# Recognize, Triage, Treat: A Practical Approach to ICI Toxicities

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## DISCLOSURES

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty and planners of this CE activity:

- **Melissa Lechner, MD, PhD**
  - Immunovant
- **Andrew Ruplin, PharmD**
  - MJH Life Sciences, Dedham Group

There are no relevant conflicts of interest to disclose for this presentation for the following planners and speakers of this CE activity:

- **Tahsin Imam, PharmD**

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## OBJECTIVES

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1. Recognize immune-related adverse events (irAEs) associated with immune checkpoint inhibitor therapy.
2. Identify the three most common tissues affected by irAEs.
3. Discuss current recommendation for the treatment of patients with pre-existing autoimmune disease.
4. Describe common treatment approaches used to manage irAEs from immune checkpoint inhibitor therapy.
5. Explain the relationship between irAEs and cancer survival outcomes.

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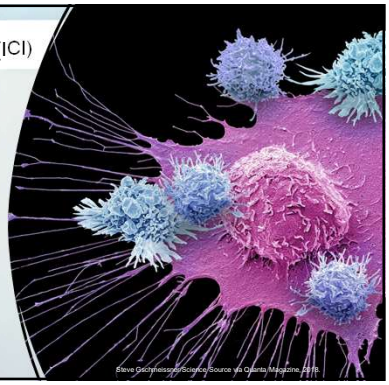
## Immune Checkpoint Inhibitors (ICI)

- Generate dramatic and durable responses
- 50% of US cancer patients now eligible
- Approval expanded to early-stage disease



Steve Gschmeissner/Science Source via Quanta Magazine, 2019

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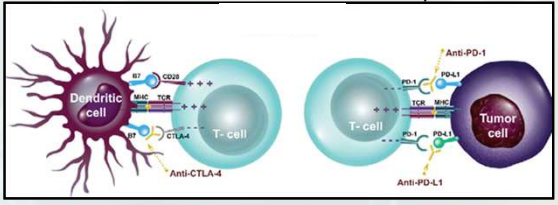
## Immune Checkpoint Blockade Releases the Brakes

CTLA-4 PD-1/PD-L1




**Abbreviations:** CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; MHC = major histocompatibility complex; TCR = T-cell receptor; B7 = B7 costimulatory molecules (CD80/CD86).

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Ramazcoll, AM et al. Diabetes. 2019;67(8):1471–1480

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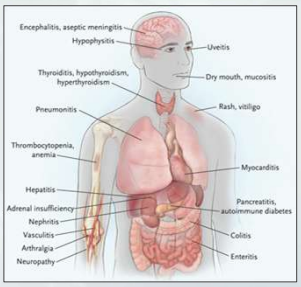
## Immune-related adverse events (irAEs)




Autoimmunity (irAEs) is a common side effect of immune checkpoint blockade

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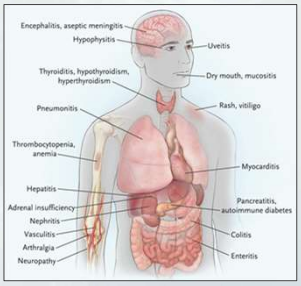
Q1

What are immune-related adverse events (irAEs)?

8

## Immune-related adverse events (irAEs)




**>60%** of ICI treated patients develop irAEs

**25%** will be hospitalized for irAEs

**70%** will have ICI treatment interrupted

1 in 5 have multiple concurrent irAEs, with a **5x** increased risk of death

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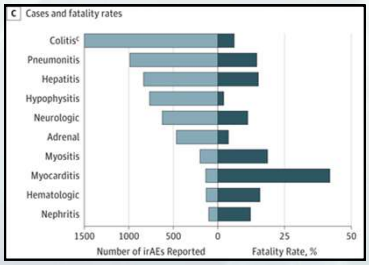
## Treatment-related mortality

**Figure 1.** Clinical Characteristics of Fatal Immune-Related Adverse Events (irAEs)




C = Includes 3905 total cases

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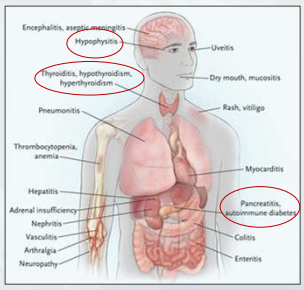
## Permanent organ damage




