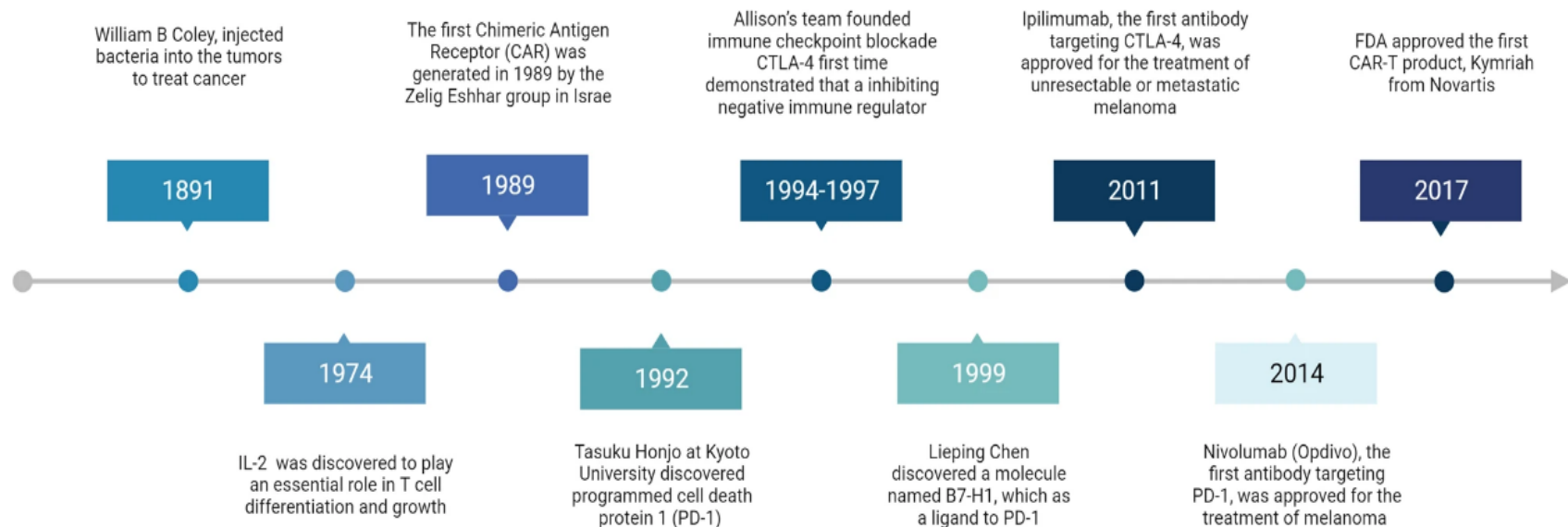
- 1) Describe the mechanism of immunotherapy related adverse events (IRAEs).
 - 2) Recognize presentations that suggest development of IRAEs.
 - 3) Describe strategies for management of IRAEs.
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Background



From: [Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response](#)



Historical landmarks in cancer immunotherapy development



Background



Agents in the Immunotherapy category include antibody therapies, T-cell therapies, cancer vaccines and checkpoint inhibitors.



The focus of today's presentation will be predominantly checkpoint inhibitors.



Immune Checkpoint Inhibitors (ICIs)



- ‘Checkpoints’ refers to proteins made by some immune system cells (T-cells) as well as cancer cells.
- Checkpoints can modulate the immune response and prevent it from being too strong which can keep T-cells from eliminating cancer cells.
- Blocking checkpoints can allow T-cells to better kill cancer cells.



Immune Checkpoint Inhibitors: Mechanism of Action

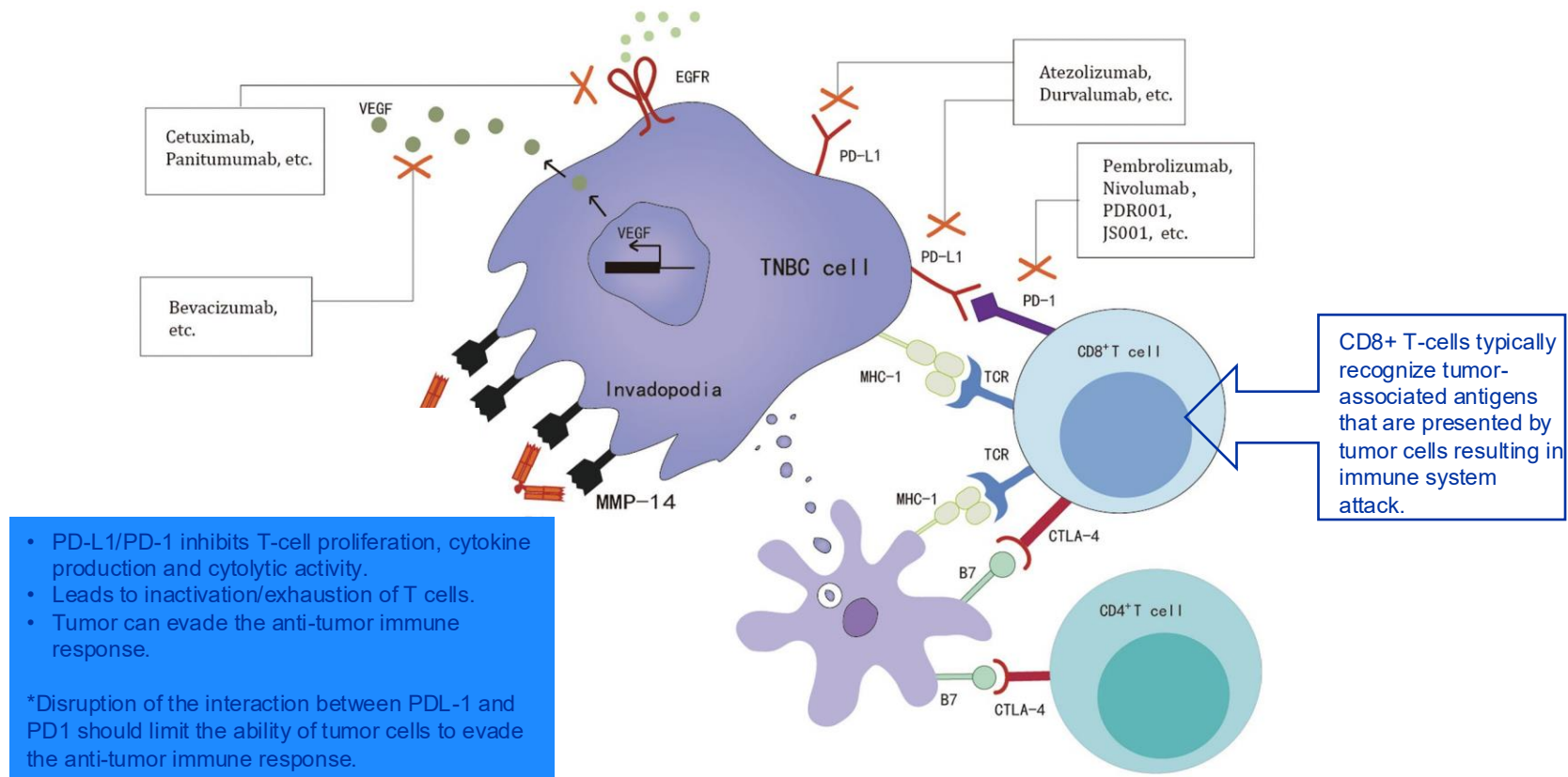


Fig. 1 Current and potential future immune-related drug targets in TNBC, including immune checkpoint inhibitors, cytokines, and their antibodies

