University of Kentucky

Immunotherapy Related Adverse Events (IRAEs)

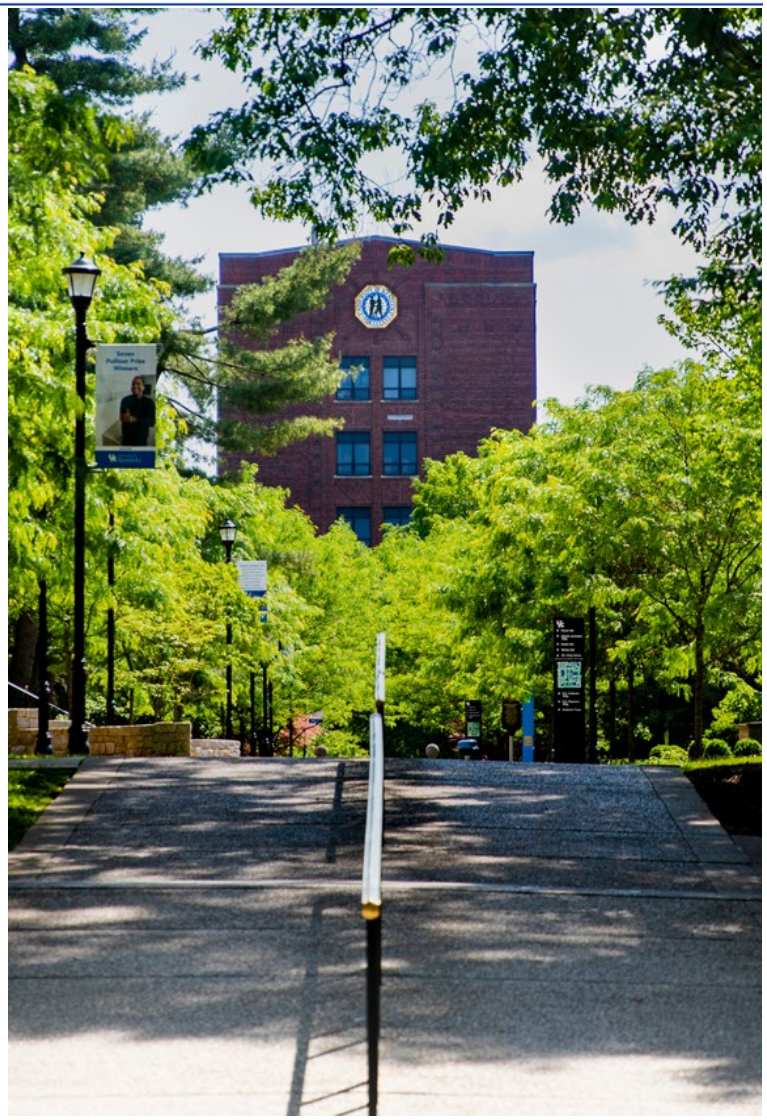
Ruta Arays, MD

Assistant Professor Oncology

University of Kentucky

Non Disclosure Statement

I have nothing to disclose.

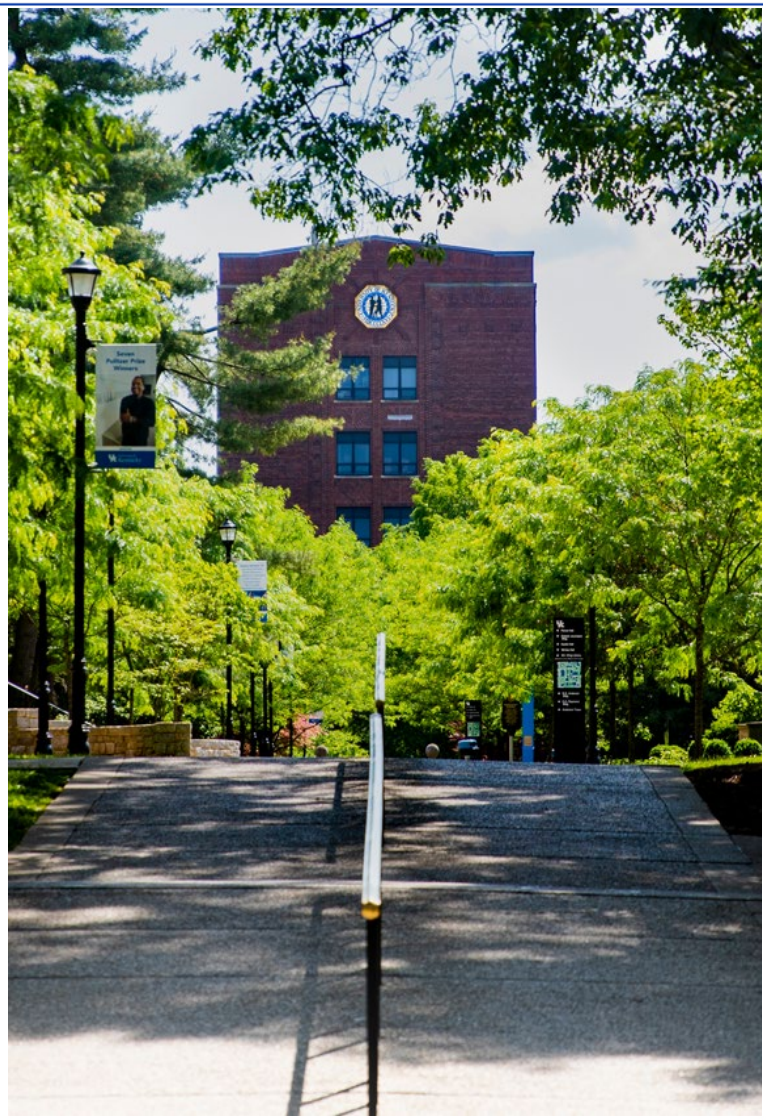


Objectives

1)Describe the mechanism of immunotherapy-related adverse events (IRAEs).

