# TOXICITY AND CONTRAINDICATIONS FOR IMMUNOTHERAPY IN NSCLC

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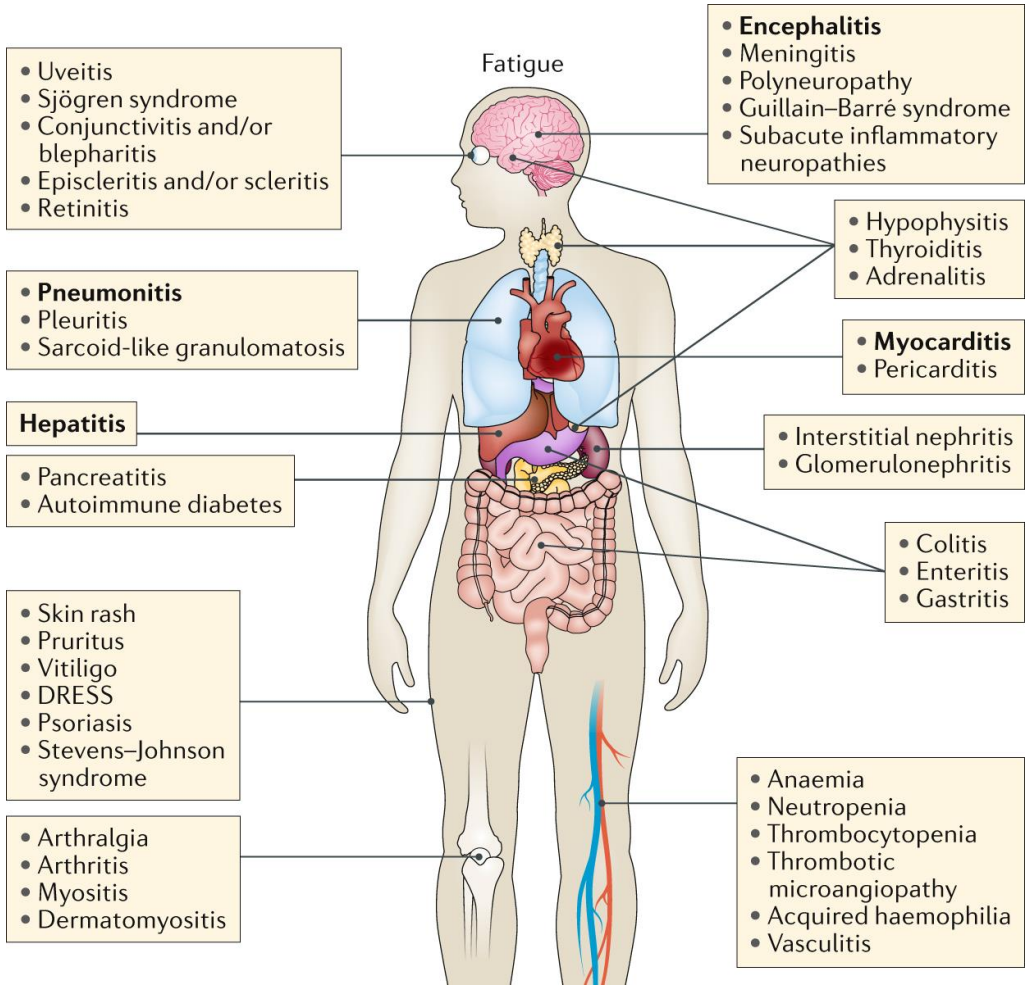
# Few questions that arise as we take care of patients with NSCLC

- Can we predict who will develop immune-related adverse events?
- When can we rechallenge with ICI after occurrence of immune toxicity?
- What is the role of ICIs in special populations, such as patients with autoimmune disorders and solid organ transplants?
- Do patients who experience immune-related adverse events live longer?