Carey K. Anders, Vandana Abramson, Tira Tan, and Rebecca Dent. [The Evolution of Triple-Negative Breast Cancer: From Biology to Novel Therapeutics](#). American Society of Clinical Oncology Educational Book 2016 :36, 34-42

Immunotherapeutic interventions of Triple Negative Breast Cancer Zehuan Li1,2, Yiran Qiu1,2, Weiqi Lu1,2, Ying Jiang1,2* and Jin Wang. Li et al. J Transl Med (2018) 16:147



Immune Checkpoint Inhibitors: Available agents

- Pembrolizumab (PD-1 blockade)
- Cemiplimab (PD-1 blockade)
- Nivolumab (PD-1 blockade)
- Dostarlimab (PD-1 blockade)
- Atezolizumab (PDL-1 blockade)
- Avelumab (PDL-1 blockade)
- Durvalumab (PDL-1 blockade)
- Ipilimumab (CTLA-4 blockade)
- Tremelimumab (CTLA-1 blockade)
- Opdualag (Nivolumab with relatlimab, combination PD-1 with LAG3 blockade)

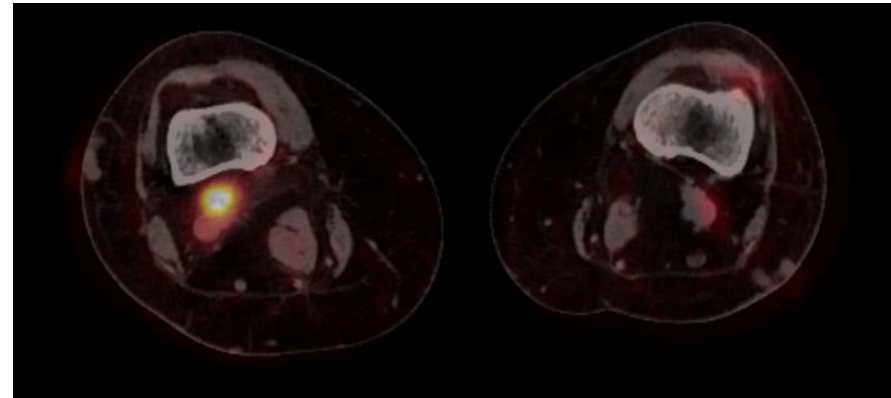
Patient Cases



Case #1



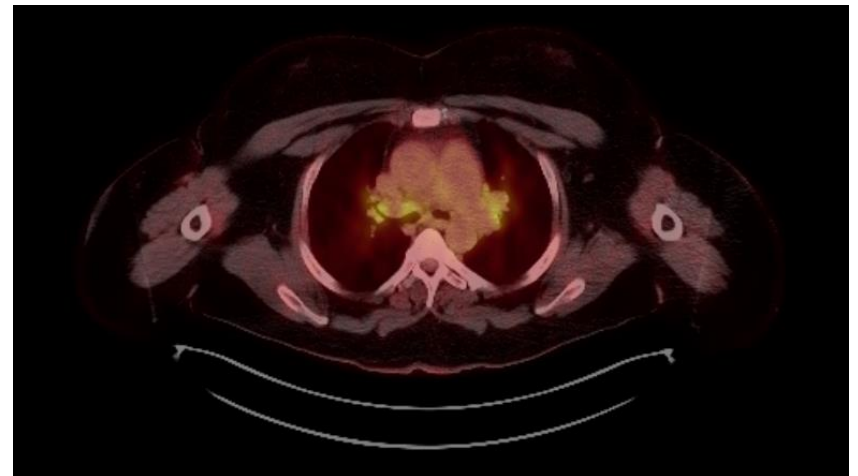
- 51 yo F with a PMH significant for migraines.
- Right toe biopsy 1/2023 with melanoma (thickness of at least 4.8 mm, pT4a).
- PET/CT 2/21/23 with FDG avidity associated with R second toe and two intensely hypermetabolic metastatic R popliteal lymph nodes. R popliteal lymph node biopsy + for melanoma.



Case ##1



- Patient was started on neoadjuvant pembrolizumab per S1801 clinical trial in order to down-stage disease and potentially avoid amputation.
- PET/CT 5/2023 after 3 cycles of immunotherapy with response in popliteal nodes but interval development of FDG avid cervical and thoracic lymph nodes.



Case#1



Activity of cervical and mediastinal lymph nodes was thought to be inflammatory in setting of a recent URI, patient continued with pembrolizumab until 7/5/23.

7 May 2023

Patient admitted 7/18-7/22/2023 due to nausea, vomiting, headaches and A. fib.

- Troponin 391 ng/L

- CRP >20

- Cardiac MRI suggestive of ICI myocarditis.

- High dose steroids started and patient underwent myocardial biopsy.

18–22 July 2023



Case #1



- Myocardial biopsy pathology report:
 - No obvious active lymphocytic myocarditis or necrosis.
 - However, IHC confirms a diffuse albeit scant distribution of CD68 positive macrophages consistent with a resolving inflammatory/injury process. IHC for PDL 1 is negative.
 - As bolus steroid therapy prior to tissue sampling may result in rapid depletion or loss of lymphocytes (in biopsies for myocarditis), clinical correlation is advised.”



Case #1



- The patient was diagnosed with ICI Myocarditis and completed Solu-Medrol 1g daily x 3 days while hospitalized. Pt was eligible for clinical trial at UK and received two infusions of Abatacept versus placebo. She was discharged on a prolonged steroid taper and further immunotherapy was held.
- R toe excision and popliteal lymph node resection 9/1/2023 without viable tumor identified (pathologic complete response). Patient started on active surveillance.
- Unfortunately, she continued to have admissions for bouts of nausea and vomiting without a clear etiology and no further abnormalities noted on ECG or TTE. She passed away 11/6/2023 after an admission for N/V.



Case#2



- 84 yo F with a PMH significant for CKD, Colon CA (diagnosed 2002 s/p colectomy and cystectomy with colostomy and urostomy), cervical CA (s/p TAH and XRT in 1983), DM2 and hypothyroidism.
- R calf lesion noted 2022 and a shave bx performed which showed malignant melanoma with a Breslow thickness of 3.4 mm (T3).
- PET/CT 1/12/23 negative for distant disease.



Figure 1. Malignant melanoma on the calf



Case #2



- Right lower extremity wide local excision and sentinel lymph node bx 2/6/2023 showed malignant melanoma, 5.7 mm in thickness and 1R inguinal sentinel lymph node positive for metastatic melanoma, pT4a pN1a, Stage IIIC.
- The patient met criteria for adjuvant Pembrolizumab and started treatment 3/14/23.
- She received 5 cycles and stopped due to fatigue and poor appetite.
- 7/18-7/24/2023: The patient was hospitalized due to Hgb of 4.6, Haptoglobin <10, LDH 489 with negative DAT. Patient was diagnosed with Autoimmune Hemolytic Anemia thought to be secondary to immunotherapy treatment.