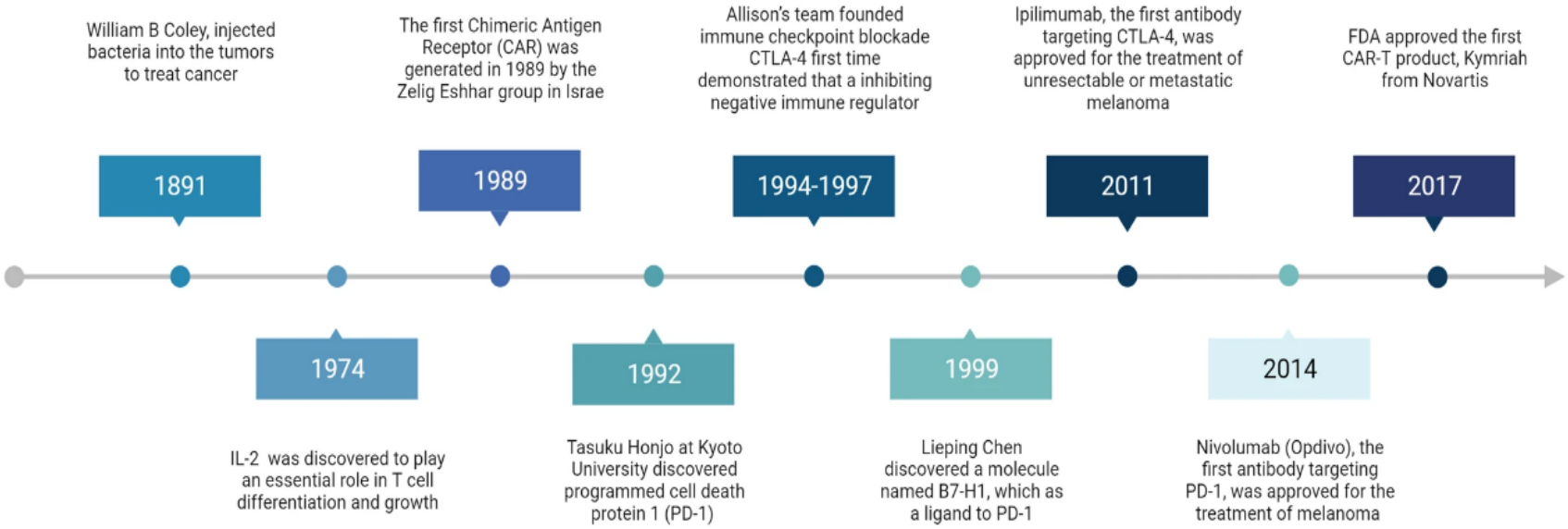
2)Recognize presentations that suggest development of IRAEs.

3) Define strategies for management of IRAEs.



Background

From: Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response



Historical landmarks in cancer immunotherapy development

Wang, DR., Wu, XL. & Sun, YL. Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response. *Sig Transduct Target Ther* **7**, 331 (2022). https://doi.org/10.1038/s41392-022-01136-2

Background

- Many agents are currently available that are classified under the Immunotherapy category including antibody therapies, T-cell therapies, cancer vaccines and checkpoint inhibitors.

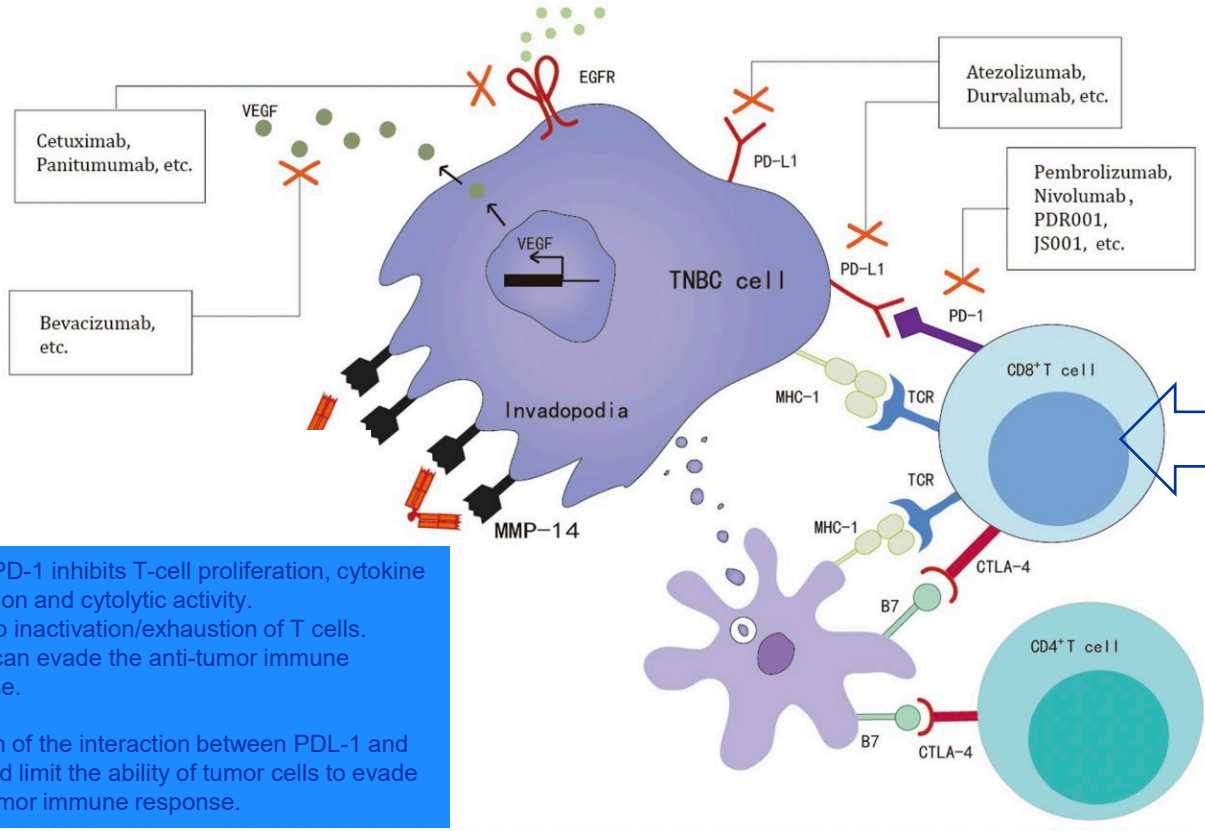
- The focus of today's presentation will be predominantly checkpoint inhibitors.

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.

National Cancer Institute. Immune Checkpoint Inhibitor. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor. Accessed Feb. 21, 2024.

Immune Checkpoint Inhibitors: Mechanism of Action



CD8+ T-cells typically recognize tumor-associated antigens that are presented by tumor cells resulting in immune system attack.

- PD-L1/PD-1 inhibits T-cell proliferation, cytokine production and cytolytic activity.
- Leads to inactivation/exhaustion of T cells.
- Tumor can evade the anti-tumor immune response.

*Disruption of the interaction between PDL-1 and PD1 should limit the ability of tumor cells to evade the anti-tumor immune response.