Endocrine tissues comprise **30%** of irAEs

**>90%** of these result in permanent organ damage

Patients require life-long treatment (e.g., insulin for Immune Checkpoint Inhibitor-related Diabetes Mellitus)

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## Incidence of Immune-Related Adverse Events by Checkpoint Inhibitor Regimen

| irAE | Ipilimumab + Nivolumab (n=313) | Nivolumab (n=313) | Ipilimumab (n=311) |
|---|---|---|---|
| **Skin** Rash, Pruritis, Vitiligo | 62% of patients | 47% of patients | 56% of patients |
| **Gastrointestinal** Colitis, Diarrhea | 48% | 23% | 38% |
| **Endocrine** Thyroid, Pituitary, Pancreas | 34% | 17% | 12% |
| **Hepatic** Hepatitis, Cholestatic | 33% | 8% | 7% |
| **Pulmonary** Pneumonitis | 7% | 2% | 2% |
| **Renal** Increased Cr | 4% | 1% | 2% |

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## Summary

- Checkpoint inhibitor cancer therapies are increasingly used in clinical practice
- Autoimmunity (irAEs) is a common treatment-related side effect
- irAEs are more frequent and occur earlier with combination regimens

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Q 2

What are the most common organs affected by cancer immunotherapy associated immune related adverse events?

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## Clinical challenges in ICI therapy

Before ICI treatment:

- Can we develop personalized algorithms to predict irAEs in patients?

During ICI treatment:

- How do we rapidly recognize and manage irAEs?
- How do we navigate new steroid-sparing approaches?

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## Can we predict the patients at highest risk of irAEs?

| Genetic risk | Autoantibodies (Ab) | Circulating immune cells populations |
|---|---|---|
| HLA-specific risk for pituitary, pancreas, and gut irAEs<br>Polygenic Risk Scores predict irAEs (OR ~1.5) | TPO Ab ↑↑ high risk of Thyroid irAEs<br>Pancreas antigen Abs ↑↑ 5x increase in DM | Increased ALC and T follicular helper responses correlate with irAE |
| | | |
| *Challenge*:<br>Genetic testing not routine<br><br>Distinct HLAs from spontaneous autoimmunity | *Challenge*:<br>Largely T cell mediated disease<br><br>Most patients with irAEs lack clinical auto-Abs | *Challenge*:<br>Circulating immune cells may not reflect tissue<br><br>Immunophenotyping not routine |

Abbreviations: HLA = human leukocyte antigen; OR = odds ratio; TPO = thyroid peroxidase; DM = diabetes mellitus; ALC = absolute lymphocyte count.

Muir CA et al. JCEM 2021; Yano S et al. Eur J Cancer 2020; Bluestone J et al. Diabetes 2018; Hasan Ali O et al. Eur J Cancer 2019; Luo J et al. Clin Can Res 2021; Khan Z et al. PNAS 2020. Middha et al. JITC 2025.

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## Is ICI Therapy Safe in Patients with Pre-existing Autoimmune Disease?

- Minimal clinical trial data on this population
- Flare of pre-existing autoimmune disease can occur
- Potential risk for increased risk of severe irAEs
- Unclear if these patients should be excluded

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## Case Example: Pre-Existing Type 1 Diabetes Mellitus (T1DM)

Case-controlled multi-center study

>12,000 individuals who received ICI therapy
- 21 with pre-existing T1DM

No significant increase after adjusting for regimen, sex, age, cancer type

Conclusion: We should not exclude these patients from ICI therapy / trials, but informed consent is needed

| | Case, n (%) | Control, n (%) | OR (95% CI) |
|---|---|---|---|
| All grade IRAEs | 5 (45.5%) | 11 (50.0%) | 0.83 (0.2–3.56) |
| Grades 1 and 2 | 2 (18.2%) | 7 (31.8%) | 0.48 (0.08–2.81) |
| Grade 3 and 4 | 3 (27.3%) | 4 (18.2%) | 1.69 (0.31–9.36) |

ALL of these patients responded to ICI therapy

Hater B. et al. Front Endocrinol 2022.