Case #2



- The patient completed a high dose steroid taper with significant improvement in her Hgb. All further immunotherapy treatments were held.
- The patient remains on active surveillance without evidence of disease. Hgb remains stable.



Immune Checkpoint Inhibitors: Mechanism of Action

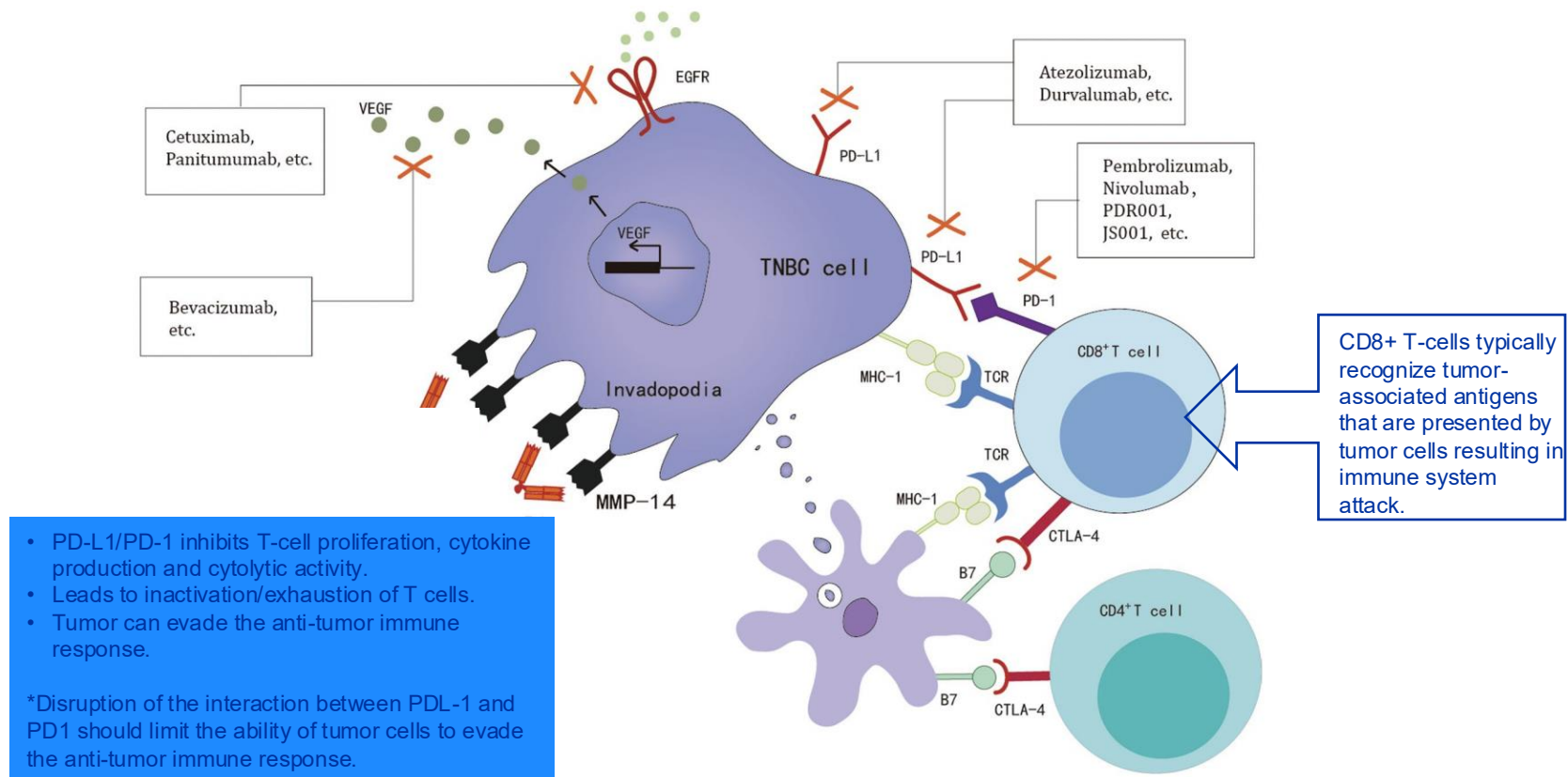


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Organs affected by and manifestations of immune-related adverse events.



Skin

- Dermatitis, erythroderma
- Erythema multiforme
- Stevens–Johnson syndrome
- Toxic epidermal necrolysis
- Psoriasis
- Vitiligo
- Alopecia

Eyes

- Conjunctivitis
- Uveitis, iritis, retinitis
- Scleritis, episcleritis
- Blepharitis

Endocrine system

- Hypo- or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes

Cardiovascular system

- Myocarditis
- Pericarditis
- Vasculitis

Lungs

- Pneumonitis
- Pleuritis
- Interstitial lung disease

Liver

- Hepatitis

Gastrointestinal tract

- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- Perforation

Kidneys

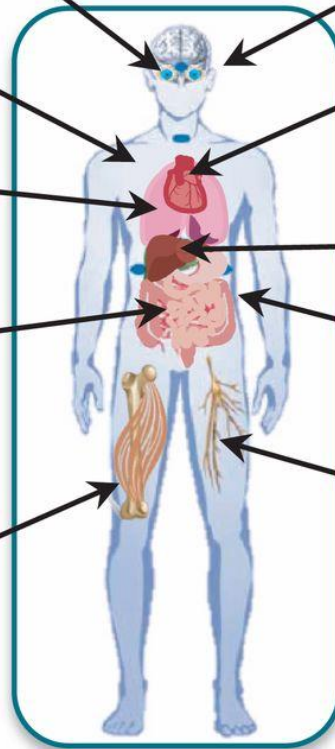
- Nephritis
- Lupus-like glomerulonephritis

Musculoskeletal system

- Arthralgias, arthritis
- Myalgias, myositis
- Enthesitis

Neurologic system

- Neuropathy
- Myelopathy
- Guillain–Barré syndrome
- Myasthenia gravis–like syndrome
- Encephalitis, meningitis



Khashayar Esfahani et al. CMAJ 2019;191:E40-E46



Populations requiring caution



Patients with autoimmune conditions such as Rheumatoid arthritis, Lupus and Crohn's colitis