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

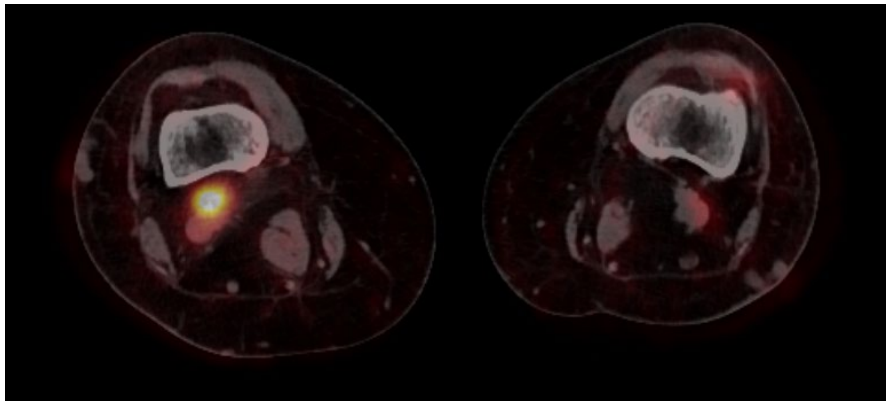
- Pembrolizumab (PD-1 blockade)
- Cemiplimab (PD-1 blockade)
- Nivolumab (PD-1 blockade)
- Dostarlimab (PD-1 blockade)
- Atezolizumab (PDL-1 blockade)
- Avelumab (PDL-1 blockade)
- Durvalumab (PDL-1 blockade)
- Ipilimumab (CTLA-4 blockade)
- Tremelimumab (CTLA-1 blockade)
- Opdualag (Nivolumab with relatlimab,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

University of Kentucky

Patient Cases

Case #1

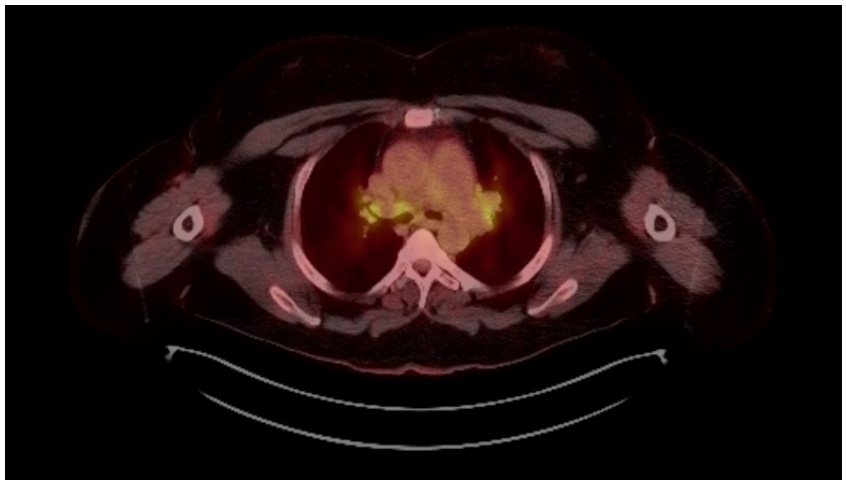
- 51 yo F with a PMH significant for migraines.
- Right toe biopsy 1/2023 with melanoma (thickness of at least 4.8 mm, pT4a).
- PET/CT 2/21/23 with FDG avidity associated with R second toe and two intensely hypermetabolic metastatic R popliteal lymph nodes. R popliteal lymph node biopsy + for melanoma.



Case #1

- Patient was started on neoadjuvant pembrolizumab per S1801 clinical trial in order to down-stage disease and potentially save the patient a toe 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.
- Patient admitted 7/18-7/22/2023 due to nausea, vomiting, headaches and A. fib.
- Tropnin elevated at 391 ng/L
- CRP >20
- Cardiac MRI with normal LVEF of 57%. Heterogenous T1 values with elevated T1 recovery time in basal segments. T2 times are high end of normal and may be related to check point inhibitor myocarditis.
- Pt was started on high dose steroids. Myocardial bx 7/20/23 consistent with resolving acute myocarditis.

Case #1

- Myocardial biopsy pathology report:
  - “Three adequate pieces of endomyocardium of native heart are evaluated. On H&E at multiple levels show 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. This is associated with very limited CD 8 positive lymphocytes and no significant increase in CD 3 cells.
  - 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.
- PET/CT 1/12/23 negative for distant disease.

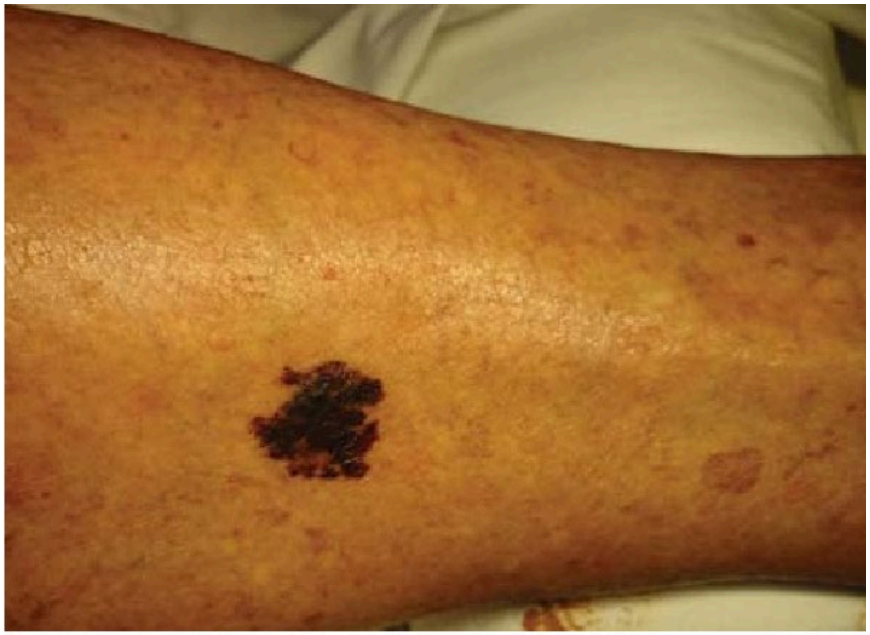


Figure 1. Malignant melanoma on the calf

Răducu, L., Filip, I., Cozma, C.N., Ardeleanu, V., Stefanescu, O.M., & Jecan, R.C. (2017). A REVIEW OF FREQUENT CUTANEOUS MALIGNANCIES – PART II: MALIGNANT MELANOMA.

Case #2

- Right lower extremity wide local excision and sentinel lymph node bx performed 2/6/2023 showed malignant melanoma, 5.7 mm in thickness and 1R inguinal sentinel lymph node positive for metastatic melanoma (0.86mm in greatest dimension), 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.