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## Summary of Retrospective Data on ICI Use in Patients with Pre-Existing Autoimmune Disease

**Table 2. Retrospective Case Series Evaluating ICI Use in Patients With AID**

| Study | N[a] | Tumor | ICI | AID | Treatment for AID[b] | ORR | AID Flare Rate[c] | irAE Rate[d] |
|---|---|---|---|---|---|---|---|---|
| Tison et al[40] | 112 | Melanoma (59%) NSCLC (35%) Other (6%) | PD-1/PD-L1 in 85% of patients | Ps/PsA, RA, IBD, SA, SLE, PMR/TA | 22% | Melanoma: 48% NSCLC: 54% | 42% Gr 3/4: 13% | 38% Gr 3-5: 16% |
| Leonardi et al[41] | 56 | NSCLC | PD-1/PD-L1 | RA, PMR/TA, Scleroderma, Ps/PsA, Thyroiditis, IBD, MG, MS | 20% | 22% | 23% Gr 3/4: 4% | 38% Gr 3/4: 10% |
| Menzies et al[42] | 52 | Melanoma | PD-1 | RA, PMR, SS, ITP, Ps, IBD, GBS, MG, Thyroiditis, SLE | 38% | 33% | 38% Gr 3/4: 6% | 29% Gr 3/4: 10% |
| Danlos et al[43] | 45 | Melanoma (80%) NSCLC (13%) Other (7%) | PD-1 | Vitiligo, Ps/PsA, Thyroiditis, RA, ITP, SA, MS, MG, PMR, PAN, Sarcoidosis, T1 DM | 16% | 38% | 24% | 22% |
| Johnson et al[44] | 29 | Melanoma | Ipilimumab | RA, Ps, Thyroiditis, MS, IBD, SLE, Sarcoidosis | 41% | 21% | 24% | 31% Gr 3-5: 31% |
| Gutzmer et al[45] | 19 | Melanoma | PD-1 | Ps/PsA, RA, Vasculitis, PMR, SA, Sarcoidosis, IBD, GBS, MS, MG, Thyroiditis | 32% | 32% | 42% | 16% |
| Richter et al[46] | 16 | Melanoma NSCLC NHL | PD-1 (69%) Ipilimumab (31%) | RA, PMR, Sarcoidosis, SLE, Vasculitis | 44% | Not stated | 6% | 38% Gr 3/4: 25% |
| Lee et al[47] | 8 | Melanoma | Ipilimumab | RA | 87.5% | 50% | 75% Gr 3/4: 25% | 50% Gr 3/4: 50% |

Kennedy et al. JNCCN. 2019;17(6):750-757.

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Q3

What factors should be considered when recommending checkpoint inhibitor cancer therapies for patients with pre-existing autoimmune disease?

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## Summary

Pre-Existing Autoimmune Disease

- Consider the potential risk of autoimmune disease exacerbation
- Patients with well-controlled autoimmune disease can likely receive ICI therapies with standard risk
- Consider increased monitoring during ICI initiation (cycles 1-3) specific to autoimmunity

Emerging data on genetic risk of irAEs, not yet validated for clinical practice

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## Management of irAEs

- Evolving evidence is reflected in rapidly changing guidelines (e.g. ASCO, NCCN)
- Reconsideration for the use of high-dose steroids in irAE management

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## ICI-Colitis

| Grading and irAE | Assessment / Workup | Management |
|---|---|---|
| • Grades 3-4<br>• Diarrhea<br>• Colitis | • Stool evaluation — rule out infectious etiology: C. difficile; NAATs for GI pathogens (bacteria, viruses); in appropriate clinical context: ova & parasites; Giardia, Cryptosporidium spp., E. histolytica, microsporidia, Cyclospora/Isospora spp.<br>• Fecal calprotectin ± lactoferrin<br>• Consider abdominal/pelvic CT with contrast<br>• Recommend GI consultation<br>• Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy | • G3: discontinue combination IO therapy<br>• G4: discontinue IO responsible for toxicity<br>• Consider inpatient care for supportive care<br>• IV methylprednisolone 1–2 mg/kg/day<br><br>If no response in 1–2 days, or unable to transition to oral steroids:<br>• Additional immunosuppression required<br>• If colonoscopy/sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis — continue steroids and strongly consider adding: Infliximab or Vedolizumab Consider Tofacitinib or Ustekinumab for infliximab- and/or vedolizumab-refractory colitis<br><br>For persistent diarrhea not resolving after above — consider other etiologies (e.g., pancreatic exocrine insufficiency, celiac disease)<br><br>For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise |