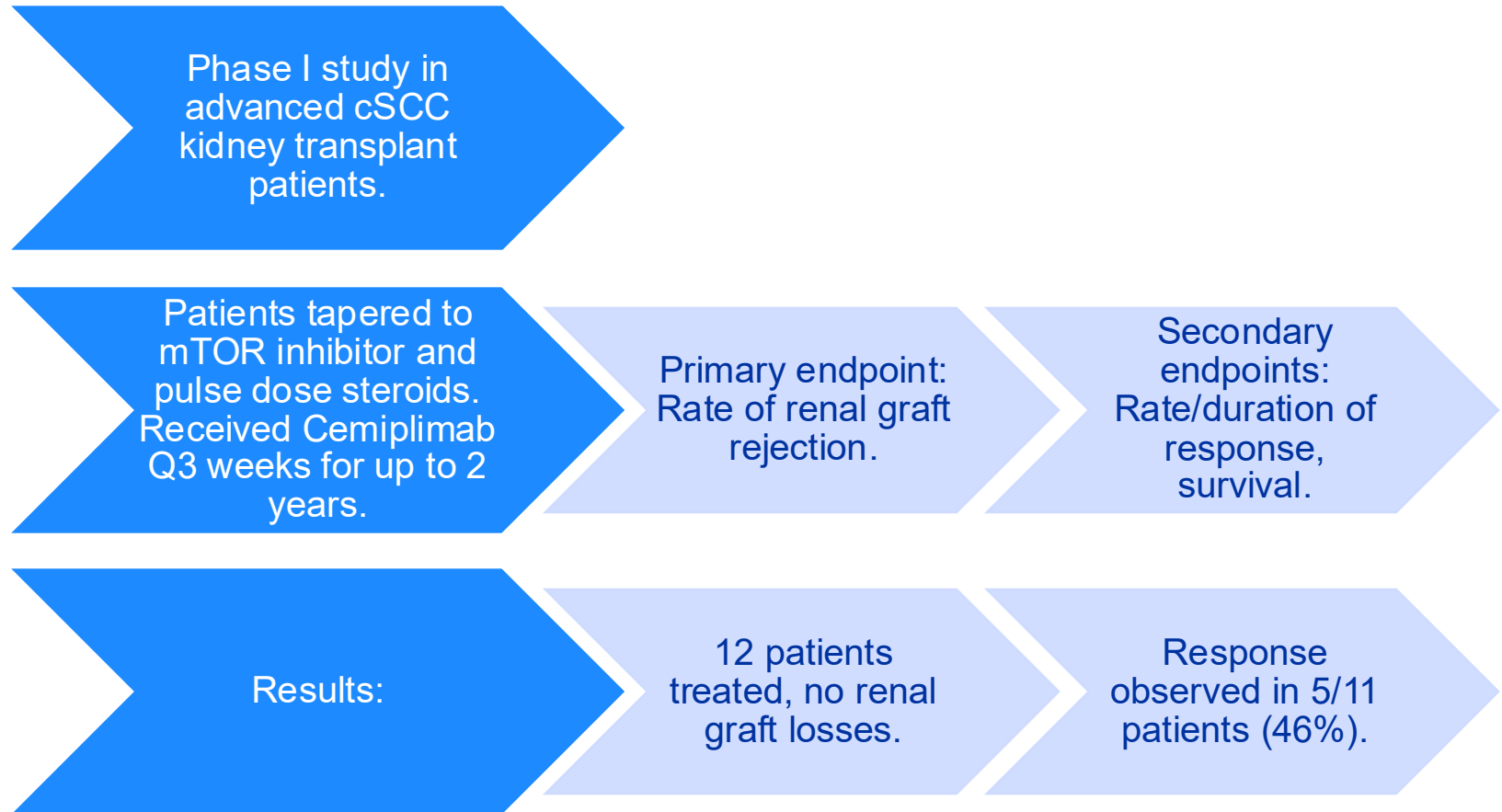
- Immunotherapy may cause a flare of underlying autoimmune disease. When considering these patients for treatment be aware of severity of autoimmune condition and any immunosuppressive agents patient is receiving.

Patients with solid organ transplant

- Concern that use of immunotherapy can lead to allograft rejection.
- Solid organ transplant recipients were excluded from clinical trials, but case reports do indicate high allograft rejection rate (41% in one retrospective study of 39 patients).



Cemiplimab for Kidney Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma



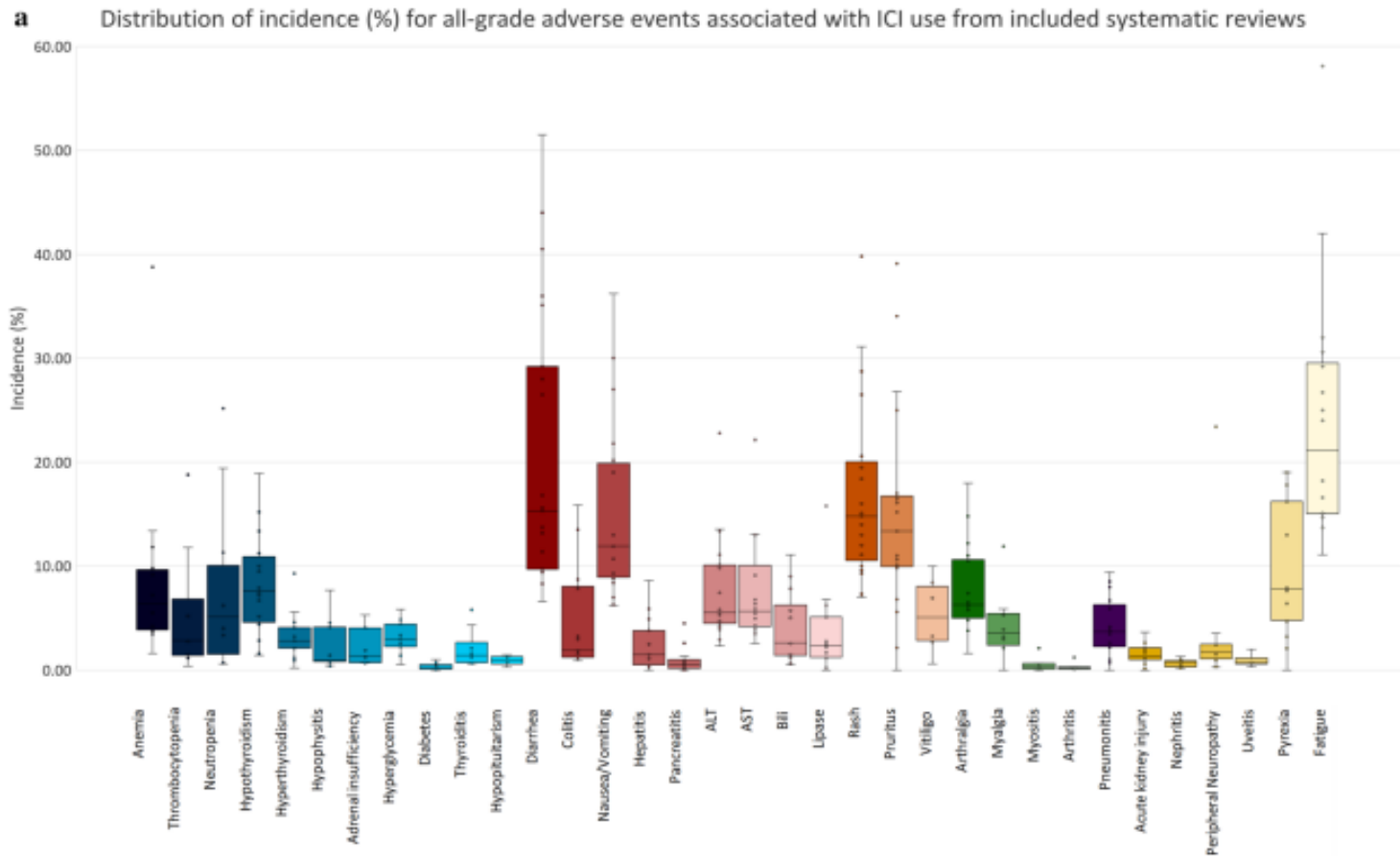
Adverse Event Grading System



Grade 1	Mild: Patient is asymptomatic, no intervention
Grade 2	Moderate: Minimal, local or non-invasive intervention is indicated.
Grade 3	Severe or medically significant but not immediately life threatening. Typically requiring hospitalization.
Grade 4	Life threatening consequences with urgent intervention required
Grade 5	Death related to adverse event.