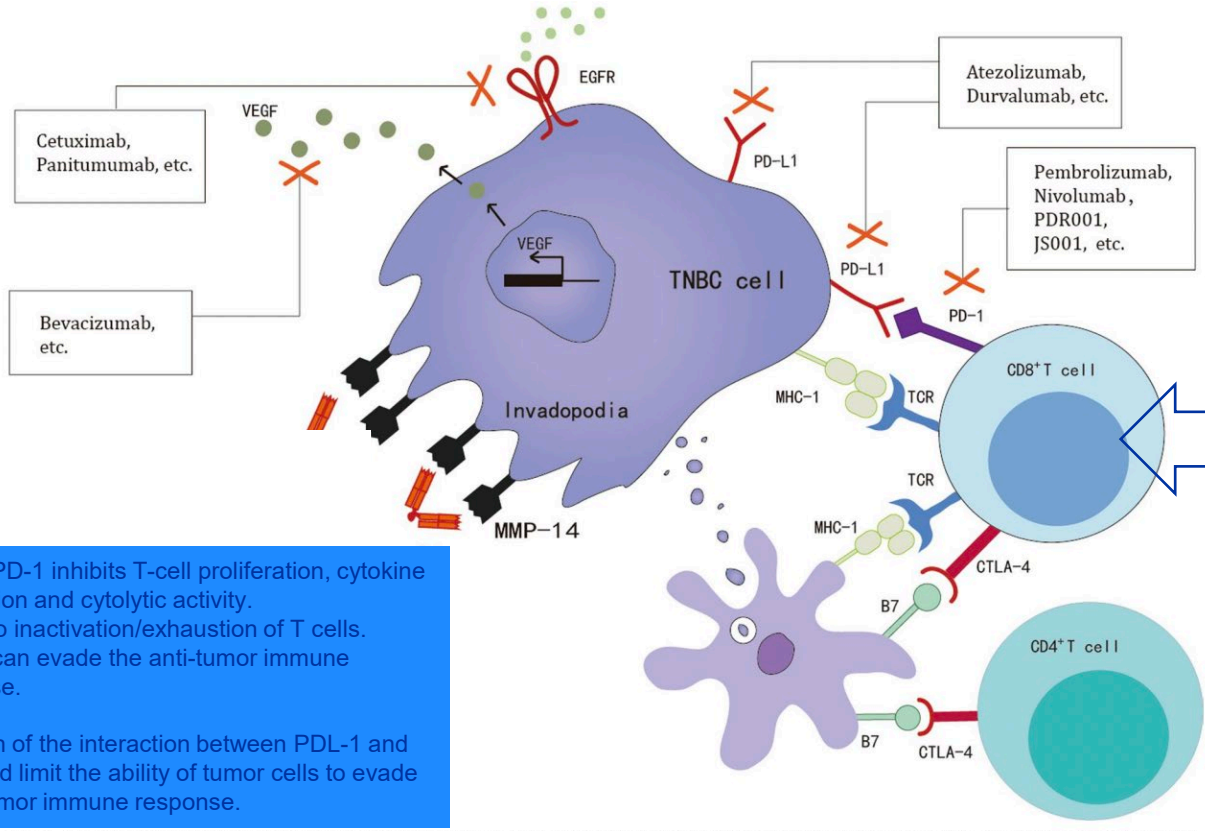
- 7/18-7/24/2023: The patient was hospitalized due to Hgb of 4.6, Haptoglobin <10, LDH 489 with negative DAT. Patient was diagnosed with Autoimmune Hemolytic Anemia thought to be secondary to immunotherapy treatment.

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



CD8+ T-cells typically recognize tumor-associated antigens that are presented by tumor cells resulting in immune system attack.

- PD-L1/PD-1 inhibits T-cell proliferation, cytokine production and cytolytic activity.
- Leads to inactivation/exhaustion of T cells.
- Tumor can evade the anti-tumor immune response.

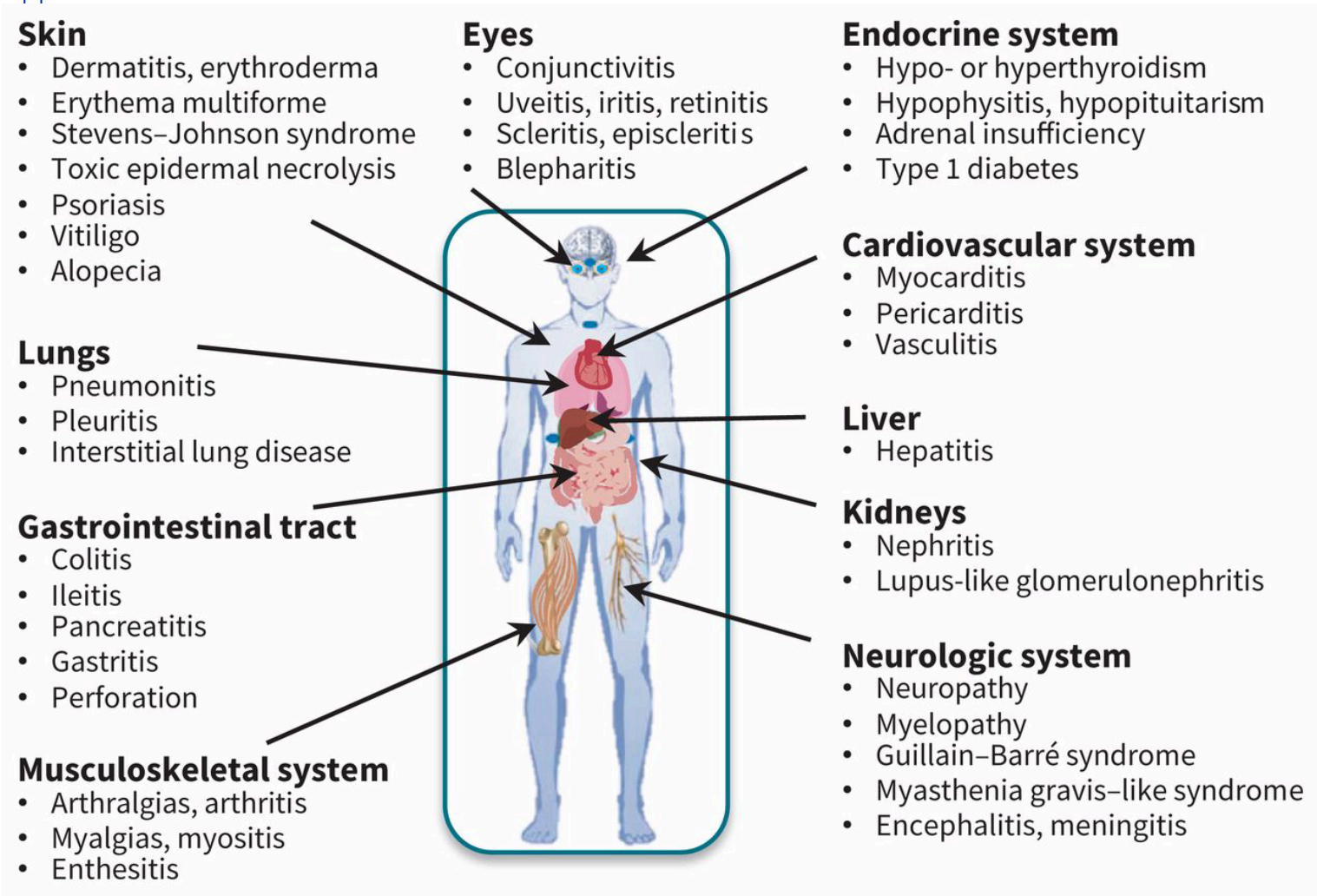
*Disruption of the interaction between PDL-1 and PD1 should limit the ability of tumor cells to evade the anti-tumor immune response.