**Hold Therapy**

**High dose steroids (48hr)**

**Consult specialist & Pivot to non-steroid:**

- Infliximab
- Vedolizumab
- JAK inhibitor, ustekinumab

Thompson JA, et al. NCCN Guidelines® Insights: Management of Immunotherapy-Related Toxicities, Version 2.2024. J Natl Compr Canc Netw. 2024;22(8):582-592.
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Management of Immune Checkpoint Inhibitor-Related Toxicities, Version 1.2026, October 23, 2025. NCCN.org

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## ICI-Hepatitis

| Grading and irAE | Assessment / Workup | Management |
|---|---|---|
| • Elevated ALT/AST<br>• G3: >5 to 20 × ULN<br>• G4: >20 × ULN | • Rule out viral etiology, disease-related hepatic dysfunction, and alternative causes of drug-induced liver injury<br>• Limit/discontinue hepatotoxic medications<br>• Consider CK, aldolase, and ferritin to rule out other causes of elevated ALT/AST (e.g., myositis, myocarditis, and HLH-like syndrome)<br>• Consider abdominal ultrasound<br>• Recommend GI/hepatology evaluation | • Monitor PT/INR weekly or more often based on liver tests and patient condition<br>• Consider diagnostic parenchymal liver biopsy if no contraindications<br>• Grade 3: Hold immunotherapy; initiate prednisone/IV methylprednisolone 0.5–1 mg/kg/day; perform liver tests every 1–5 days depending on magnitude and rate of change<br>• Grade 4: Discontinue immunotherapy; initiate prednisone/IV methylprednisolone 0.5–1 mg/kg/day; Perform liver tests every 1–3 days<br>• Grade 3/4: If no improvement in 1-2 days → consider adding mycophenolate mofetil or tacrolimus<br>• Grade 3/4: If refractory → consider tocilizumab or other steroid-sparing immunosuppressive therapy<br>• Grade 3/4: Urgent GI/hepatology referral if no improvement after 7 days, or if 2 immunosuppressive agents do not yield adequate response within an additional 7 days<br>• Inpatient care, particularly if synthetic hepatic dysfunction is observed |

**Hold Therapy**

**High dose steroids (48hr)**

**Consult specialist & Pivot to non-steroid:**
- Mycophenolate
- Tacrolimus, Tocilizumab, ATG

Thompson JA, et al. NCCN Guidelines® Insights: Management of Immunotherapy-Related Toxicities, Version 2.2024. *J Natl Compr Canc Netw.* 2024;22(9):582-592.
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Management of Immune Checkpoint Inhibitor-Related Toxicities. Version 1.2026. October 23, 2025. NCCN.org

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## ICI-Myocarditis

| Grading and irAE | Assessment / Workup | Management |
|---|---|---|
| • Suspected myocarditis / pericarditis / large vessel vasculitis | • Immediate cardiology consultation (preferably cardio-oncology)<br>• ECG (compare to baseline for any suspected cardiovascular AE)<br>• Telemetry monitoring (inpatient) / topical patch monitoring (outpatient)<br>• Echocardiogram (if possible with LV strain measurement)<br>• Cardiac biomarkers (troponin I or T, BNP, or NT-proBNP)<br>• Evaluate for concomitant irAEs, myasthenia gravis/myasthenia gravis-like syndrome, and myositis — which can exist as an overlap syndrome with myocarditis<br>• Cardiac MRI with and without contrast (if possible)<br>• Consider cardiac catheterization and/or myocardial biopsy as clinically indicated<br>• Consider viral titers | Myocarditis:<br>• Discontinue immunotherapy<br>• Management is tailored to response and acuity of presentation<br>• High-dose steroids: IV methylprednisolone 1 g/day × 3–5 days<br>• If responding and stable, switch to oral prednisone (1 mg/kg/day) → taper slowly over 6–12 weeks based<br>• Initiate additional immunosuppression (i.e., abatacept, alemtuzumab, ATG, infliximab, methotrexate, mycophenolate mofetil, plasmapheresis, IVIG)<br>• Abatacept with ruxolitinib has been used in concomitant myositis and myocarditis<br>• ICU-level monitoring<br>• Temporary or permanent pacing as required |