# Immune-related adverse events are unpredictable, potentially severe, and can affect any organ system

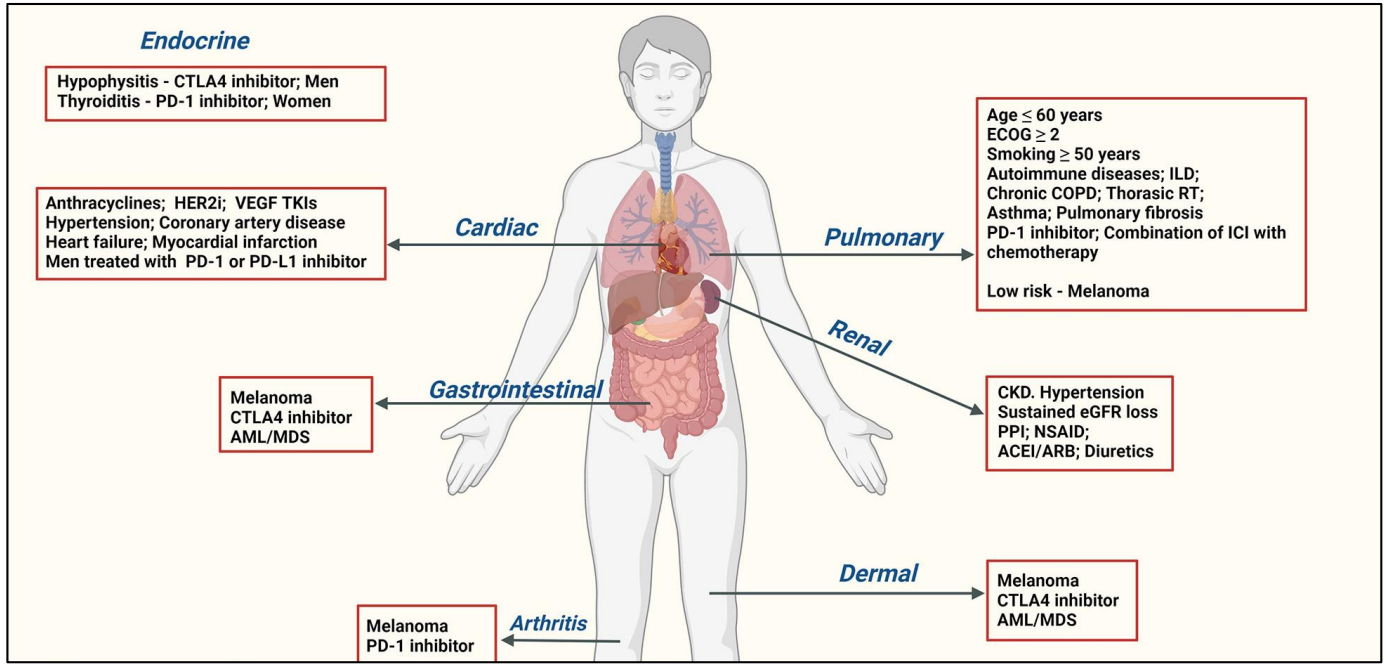
- Most common irAEs in NSCLC: thyroiditis, pneumonitis, colitis, derm toxicities, hepatitis
- Incidence any grade irAEs between 20%-50% and ≥ grade 2 irAEs between 3-12%
- Variation represents heterogeneity in study setting, patient characteristics, treatment parameters, irAE grading
- While most irAEs are mild/reversible, irAEs may cause substantial or even permanent morbidity and may be fatal in ~1% of patients



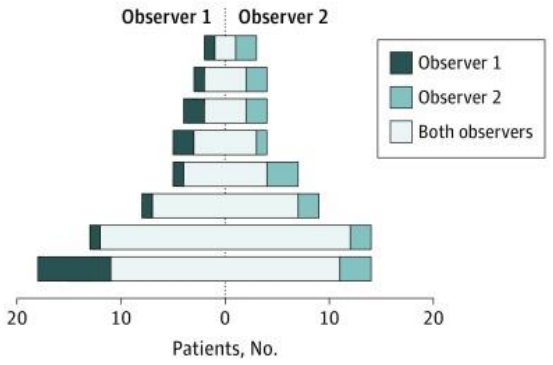

Martin F, et al. Nat Rev Clin Oncol, 2019; Cook S, et al. JAMA Netw Open, 2024

# Despite our clinical experience with immunotherapy, prediction and diagnosis of irAEs remains challenging

- Variety of predictive factors have been described – yet other than autoimmune disease, no clinical parameters routinely used to predict risk
- Conflicting data regarding risk factors
- Apart from hypothyroidism, interobserver agreement of irAE occurrence and grading is poor




| irAE | Cohen κ | Weighted κ |
|---|---|---|
| Hypophysitis | 0.37 | 0.31 |
| Hyperthyroidism | 0.64 | 0.57 |
| Adrenal insufficiency | 0.46 | 0.40 |
| Rash | 0.64 | 0.64 |
| Colitis | 0.62 | 0.68 |
| Hepatitis | 0.63 | 0.59 |
| Hypothyroidism | 0.80 | 0.75 |
| Pneumonitis | 0.55 | 0.58 |