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

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



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, must take into account 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).

Abdel-Wahab, N., Safa, H., Abudayyeh, A. *et al.* Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature. *j. immunotherapy cancer* **7**, 106 (2019). https://doi.org/10.1186/s40425-019-0585-1

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.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Nov. 27, 2017.

Incidence of IRAEs

Rates of the more common immune-related adverse events stratified by immune checkpoint inhibitor strategy

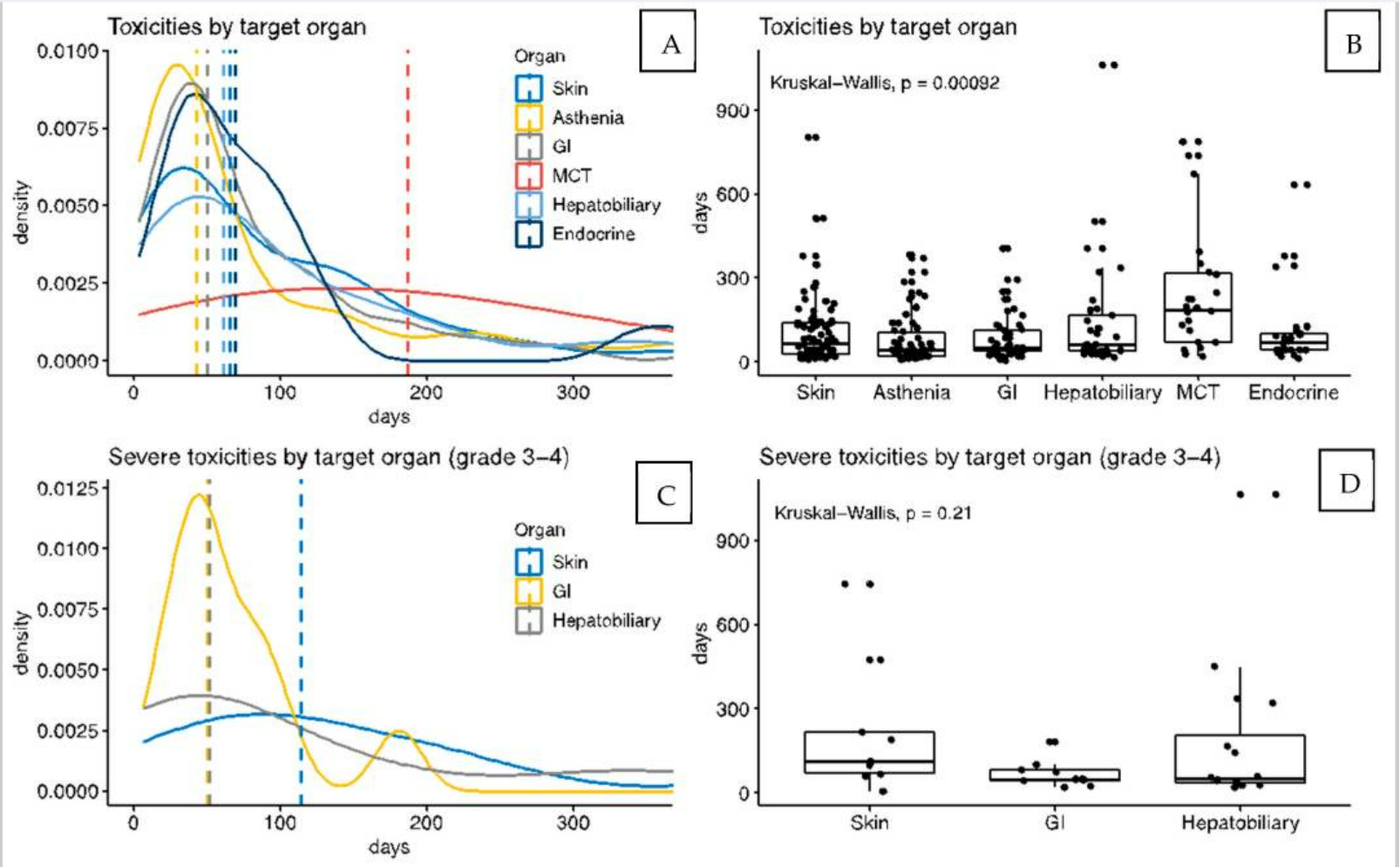
Immune-related adverse events	Anti-CTLA-4 (ipilimumab)		Anti-PD-1 (nivolumab)		Anti-CTLA4 + Anti-PD1 (ipilimumab + nivolumab)	
	Any grade, %	Grade ≥ 3,' %	Any grade, %	Grade ≥ 3,' %	Any grade, %	Grade ≥ 3,' %
All immune-related adverse events	86	27	82	16	96	55
Rash	33	2	26	1	40	5
Colitis	12	9	1	1	12	8
Diarrhea	33	6	20	2	44	10
Hepatitis	4	2	4	1	18	8
Hypothyroidism	4	0	9	0	15	1
Discontinuation owing to immune-related adverse events	15	13	8	5	36	30

Summary: Rash and diarrhea most common IRAEs (20-40% incidence depending on single versus dual agent therapy).

University of Kentucky

Esfahani K, Meti N, Miller WH Jr, Hudson M. Adverse events associated with immune checkpoint inhibitor treatment for cancer. CMAJ. 2019 Jan 14;191(2):E40-E46. doi: 10.1503/cmaj.180870. PMID: 30642824; PMCID: PMC6333545.

Timing of IRAEs



University of Kentucky

Villa-Crespo L, Podlipnik S, Anglada N, Izquierdo C, Giavedoni P, Iglesias P, Dominguez M, Aya F, Arance A, Malvehy J, Puig S, Carrera C. Timeline of Adverse Events during Immune Checkpoint Inhibitors for Advanced Melanoma and Their Impacts on Survival. Cancers (Basel). 2022 Feb 27;14(5):1237. doi: 10.3390/cancers14051237. PMID: 35267545; PMCID: PMC8909485.

Timing of IRAEs

- IRAEs have been reported as quickly as a few days after treatment and as late as >1 year after initiation of therapy.
- In general dermatologic IRAEs occur within the first 1-2 months of treatment. Followed by GI and liver IRAEs around the same time frame.
- Endocrine IRAEs can occur within 2-3 months of starting treatment.
- Renal IRAEs can be observed >3 months after starting treatment.
- It is possible for IRAEs to occur after treatment has been discontinued as activated T-cell clones may still be present in the patient's body.