**Discontinue immunotherapy**

**High dose steroids (48hr)**

**Consult specialist & Pivot to non-steroid:**
- Abatacept + JAK inhibitor

Thompson JA, et al. NCCN Guidelines® Insights: Management of Immunotherapy-Related Toxicities, Version 2.2024. *J Natl Compr Canc Netw.* 2024;22(9):582-592.
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Management of Immune Checkpoint Inhibitor-Related Toxicities. Version 1.2026. October 23, 2025. NCCN.org

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## ICI-Pnuemonitis

| Grading and irAE | Assessment / Workup | Management |
|---|---|---|
| • Severe (grade 3-4) Pneumonitis | Minimally Invasive Evaluation<br>• Infectious workup<br>• Consider that patient may be immunocompromised<br>• Nasal swab for potential viral pathogens<br>• Sputum culture (bacterial, fungal, AFB), blood culture, urine antigen test (e.g., pneumococcus, legionella)<br>• Consider cardiac evaluation to exclude cardiac causes<br><br>Invasive Evaluation<br>• Bronchoscopy with BAL (send for institutional immunocompromised panel) if feasible — to rule out infection, malignant lung infiltration, or steroid-responsive ILD; consider transbronchial lung biopsy if feasible and clinically indicated<br><br>Consider empiric broad-spectrum antibiotics (including atypical coverage) if infection not yet fully excluded | • Hold immunotherapy<br>• Inpatient care<br>• Pulmonary and ID consultation<br>• IV methylprednisolone 1–2 mg/kg/day<br><br>If no improvement after 48 hours → Consider adding any of the following: IVIG or Tocilizumab (preferred)<br>• Other recommended: Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service; Infliximab 5 mg/kg; a second dose may be repeated 14 days later at the discretion of the treating provider |

**Hold Therapy**

**High dose steroids (48hr)**

**Consult specialist & Pivot to non-steroid:**
- IVIG
- Mycophenolate
- Tocilizumab
- Infliximab

Thompson JA, et al. NCCN Guidelines® Insights: Management of Immunotherapy-Related Toxicities, Version 2.2024. *J Natl Compr Canc Netw.* 2024;22(9):582-592.
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Management of Immune Checkpoint Inhibitor-Related Toxicities. Version 1.2026. October 23, 2025. NCCN.org

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## Endocrine irAEs helped shift the paradigm for steroid treatment for all irAEs

- Hypophysitis[1,2]: Increased mortality and no benefit with high-dose steroids

- Thyroiditis[3] : Hypothyroidism is permanent and not affected by high-dose steroids

- Diabetes Mellitus[4]: No benefit for steroids in recovery of pancreatic beta cell function and can precipitate DKA

Fujii AT *et al. Cancer* 2018;124:3706-3714. 2. Min L *et al. Clin Cancer Res.* 2015 Feb 15; 21(4): 749–755.
Mir C, *et al. Cancer Immunol Res.* 2019. 4. Mosefiel *et al. Thyroid.* 2022. 5. Stamatouli, Quandt *et al. Diabetes* 2018

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## Endocrine irAEs are permanent and require hormone replacement therapy

- Hypophysitis (secondary adrenal insufficiency):
  - Physiologic Hydrocortisone 20mg qAM / 10mg qPM

- Thyroiditis:
  - Levothyroxine 1.45mcg/kg/day[5]

- Diabetes Mellitus:
  - Insulin therapy as for spontaneous type 1 DM with early CGM

Fujii AT *et al. Cancer* 2018;124:3706-3714. 2. Min L *et al. Clin Cancer Res.* 2015 Feb 15; 21(4): 749–755.
Mir C, *et al. Cancer Immunol Res.* 2019. 4. Mosefiel *et al. Thyroid.* 2022. 5. Stamatouli, Quandt *et al. Diabetes* 2018

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## Mass General Hospital Experience

Article Conclusion: "Establishing a highly subspecialized care team focused on irAEs is associated with improved patient outcomes and reduced healthcare utilization."