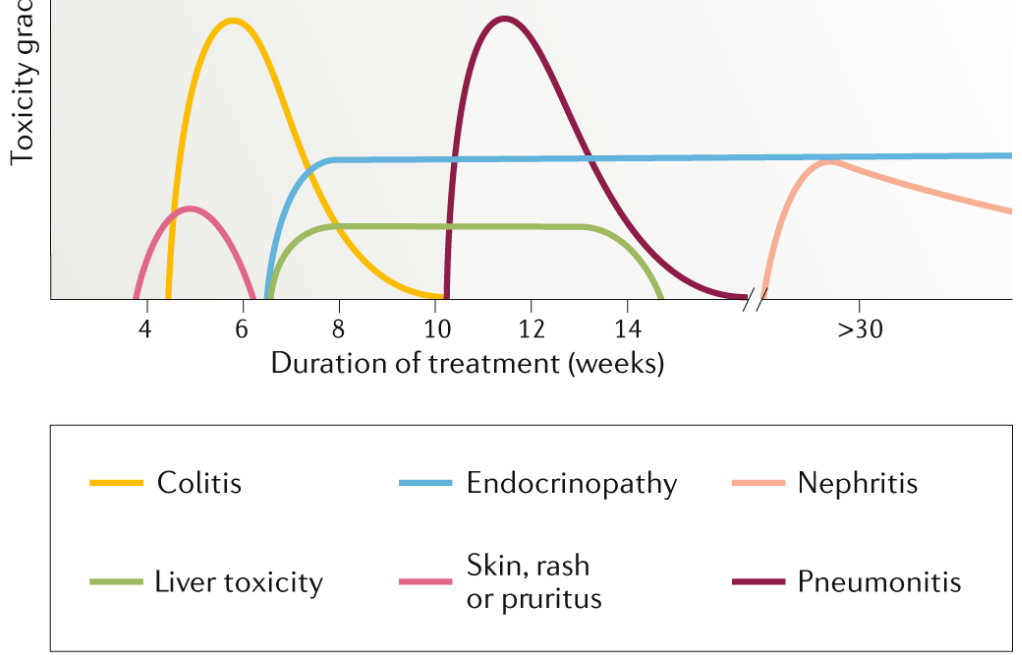



Chennamadhavuni A, et al. Front Immunol, 2022; Hsiehchen D, et al. JAMA Netw Open, 2019

# Although characteristic temporal windows of occurrence exist, irAEs can occur at any point throughout ICI therapy, even after treatment discontinuation

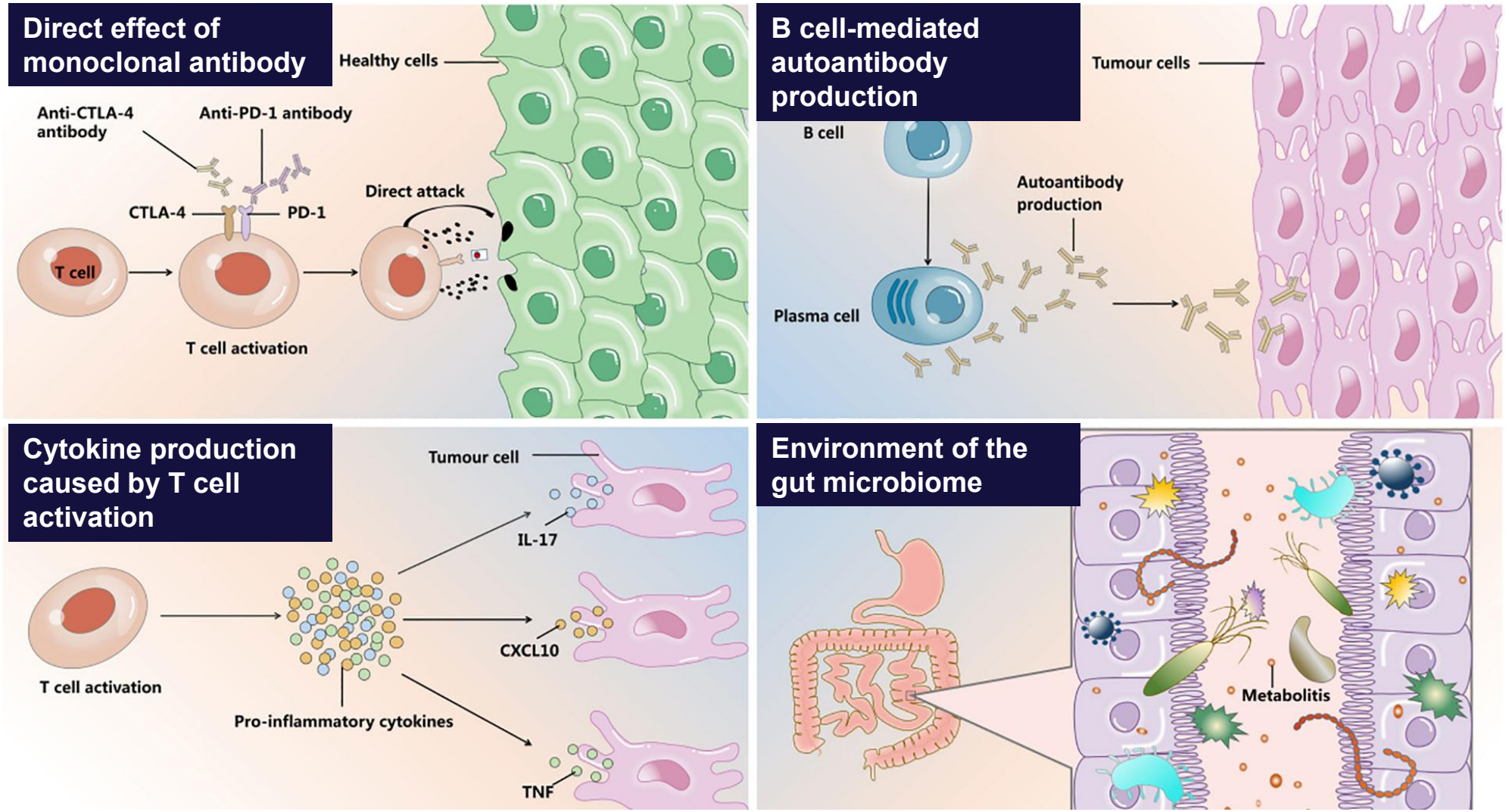
| System | Toxicities | Time to toxicity onset (median, range) |
|---|---|---|
| Pulmonary | Pneumonitis | 11-34 wk (1.5-127 wk) |
| Cardiac | Myocarditis, pericarditis, arrhythmias, vasculitis | 6 wk (2-54 wk) |
| Endocrine | Hypothyroidism, thyrotoxicosis, primary adrenal insufficiency, hypophysitis, diabetes | 14.5 wk (1.5-130 wk) |
| Cutaneous | Inflammatory dermatoses, bullous dermatoses, severe cutaneous adverse reactions | 4.5 wk (2-150 wk) |
| Renal | Immune-related AKI, nephritis | 14 wk (6.5-21 wk) |
| GI | Hepatitis, colitis, gastritis, enterocolitis, esophagitis | 6 wk (1-107.5 wk) |
| Neurologic | Myasthenia gravis, aseptic meningitis, encephalitis, Guillain-Barre-like syndrome | 4 wk (1-68 wk) |