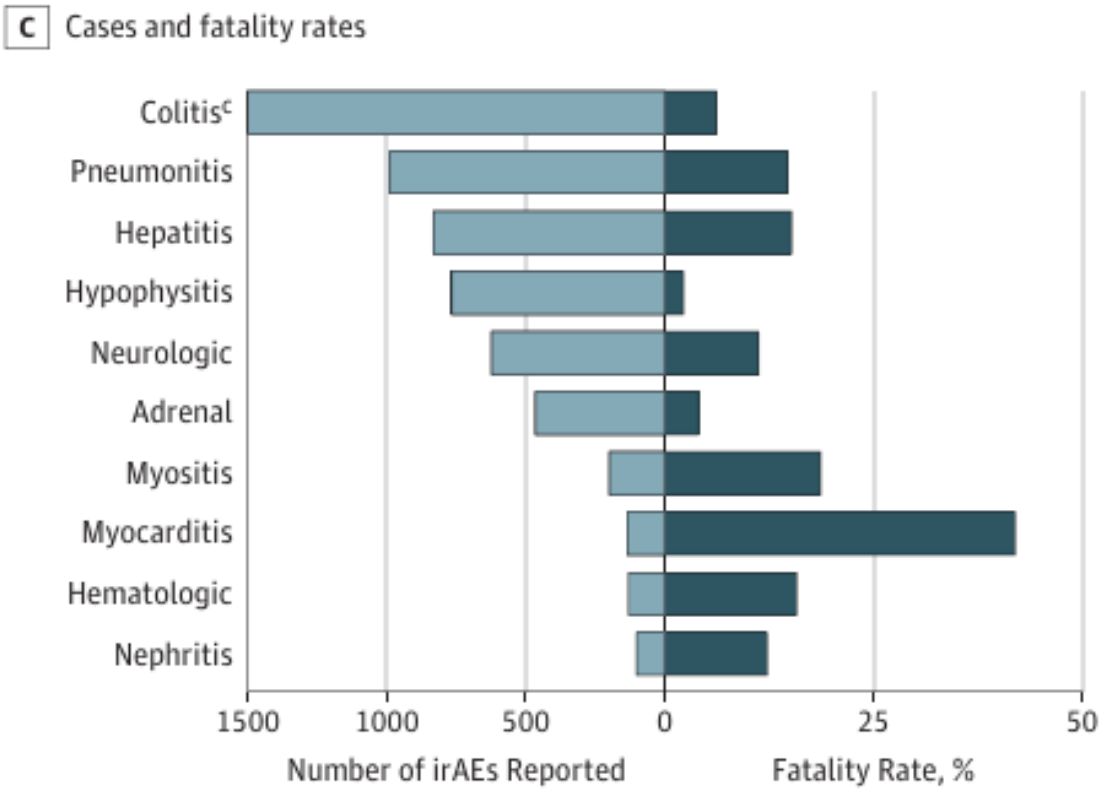
Ramos-Casals, M; Siso-Almirall A. Immune-Related Adverse Events of Immune Checkpoint Inhibitors. Annals of Internal Medicine. February 12, 2024.

IRAE Fatalities

- Meta-analysis of 112 trials involving 19,2017 patients showed that fatality rates related to toxicity from immunotherapy treatments 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 oncologist surgeries (such as Whipple procedure).

Wang DY, Salem J, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2018;4(12):1721–1728. doi:10.1001/jamaoncol.2018.3923

IRAE Fatalities

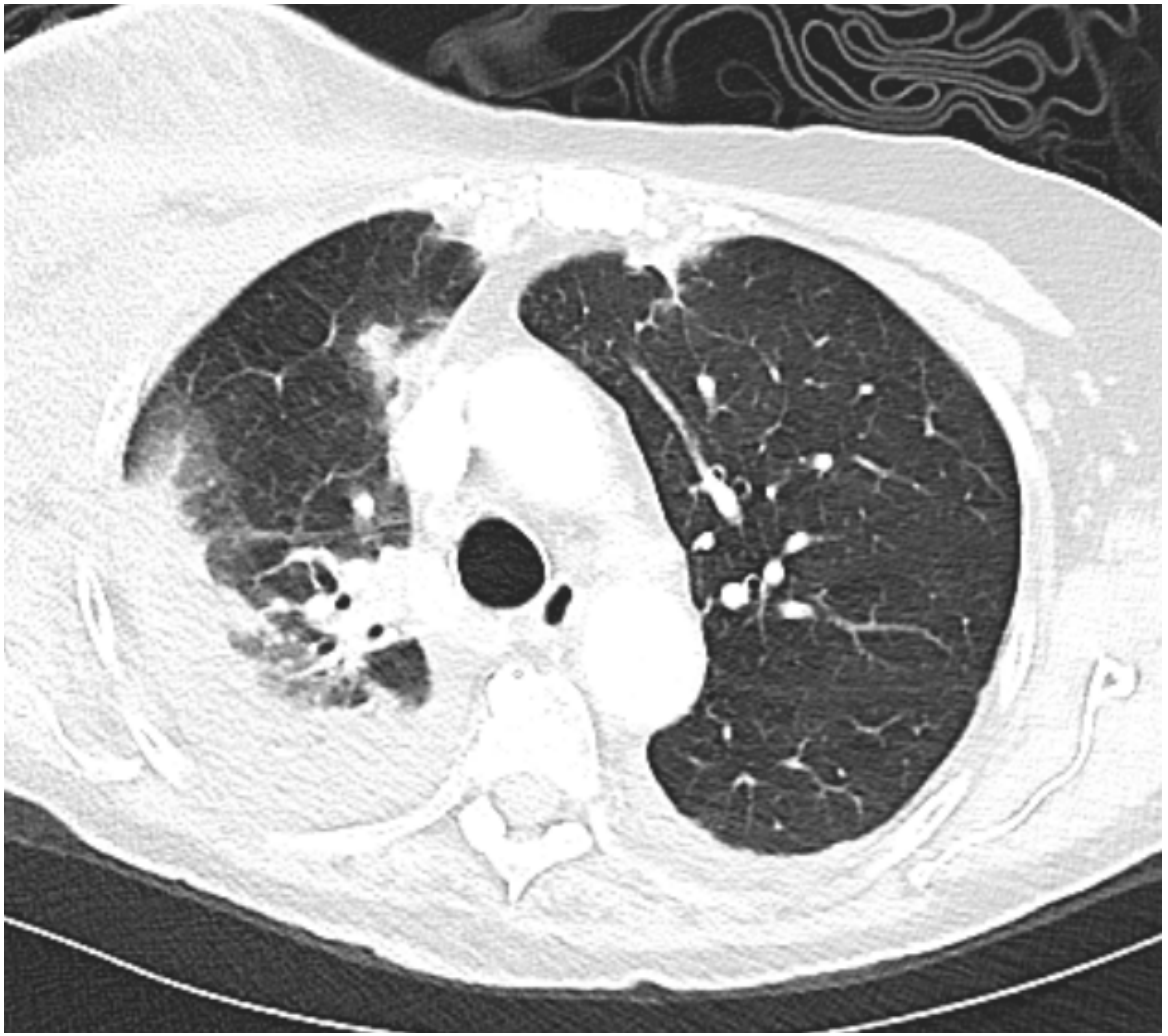


Wang DY, Salem J, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2018;4(12):1721–1728. doi:10.1001/jamaoncol.2018.3923