- After ITox service initiation, reductions were observed in irAE readmission rate
  - (14.8% post vs 25.9% pre; OR 0.46; 95% CI 0.22 to 0.95; p=0.036)
- Readmission length of stay (LOS) (median 6 days post vs 7 days pre; p=0.046)

ITOX = immune-toxicity service

Original research

**Effect of a multidisciplinary Severe Immunotherapy Complications Service on outcomes for patients receiving immune checkpoint inhibitor therapy for cancer**

Leyre Zubiri, Gabriel E Molina, Meghan J Mooradian, Justine Cohen, Sienna M Durbin, Laura Petrillo, Genevieve M Boland, Dejan Juric, Michael Dougan, Molly F Thomas, Alex T Faje, Michelle Rengarajan, Amanda C Guidon, Steven T Chen, Daniel Okin, Benjamin D Medoff, Mazen Nasrallah, Minna J Kohler, Sara R Schoenfeld, Rebecca K Leaf, Meghan E Sise, Tomas G Neilan, Daniel A Zlotoff, Jocelyn R Farmer, Aditya Bardia, Ryan J Sullivan, Steven M Blum, Yevgeniy R Semenov, Alexandra-Chloé Villani, Kerry L Reynolds

Zubiri L, et al. *J Immunother Cancer.* 2021;9:e002865

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## Johns Hopkins Experience

**73.5%** of referring providers said the ITox team recommendations changed their diagnostic evaluation or management of immune-related toxicity.

Most respondents **(97%)** who used the ITox team rated it as helpful.

**A Multidisciplinary Toxicity Team for Cancer Immunotherapy–Related Adverse Events**

Jerushka Naidoo, MBBCh[1]; Jiajia Zhang, MD, PhD[2]; Evan J. Lipson, MD[3]; Patrick M. Forde, MBBCh[4]; Karthik Suresh, MD[5]; Kendall F. Moseley, MD[1]; Seema Mehta, MD[6]; Shawn G. Kwatra, MD[6]; Alyssa M. Parian, MD[7]; Amy K. Kim, MD[7]; John C. Probasco, MD, PhD[8]; Roxanne Rouf, MD[9]; Jennifer E. Thorne, MD, PhD[1]; Satish Shanbhag, MD[10]; Joanne Riemer, RN, BSN[1]; Ami A. Shah, MD[1]; Drew M. Pardoll, MD, PhD[1]; Clifton O. Bingham III, MD[1]; Julie R. Brahmer, MD, MHS[1]; and Laura C. Cappelli, MD, MHS[1]

Common Questions asked of the ITox Team:

1. Suitability for Immunotherapy (or rechallenge)
2. irAE Diagnosis
3. Management of steroid-refractory of severe irAEs

Naidoo et al. NCCN 2019

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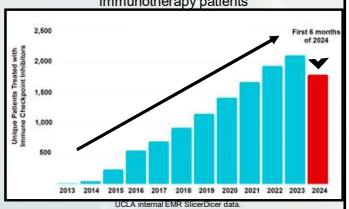
## UCLA Experience

Barriers to irAE care and referrals for Oncology Providers:

1. I don't know who to contact
2. Time to consult took too long
3. Difficulty in scheduling patient with subspecialty
4. Consult provider lacked experience in irAE management

Rapidly increasing volume of immunotherapy patients




UCLA internal EMR SlicerDicer data.

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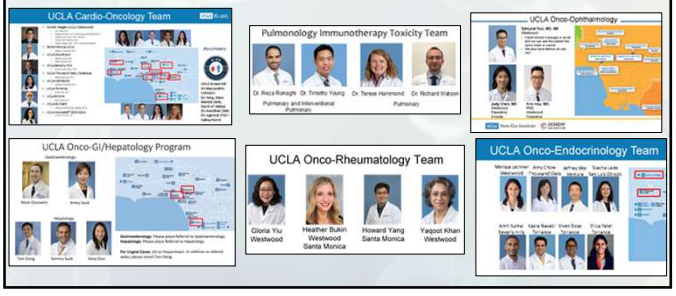
## Dedicated Specialty ITox Teams at UCLA