***Time of onset and grade of irAEs in patients receiving anti-PD-1 or PD-L1 therapy***




Martin F, et al. Nat Rev Clin Oncol, 2019; O'Leary CL, et al. J Thorac Oncol, 2024

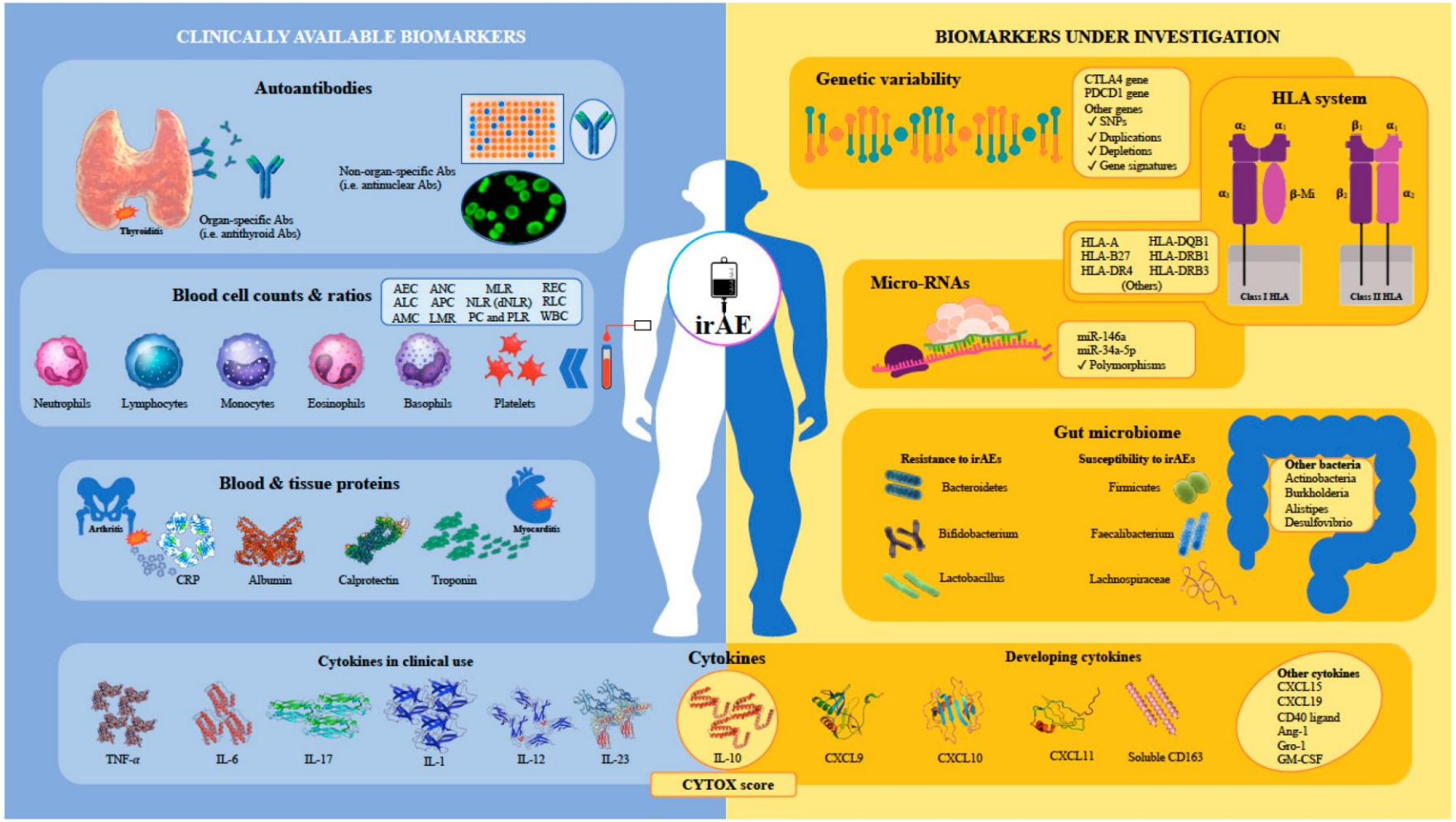
# Emergence and intensity of irAEs influenced by various immune mechanisms