University of Kentucky

Overview of Potentially Serious IRAEs

Pneumonitis



Pneumonitis

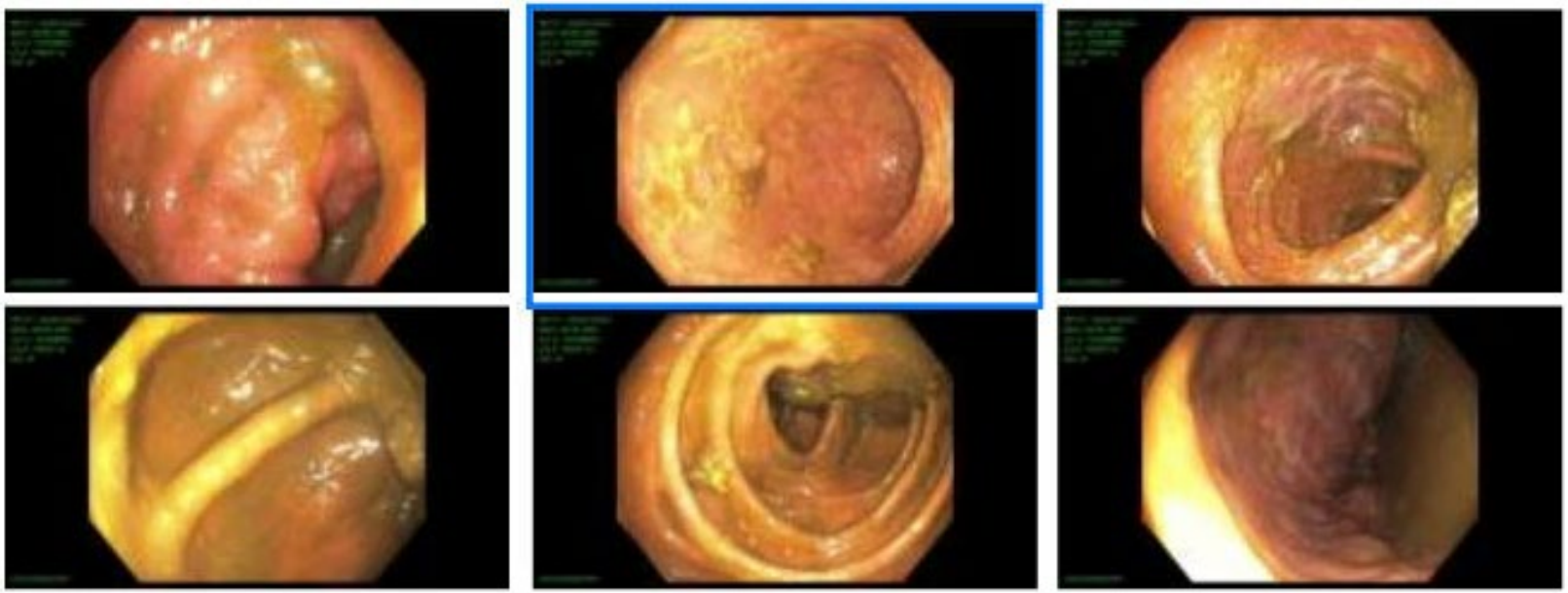
- Grade 1: Asymptomatic, confined to one lobe of the lung or <25% of lung parenchyma.
  - Consider holding immunotherapy
  - Consider CT Chest with repeat in 4-6 weeks if symptoms persist.

- Grade 2: Presence of new/worsening symptoms in addition to above
  - Rule out infectious etiologies/respiratory viral panel.
  - CT Chest with contrast
  - Consider Pulmonary consultation with bronchoscopy and BAL as well as transbronchial bx to rule out progression of malignancy/fungal etiology.
  - Broad spectrum abx if infection has not yet been excluded
  - 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 (may not improve steroid-unresponsive pneumonitis immediately but may have clinical benefit to avoid steroid dependence).

Colitis



Colitis

- Grade 1: Fewer than 4 bowel movements above baseline/day without colitis symptoms.
  - Consider holding immunotherapy
  - Can utilize Imodium or diphenoxylate/atropine 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).
  - If persistent/progressive symptoms check lactoferrin/calprotectin and if positive treat as G2.