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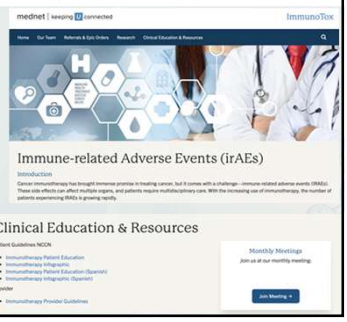
## Institutional & Society Resources

- Mini In-Service ITox trainings available as an educational resource

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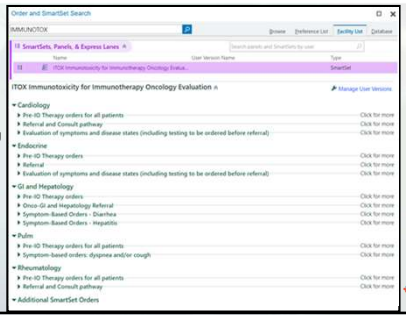
## Smart Sets to Guide Providers

- Pharmacy guidelines
- Diagnostic labs and imaging

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Q4

## What are guiding general principles in the approach to treating irAEs?

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## Summary: Improve patient irAE outcomes during ICI therapy by…

1. Early recognition and treatment: ITox team approach
2. Consider non-steroid therapies
3. Initiate replacement therapy for permanent endocrine irAEs

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## irAEs can Correlate with Improved Cancer Response

Longer Overall Survival (OS): HR 0.4-0.5
Longer Progression Free Survival (PFS): ~3 fold

- Stronger association with Grade ≥3 or multiple irAEs
- **Endocrine**, Skin, and GI

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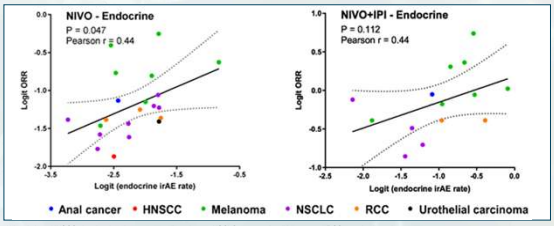
## irAEs & ICI Efficacy




Abbreviations: HNSCC= head and neck squamous cell carcinoma; NSCLC= non-small cell lung cancer; RCC= renal cell carcinoma.

Xing et al. J Immunother 2019; 7:341

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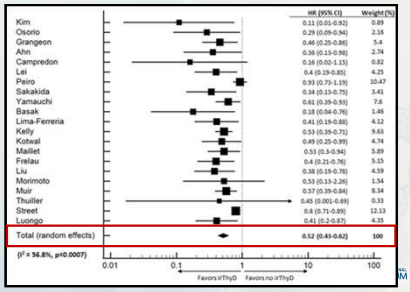
## Development of Thyroid irAEs Associated with a Survival Benefit on Checkpoint Immunotherapy

**Thyroiditis** (Cheung *et al.*)
Meta-analysis

Greater Overall Survival

Cox proportional hazard ratio
0.52 (0.43-0.62) p<0.0001




irThyD= immune-related thyroid disease

Cheung et al. Cancer Immunol Immunother. 2022; 71: 1795-1812

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## Q5

What is the relationship between endocrine irAEs and survival outcomes in cancer patients treated with checkpoint inhibitors cancer therapies?

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## SUMMARY

- irAEs occur in >60% of patients receiving ICI cancer therapy
- Skin, gut, and endocrine tissues are the most commonly affected, with myocarditis, pneumonitis, and hepatitis among the most fatal
- Prompt recognition and treatment using a team-based approach improves patient outcomes
- Recommend early consideration for non-steroid therapies for irAEs
- Endocrine irAEs are usually permanent and should receive prompt hormone replacement therapy

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QUESTION & ANSWER
2026 NCODA INTERNATIONAL SPRING FORUM
Recognize, Triage, Treat:
A Practical Approach to ICI Toxicities
Melissa Lechner, MD, PhD
Associate Professor of Medicine
UCLA Geffen School of Medicine
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ALIGNMENT IN ACTION
The Power of Integrated Oncology Care

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