***Adverse effects of ICI therapy are mediated via modulation of patient's immune system – more complex consideration than plasma drug levels or target distribution***

Yan T, et al. Front Immunol, 2024

# To improve patient safety and selection for ICI use, biomarkers for diagnosis and prediction of irAE are under investigation




- Screening biomarkers may be most useful if detectible few weeks before onset of clinical signs & symptoms (typical frequency of ICI administration and routine blood draws)
- Cytokines and autoantibodies are promising – can be measured frequently and have rapid turnaround time
- Larger prospective studies needed

Les I, et al. Cancers, 2023

# Around 20% of patients with lung cancer have pre-existing autoimmune disorders and are often not included in clinical trials

***Select retrospective cohorts of patients with autoimmune disease (AID) treated with ICIs***

| | Leonardi et al | Khozin et al | Danios et al | Cortellini et al |
|---|---|---|---|---|
| Tumor types | NSCLC | NSCLC | Multiple (16% NSCLC) | Multiple (66% NSCLC) |
| Patients with AID | 56 | 531 | 45 | 85 |
| Active AID | 18% | NR | 56% | 18% |
| Treatment for AID | 20% | NR | 16% | 17% |
| Flare AID | 23% | NR | 24% | 47% |
| irAEs / ≥grade 3 irAEs | 38% / 11% | 27% / NR | 44% / 11% | 66% / 9% |
| Discontinued | 14% | NR | 11% | 7% |

**25-50% of patients may experience AID flares**

- *ICIs are reasonable in some patients with quiescent AID after discussion of risk-benefit ratio*
- *Incorporate multidisciplinary team to identify AID flares and implement early therapeutic intervention*
- *Prospective evaluation of ICIs with autoimmune disease underway – NCT03816345*

Khan S, et al. JAMA Oncol, 2017; Remon J, et al. J Thorac Oncol, 2019; Leonardi GC, et al. J Clin Oncol, 2018; Khozin S, et al. J Clin Oncol, 2019; Danlos FX, et al. Eur J Cancer, 2018; Cortellini A, et al. Oncologist, 2019.