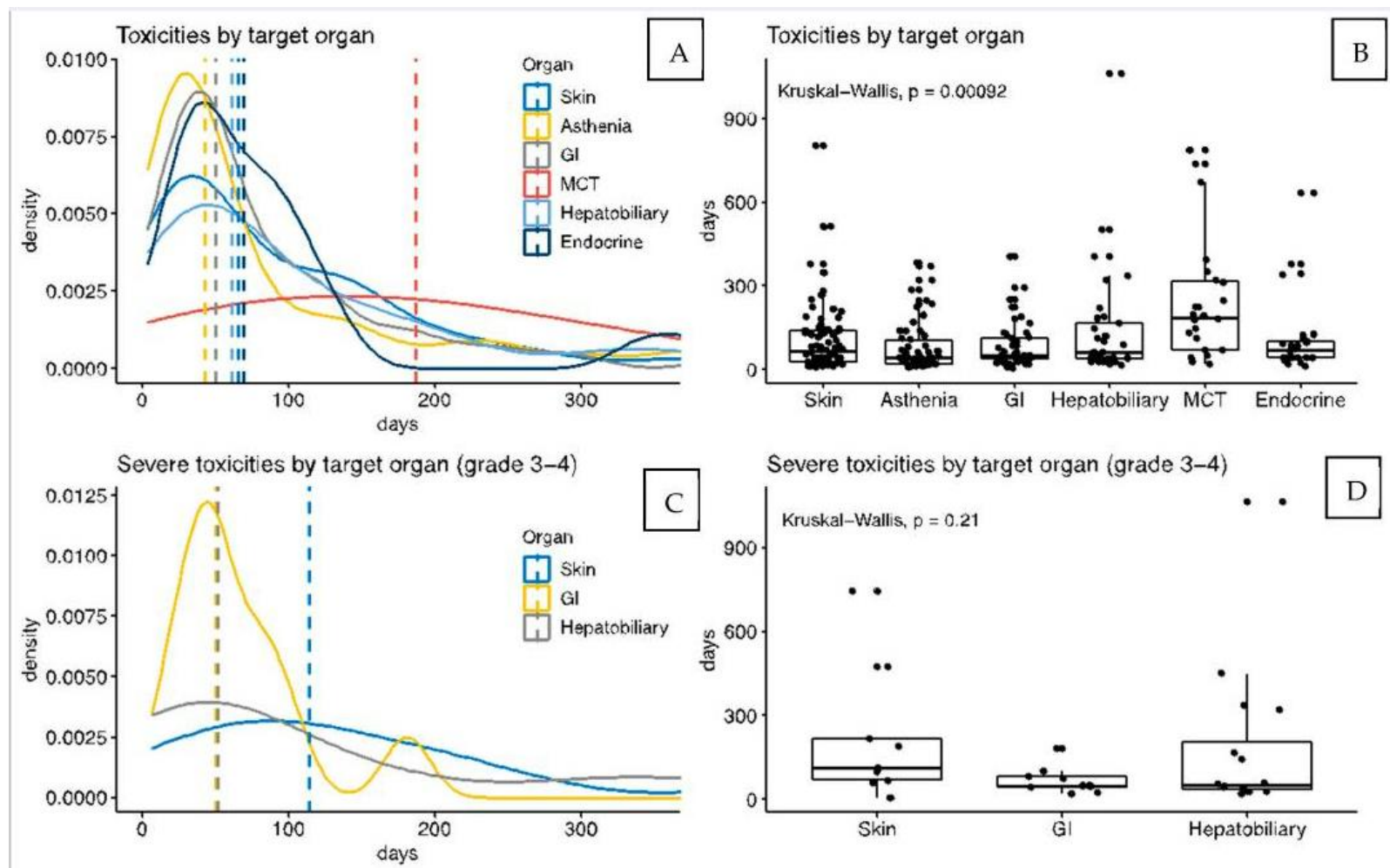
Incidence of IRAEs



Summary of Systematic Reviews of Immunotherapy use: Rash and diarrhea most common IRAEs (20-30% incidence).



Timing of IRAEs



Timing of IRAEs



IRAEs have been reported days after treatment and as late as >1 year after treatment start.



Dermatologic IRAEs usually occur in the first 1-2 months of treatment. GI and Liver have similar time frame.



Endocrine IRAEs can occur within 2-3 months of starting treatment.



Renal IRAEs can be observed >3 months after starting treatment.



IRAEs can occur after treatment has been discontinued. Activated T-cell clones may remain in the patient's system.



IRAE Fatalities



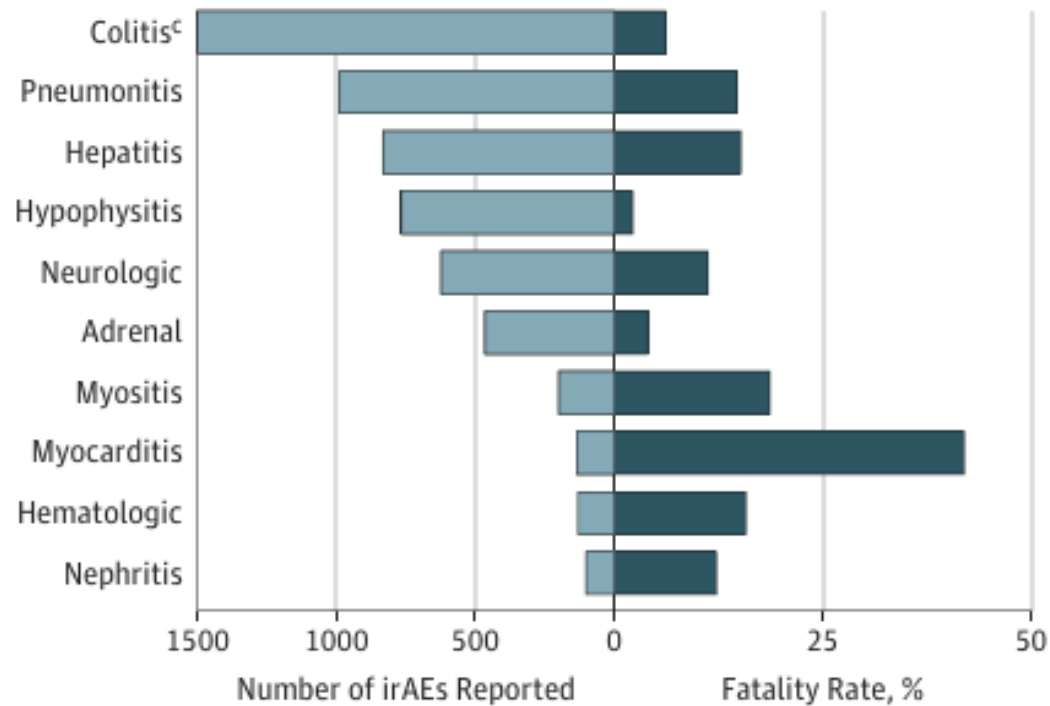
- Meta-analysis of 112 trials involving 19,2017 patients showed that fatality rates related to toxicity from immunotherapy ranged from 0.36%-1.23%.
 - Depending on agents as well as combination versus single drug.
- Highest fatality rate reported for myocarditis (39.7%).
- Endocrine events and colitis reported a 2-5% fatality rate.
- Fatality rates for other organ systems ranged from 10-17%.
- Of note, fatality rates for other common treatments in oncology were reported as 0.9% for platinum doublet chemotherapy, approx. 15% for allogeneic stem cell transplant and 1-10% for complex oncologic surgeries (such as Whipple procedure).