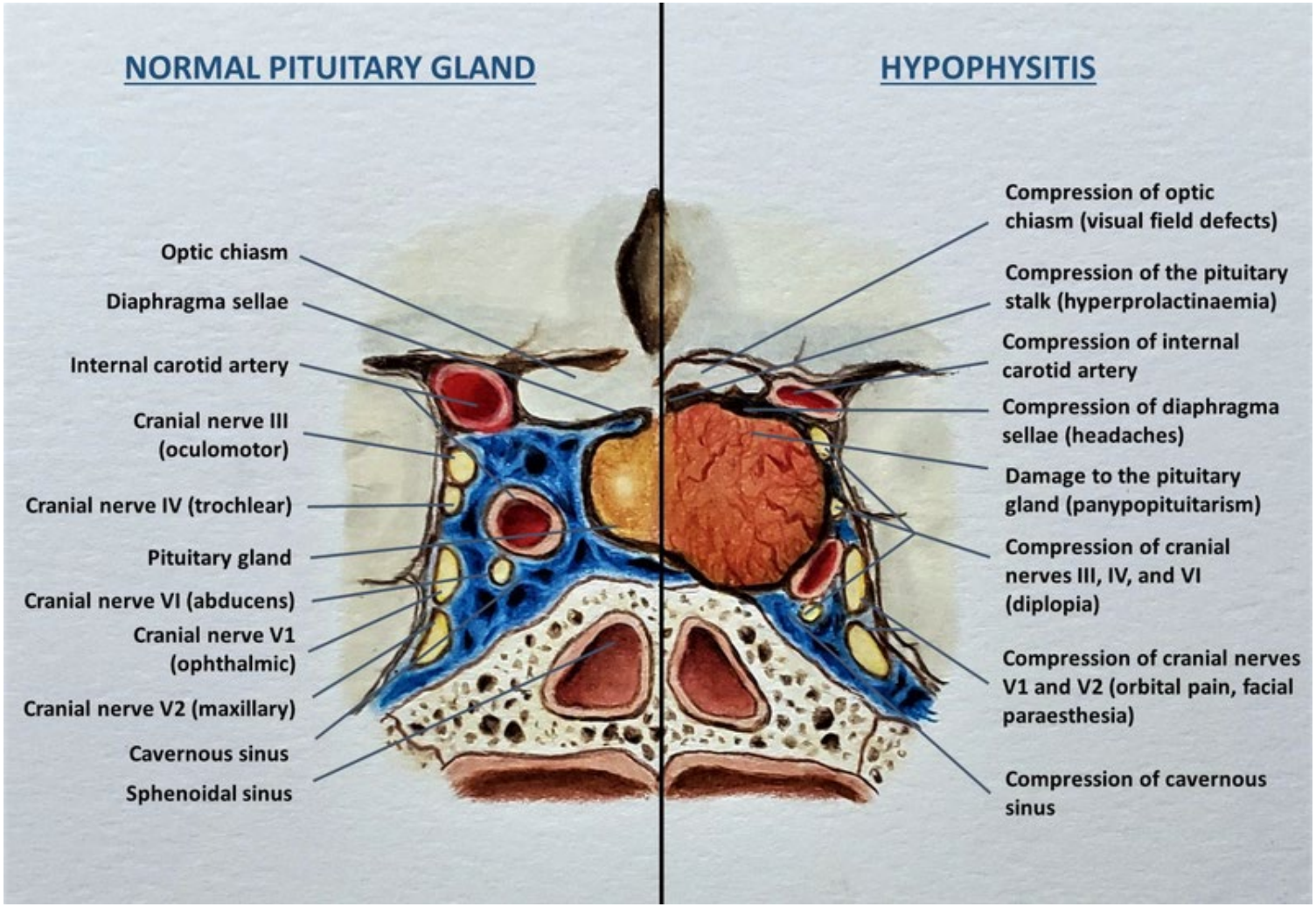
Colitis

- Grade 2: 4-6 bowel movements above baseline/day but not interfering with ADLs.
  - Check C. diff
  - GI panel for other GI pathogens as well as ova and parasites
  - Consider CT Abd/pelvis
  - Consider GI consultation for endoscopy
  - Hold immunotherapy. If pathologically confirmed microscopic colitis consider budesonide 9 mg daily prior to systemic steroids.
  - Prednisone/IV methylprednisolone (1-2mg/kg/day). If not response to oral steroids after 3 days consider IV steroids or infliximab or vedolizumab

Colitis

- 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



University of Kentucky

Gubbi S, Hannah-Shmouni F, Verbalis JG, Koch CA. Hypophysitis: An update on the novel forms, diagnosis and management of disorders of pituitary inflammation. Best Practice & research. Clinical Endocrinology & Metabolism. 2019 Dec;33(6):101371. DOI: 10.1016/j.beem.2019.101371. PMID: 31866206; PMCID: PMC7078033.

Adrenal Insufficiency/Hypophysitis

- This IRAE should be suspected if patients are complaining of nausea/vomiting, fatigue and are noted to have persistent hypotension and dizziness. 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 (if issue is central it is possible thyroid function can also be affected).
  - Can consider LH, FSH, IGF1, Prolactin and sex hormone as indicated based on symptoms/presentation.
- Brain MRI with/without contrast with pituitary sellar cuts to assess for hypophysitis.

Adrenal Insufficiency/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) with instructions for stress dosing during times of illness/surgery. Hormone replacement is usually indefinite.
  - If central hypothyroidism is noted (normal/low TSH and low free T4) thyroid hormone replacement should be titrated to free T4 levels.

Important Considerations

- Whenever IRAE is suspected it is very important to involve Oncology early on to determine best management steps.

- Early initiation of high dose steroids crucial in improving symptoms and preventing complications.
  - Given frequent need for prolonged steroid tapers patients should be placed on Pneumocystis jirovecii pneumonia prophylaxis with sulfamethoxazole-trimethoprim as well as be placed on PPI or H2 blockers for gastritis prophylaxis.

  - There is a risk for hepatitis B reactivation with anti-TNFα agents, rituximab and other immunosuppressive drugs that may be used to control IRAEs. Testing for HBV and occasionally HCV and HIV is recommended prior to starting these therapies.

Maslov DV, et al. J Immunother Cancer 2021;9:e002261; Bai X, et al. Clin Cancer Res 2021;27:5993-6000.

University of Kentucky

IRAEs, Steroids and Immunotherapy Efficacy

Relationship between Immunotherapy mediated adverse effects and Response to treatment

- Retrospective study in 97 patients with Non-Small Cell Lung Cancer (NSCLC) treated with pembrolizumab on KEYNOTE 001 trial.
  - 39 patients that experiences IRAEs had increased ORR (38.5% compared to 8.9% in those who did not). As well as OS (median 493 days compared with 144.5 days in those patients who did not).

- Another 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.

1) Lisberg et al. Treatment-related adverse events predict improved clinical outcome in NSCLC patients on KEYNOTE-001 at a single center. Cancer Immunol Res (2018): 288-294.
2) 2) Cortellini et al. Correlations between immune-related adverse events spectrum and efficacy of anti-PD1 immunotherapy in NSCLC patients. Clinical Lung Cancer. July 2019: 237-247.

Relationship between Immunotherapy mediated adverse effects and Response to treatment

- Retrospective review of 186 melanoma patients treated with single agent pembrolizumab or nivolumab in Alberta, Canada.
  - Median follow up was 24 months.
  - 88 patients (47%) had any grade and grade ≥ 3 IRAEs.
  - Median Overall Survival (OS) was 39 versus 23 months in the any IRAE group versus no IRAEs respectively. Median OS was not reached in patients who developed grade ≥ 3 IRAEs.

Sua A et al. Anti-PD1-Induced Immune-Related Adverse Events and Survival Outcomes in Advanced Melanoma. The Oncologist, Volume 25, Issue 5: May 2020, 438-446.

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.

Goodman RS, Johnson DB, Balko JM. Corticosteroids and Cancer Immunotherapy. Clin Cancer Res. 2023 Jul 14;29(14):2580-2587. doi: 10.1158/1078-0432.CCR-22-3181. PMID: 36648402; PMCID: PMC10349688.

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.
  - Murine models have shown that use of immunotherapy and steroids together appeared to blunt anti-tumor responses.

Goodman RS, Johnson DB, Balko JM. Corticosteroids and Cancer Immunotherapy. Clin Cancer Res. 2023 Jul 14;29(14):2580-2587. doi: 10.1158/1078-0432.CCR-22-3181. PMID: 36648402; PMCID: PMC10349688.

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.

Goodman RS, Johnson DB, Balko JM. Corticosteroids and Cancer Immunotherapy. Clin Cancer Res. 2023 Jul 14;29(14):2580-2587. doi: 10.1158/1078-0432.CCR-22-3181. PMID: 36648402; PMCID: PMC10349688.

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.

Goodman RS, Johnson DB, Balko JM. Corticosteroids and Cancer Immunotherapy. Clin Cancer Res. 2023 Jul 14;29(14):2580-2587. doi: 10.1158/1078-0432.CCR-22-3181. PMID: 36648402; PMCID: PMC10349688.

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 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.

Goodman RS, Johnson DB, Balko JM. Corticosteroids and Cancer Immunotherapy. Clin Cancer Res. 2023 Jul 14;29(14):2580-2587. doi: 10.1158/1078-0432.CCR-22-3181. PMID: 36648402; PMCID: PMC10349688.

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?