# ICIs in solid organ transplant (SOT) patients carries risk of allograft rejection

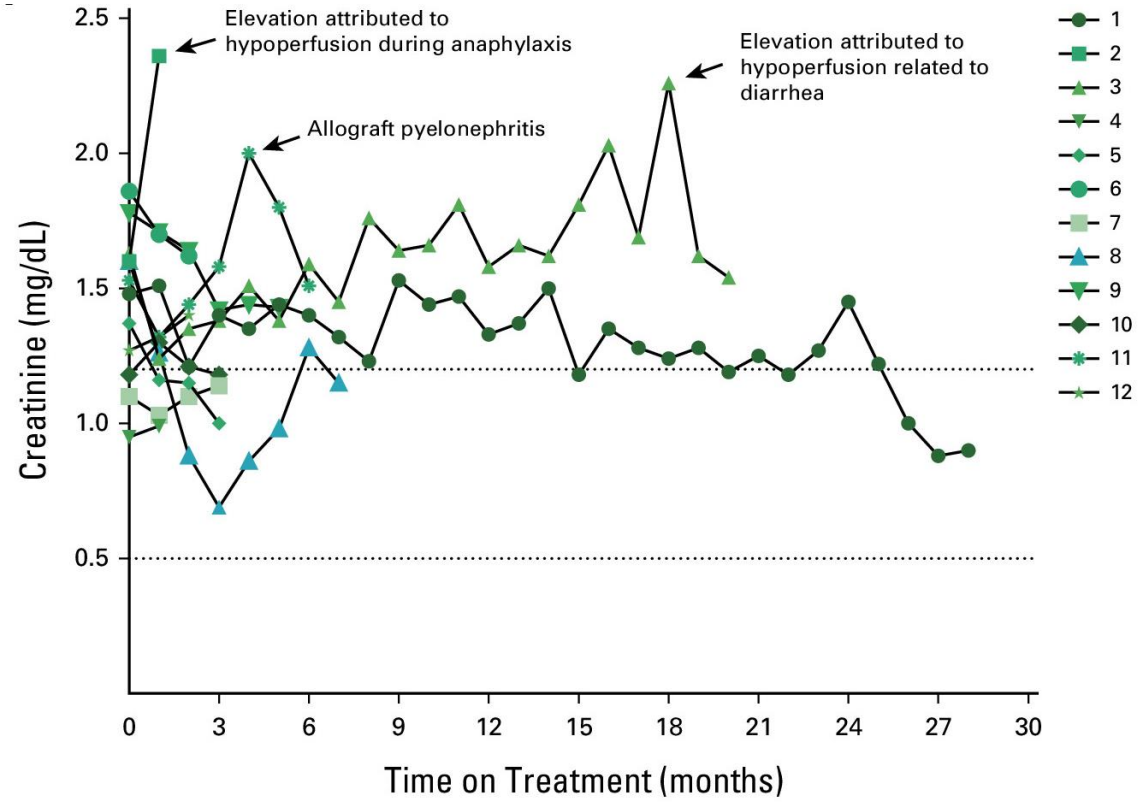
- Patients with SOT are excluded from clinical trials, yet at increased risk for cancer with chronic immunosuppression
- Review of 144 published cases suggests IO with retained transplant is feasible, particularly in patients with kidney transplants and among cutaneous cancers
- Patients treated with mTOR inhibitors have better outcomes

| | Response rate | Response rate in patients with retained transplants |
|---|---|---|
| **Transplant** | | |
| All transplants (n=130) | 37% | 31% |
| Kidney (n=90) | 38% | 29% |
| Non-Kidney (n=41) | 34% | 34% |
| **Cancer** | | |
| Melanoma (n=58) | 33% | 28% |
| Non-Melanoma (n=72) | 40% | 33% |
| cSCC (n=32) | 59% | 50% |
| HCC (n=18) | 22% | 22% |
| NSCLC (n=8) | 0% | 0% |

Runger A, et al, Eur J Cancer, 2022

# Prospective studies of ICIs in SOT have primarily focused on kidney transplant recipients and cutaneous malignancies

- Phase 1 study of cemiplimab for kidney transplant recipients with advanced cSCC
  - ➢ Treated with cemiplimab **+** everolimus or sirolimus and prednisone (pulse dosing)
  - ➢ Durable antitumor response and no kidney rejection events with mTOR inhibitor and steroid immunosuppression regimen




- Ongoing trial with ipilimumab + nivolumab with sirolimus and prednisone in similar population (NCT05896839)

- Future trials may explore the role of mTOR inhibitor conversion in organ transplant recipients with other advanced cancers…

Hanna GJ, et al. J Clin Oncol, 2024; Schenk KM, et al. J Clin Oncol, 2024

# What are the risks of rechallenge after prior immune toxicity?

***Select retrospective studies assessing irAE recurrence after rechallenge in solid tumors including NSCLC***

| Study | Number of patients with irAE | Number of patients rechallenged | IO target | Patients with any irAE recurrence after rechallenge, % | Patients with identical irAE recurrence, % |
|---|---|---|---|---|---|
| Santini et al (2018) | 68 | 38 | PD-L1 | 52% | 26% |
| Abu-Sbeih et al (2019) | 167 | 167 | CTLA-4, PD-1, PD-L1 | N/A | 34% |
| Simonaggio et al (2019) | 93 | 40 | PD-1, PD-L1 | 55% | 42% |
| Allouchery et al (2020) | 180 | 180 | CTLA-4, PD-1, PD-L1 | 39% | 29% |
| Dolladille et al (2020) | 24,079 | 6,123 | CTLA-4, PD-1, PD-L1 | 33% | 29% |
| Guo et al (2022) | 1,051 | 40 | CTLA-4, PD-1, PD-L1 | 60% | 40% |