IRAE Fatalities



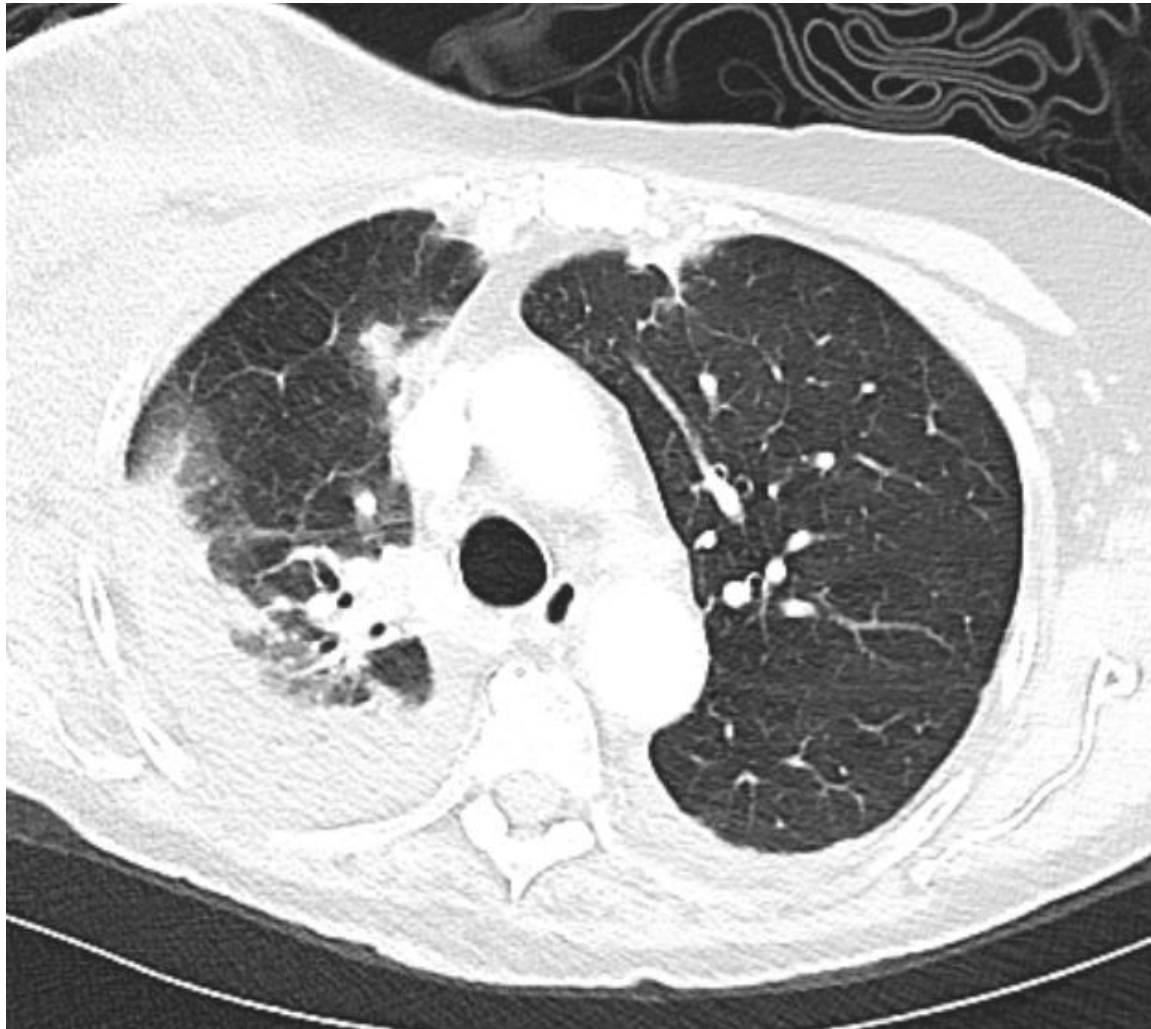
C Cases and fatality rates



Overview of Potentially Serious IRAEs



Pneumonitis



Pneumonitis



Grade 1:
Asymptomatic,
confined to one
lobe of the lung
or <25% of lung
parenchyma.

- Consider holding immunotherapy
- Consider CT Chest with repeat in 4-6 weeks if symptoms persist.

Grade 2:
Presence of
new/worsening
symptoms in
addition to above

- Consider holding immunotherapy
- Rule out infectious etiologies.
- CT Chest with contrast
- Consider Pulmonary consultation with bronchoscopy and BAL
- Prednisone/IV methylprednisolone 1-2 mg/kg/day. If no improvement in 48-72 hours treat as Grade 3.
- Treat until symptoms are Grade 1 then taper over 4-6 weeks.



Pneumonitis

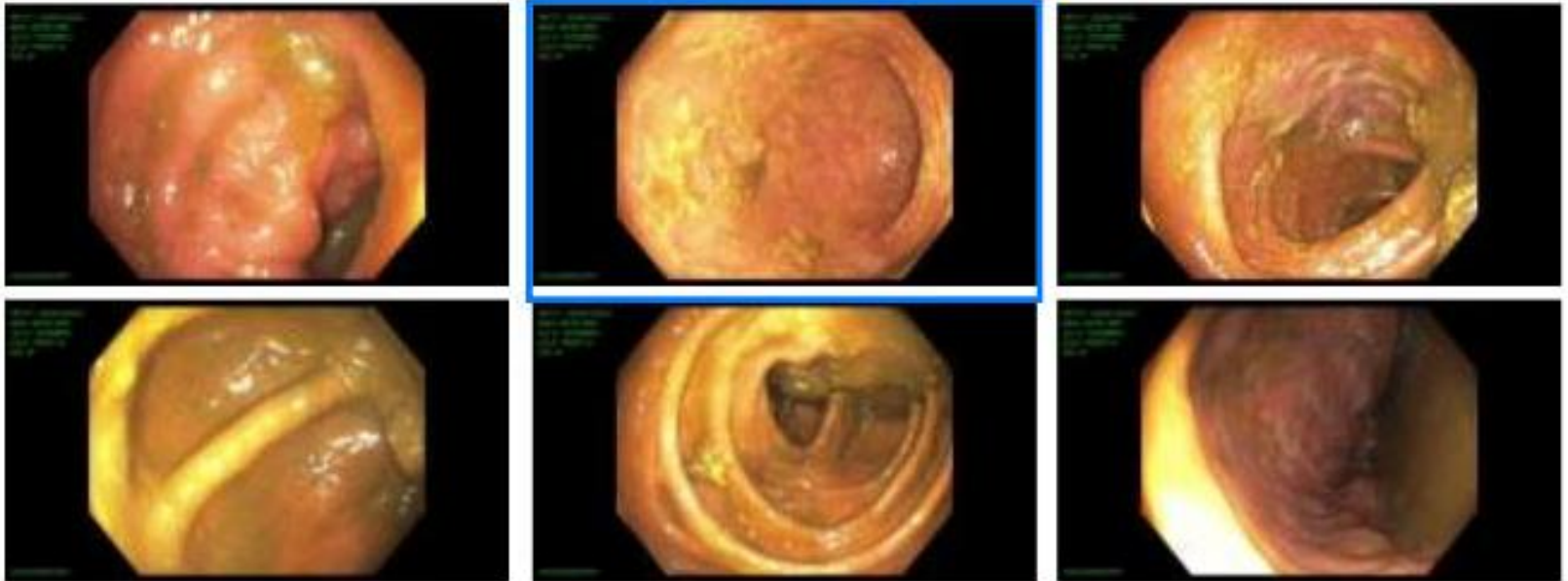


Grade 3: Involving all lung lobes or >50% of lung parenchyma.