**About 1 in 3 patients will have recurrence of the same irAE after rechallenge**

Nakajima EC, et al. J Clin Oncol, 2019; Abu-Sbeih H, et al. J Clin Oncol, 2019; Santini FC, et al. Cancer Immunol Res, 2018; Simonaggio A, et al. JAMA Oncol 2019; Allouchery M, et al. J Immunother Cancer, 2020; Dolladille C, et al. JAMA Oncol, 2020; Guo M, et al. Clin Lung Cancer, 2022

# With some exceptions, resumption of IO following grade 2-3 irAE can be considered once resolution to ≤ grade 1

- Recurrent or new irAEs are typically grade 1-2
- Recurrent/new irAEs more common among
  - ➢ Anti-CTLA-4 regimen
  - ➢ Colitis, hepatitis, and pneumonitis
  - ➢ Hospitalization for initial irAE
  - ➢ Complete or partial response

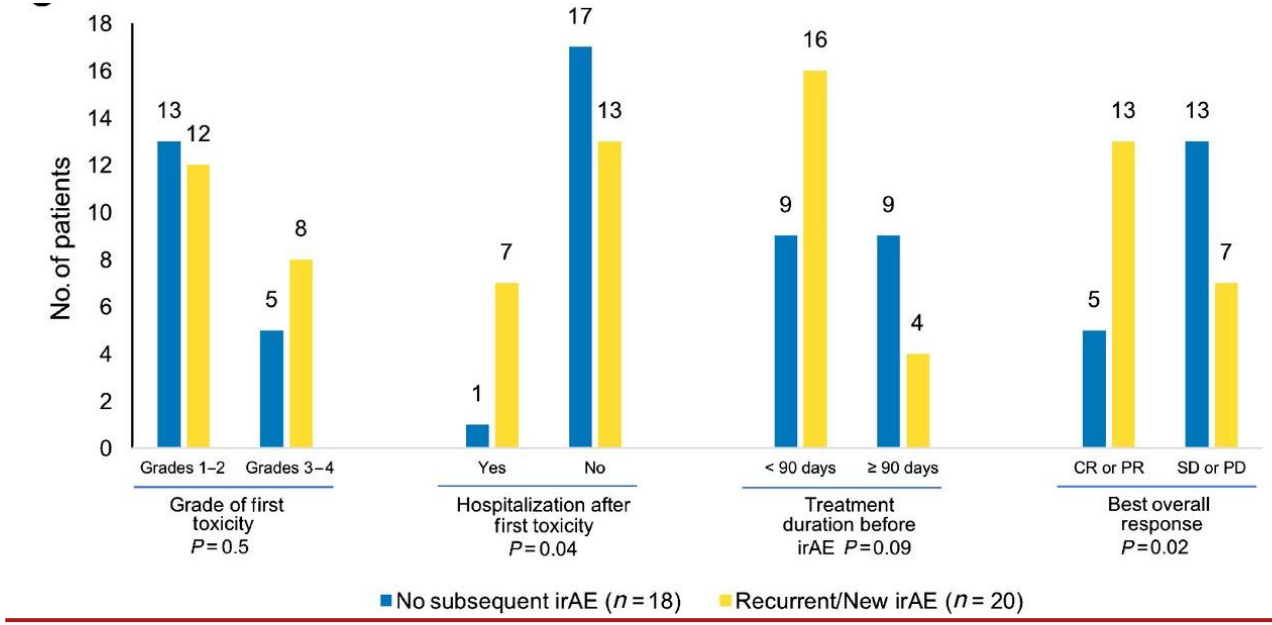


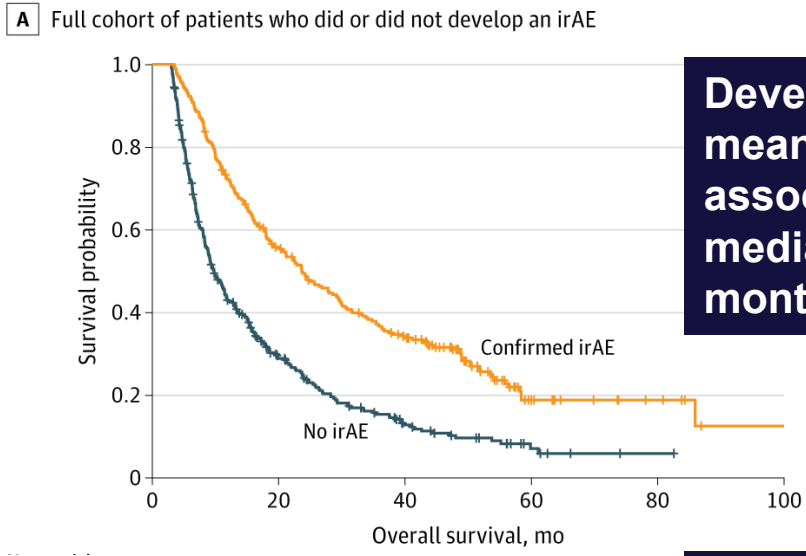

**Table 2. Factors Associated With the Recurrence of the Same Immune-Related Adverse Event**

| Initial irAE | No. (%) | | Reporting OR (95% CI) | |
|---|---|---|---|---|
| | Recurrence after ICI rechallenge (n = 130) | No recurrence after ICI rechallenge (n = 322) | Univariate analysis | Multivariate analysis |
| ICI | | | | |
| Anti-PD-1 or anti-PD-L1 alone | 105 (80.8) | 265 (82.3) | 0.9 (0.54-1.52) | NA |
| Anti-CTLA-4 alone | 7 (5.4) | 15 (4.7) | 1.16 (0.46-2.93) | 3.5 (1.05-11.64) |