- Discontinue immunotherapy.
- IV methylprednisolone 1-2 mg/kg/day with taper over 6 weeks.
 - If no improvement in 48 hours consider Infliximab, IVIG or Mycophenolate mofetil



Colitis





Grade 1: Fewer than 4 bowel movements above baseline/day without colitis symptoms.

- Consider holding immunotherapy
- Can utilize antidiarrheals for 2-3 days for symptoms.
- If symptoms persist then obtain labs for infectious workup (do not have to wait for test results to start treatment).





Grade 2: 4-6 bowel movements above baseline/day but not interfering with ADLs.

- Check C. diff, GI panel, Ova/parasites
- Consider CT Abd/pelvis
- Consider GI consultation for endoscopy
- Hold immunotherapy. Prednisone/IV methylprednisolone (1-2mg/kg/day).
 - If no response to oral steroids after 3 days, consider IV steroids or infliximab or vedolizumab



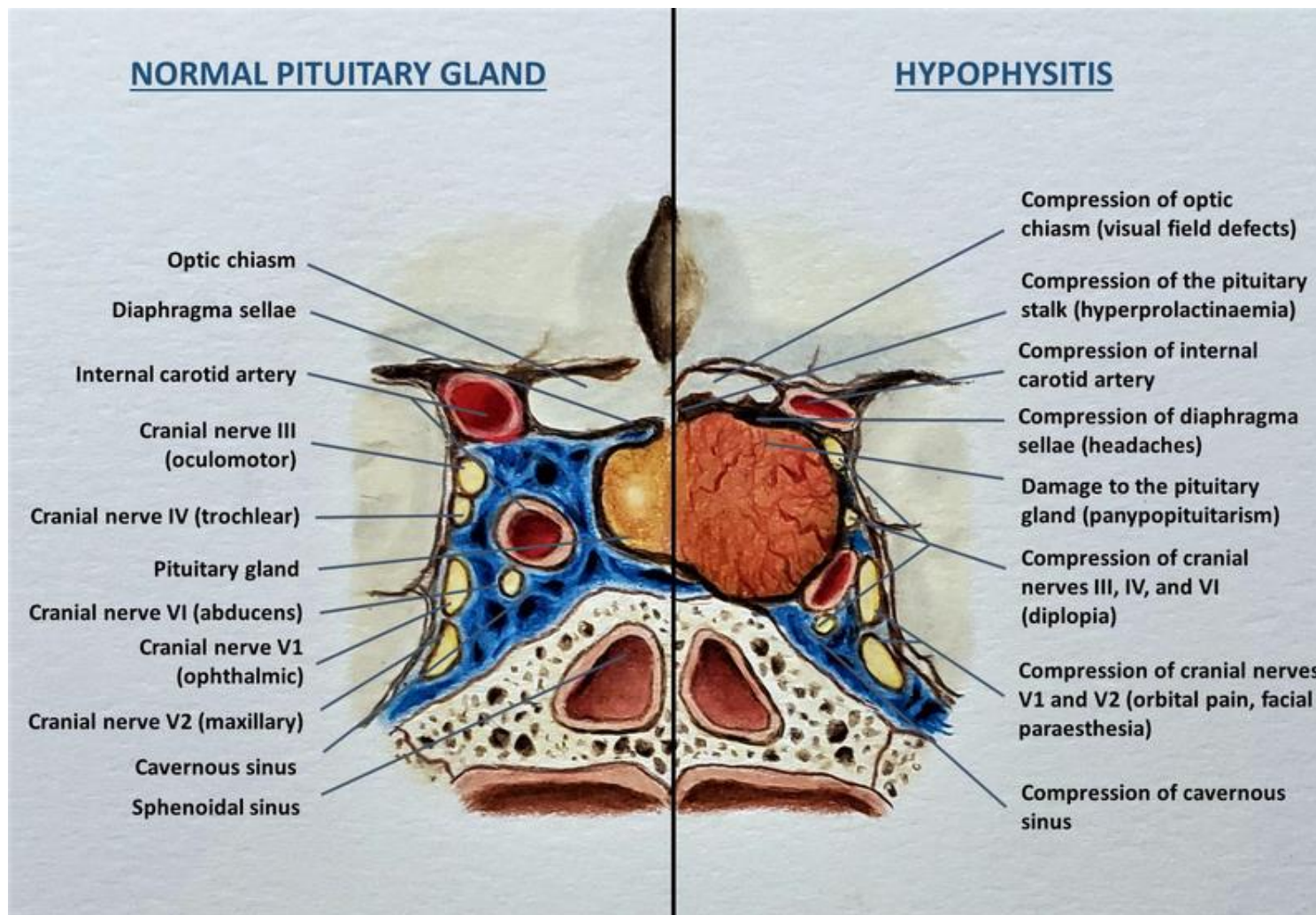


Grade 3-4: More than 6 bowel movements above baseline/day, colitis symptoms, interference with ADLs, hemodynamic instability or hospitalization.

- If patient on dual immunotherapy and Grade 3 toxicity, consider re-initiation with single agent once toxicity resolves.
- IV methylprednisolone 1-2 mg/kg/day. If no response in 1-2 days or unable to transition to PO continue steroids and strongly consider Infliximab or vedolizumab.



Adrenal Insufficiency/Hypophysitis



Adrenal Insufficiency/Hypophysitis



- Suspect if patients are complaining of nausea/vomiting, fatigue and are noted to have persistent hypotension. Low serum Na⁺ can also be an indication of this toxicity.
- Headache and vision change can occur if mass effect from pituitary enlargement is present.

- Initial workup includes Cortisol and ACTH (morning preferred) as well as TSH and free T4.
- Can consider LH, FSH, IGF1, prolactin and sex hormones as indicated

Brain MRI with/without contrast with pituitary sellar cuts to assess for hypophysitis.





Management:

- Consultation with Endocrinology
- Holding immunotherapy until acute symptoms have improved and hormone replacement has been initiated.
- Patients should be treated with physiologic hormone replacement (hydrocortisone).
 - Need instructions for stress dosing during illness.
- If central hypothyroidism is noted (normal/low TSH and low free T4) thyroid hormone replacement should be titrated to free T4 levels.



Important Considerations



Consult Oncology early when IRAE suspected

Early initiation of high dose steroids crucial in improving symptoms and preventing complications.



IRAEs, Steroids and Immunotherapy Efficacy



Relationship between Immunotherapy mediated adverse effects and Response to treatment



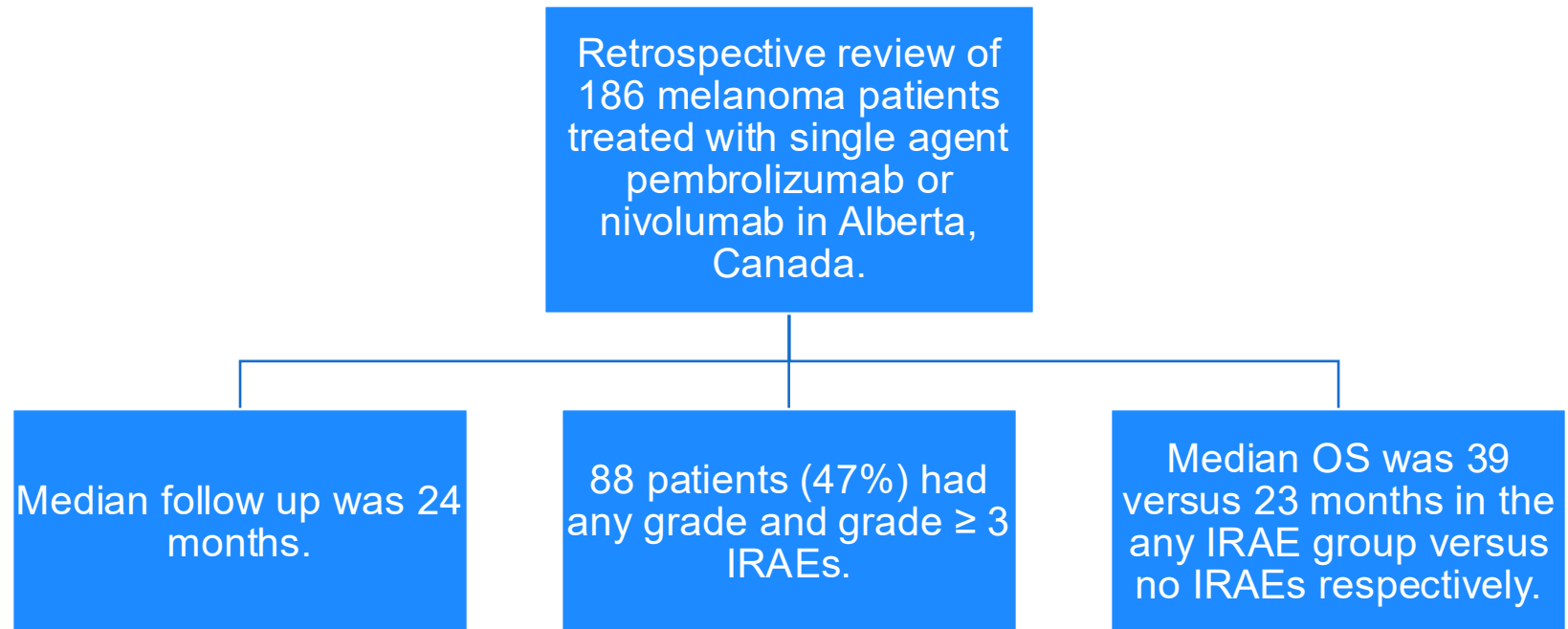
A study of advanced NSCLC patients had a larger cohort of 559 patients enrolled from Sept. 2013-May 2018.

41.3% of patients developed irAEs of any grade.

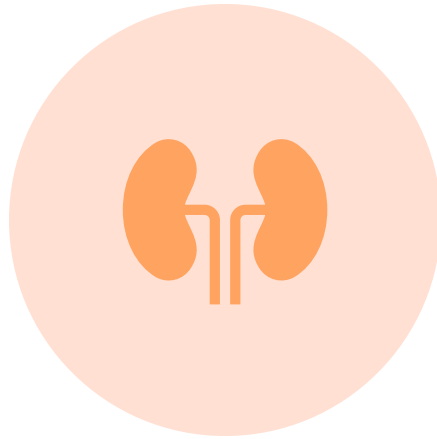
At the 6 week landmark analysis, irAEs of any grade confirmed as an independent predictor of higher ORR, longer PFS and longer OS.



Relationship between Immunotherapy mediated adverse effects and Response to treatment



Relationship between Immunotherapy mediated adverse effects and Response to treatment: Summary



ALTHOUGH MANY PATIENTS WITH DURABLE RESPONSES TO IMMUNOTHERAPY DEVELOP MINIMAL OR NO TOXICITIES, A TREND EXISTS IN NUMEROUS STUDIES SHOWING ASSOCIATION BETWEEN PATIENTS WITH IRAES AND BETTER OUTCOMES.



IRAES MAY SERVE AS A BIOMARKER FOR IMMUNOTHERAPY RESPONSE, THOUGH MORE STUDIES ARE NEEDED.



Relationship between steroid use and Immunotherapy Effectiveness



- Corticosteroids can lead to immunosuppression by impairing IL-2 mediated effector T-cell activation which leads to increased regulatory T cells.
 - In malignancies corticosteroids can affect release of tumor antigens and immune-mediated tumor killing.
- Due to their mechanism of action, steroids and ICIs are theorized to counteract each other's effects.



Relationship between steroid use and Immunotherapy Effectiveness



- Most immunotherapy clinical trials excluded patients receiving steroids above physiologic levels (7.5 mg of prednisone or higher). However, retrospective studies have shown worsened survival outcomes with concurrent corticosteroids use.
 - Higher steroid dose (>20 mg prednisone equivalents) associated with worse outcomes than lower doses in immunotherapy treated patients.
 - Retrospective study of >2000 patients treated with immunotherapy for melanoma, Non-Small Cell Lung Cancer (NSCLC) and urothelial cancer showed baseline corticosteroid use (within 30 days of immunotherapy start) was associated with 23-47% risk of mortality.
 - Patients on steroids in this study tended to have more advanced staging at diagnosis, distant metastasis (including to brain) and poorer performance status although outcomes appeared worse even when considering these issues suggesting a causal link.



Relationship between steroid use and Immunotherapy Effectiveness



- Given there is a trend toward patients who develop IRAEs and better outcome concern remains for steroids potentially blunting these responses although they are necessary for treatment.
 - Studies in melanoma and NSCLC of patients who required corticosteroid use for IRAEs did not show significant difference in outcomes.
 - Lower steroid doses for IRAEs associated with improved survival outcomes compared to higher doses.



Relationship between steroid use and Immunotherapy Effectiveness: Summary



- While there is concern regarding concomitant use of corticosteroids and immunotherapy there are many confounding factors that may lead to poorer outcomes in these patients.
 - Example: Patients with brain metastasis typically have poorer outcomes from their disease and require steroids for treatment of CNS edema. This is independent of immunotherapy efficacy/use.
- The NCCN notes that use of corticosteroids for IRAEs has not been shown to reduce efficacy of immunotherapy which is borne out by several studies.



Summary



Timing and severity of IRAEs varies and it is important to consider these in the differential when evaluating a patient with new symptoms who is on immunotherapy.

Prompt involvement of Oncology and initiation of steroids is crucial to prevent morbidity and mortality from IRAEs.

There is evidence that patients who experience IRAEs may have better Overall response rates as well as Overall Survival although more studies are needed.



Questions?