| Combination therapy | 18 (13.8) | 42 (13.0) | 1.07 (0.59-1.94) | NA |
| Type of initial irAE[a] | | | | |
| Adrenal | 5 (3.8) | 35 (10.9) | 0.33 (0.13-0.86) | NA |
| Arthritis | 13 (10.0) | 16 (5.0) | 2.12 (0.99-4.55) | NA |
| Colitis | 47 (36.2) | 78 (24.2) | 1.77 (1.14-2.75) | 2.99 (1.60-5.59) |
| Diabetes | 0 | 13 (4.0) | NA | NA |
| Hematological | 3 (2.3) | 7 (2.2) | 1.06 (0.27-4.18) | NA |
| Hepatitis | 11 (8.5) | 22 (6.8) | 1.26 (0.59-2.68) | 3.38 (1.31-8.74) |
| Hypophysitis | 6 (4.6) | 17 (5.3) | 0.87 (0.33-2.25) | NA |
| Mucositis | 2 (1.5) | 3 (0.9) | 1.66 (0.27-10.06) | NA |
| Myocarditis | 0 | 3 (0.9) | NA | |
| Myositis | 2 (1.5) | 7 (2.2) | 0.7 (0.14-3.43) | NA |
| Nephritis | 4 (3.1) | 4 (1.2) | 2.52 (0.62-10.25) | 4.92 (0.94-25.64) |
| Neurological | 3 (2.3) | 16 (5.0) | 0.45 (0.13-1.58) | NA |
| Pancreatitis | 3 (2.3) | 11 (3.4) | 0.67 (0.18-2.43) | NA |
| Pneumonitis | 36 (27.7) | 67 (20.8) | 1.46 (0.91-2.33) | 2.26 (1.18-4.32) |
| Skin | 6 (4.6) | 10 (3.1) | 1.51 (0.54-4.24) | 3.21 (0.81-12.75) |
| Thyroiditis | 11 (8.5) | 50 (15.5) | 0.5 (0.25-1.00) | 0.37 (0.12-1.16) |
| Uveitis | 1 (0.8) | 10 (3.1) | 0.24 (0.03-1.91) | NA |
| Vasculitis | 1 (0.8) | 0 | NA | NA |

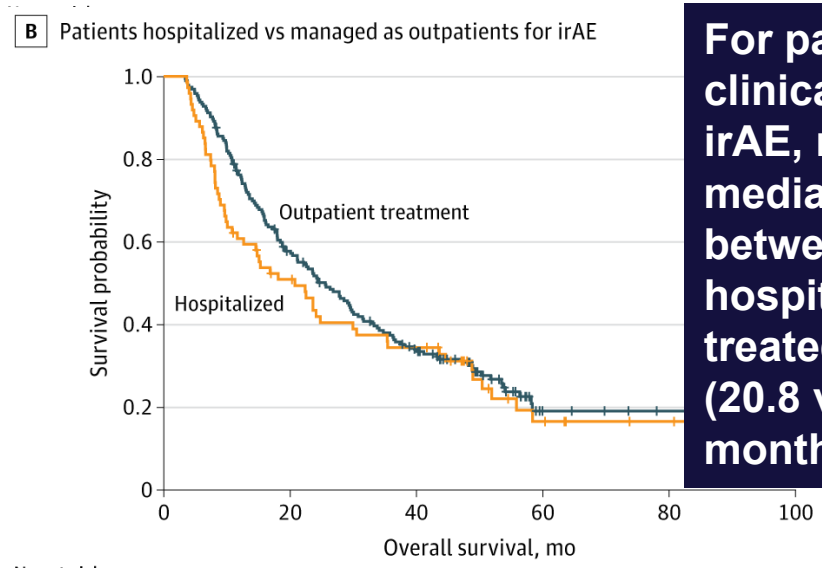
Santini FC, et al. Cancer Immunol Res, 2018; Dolladille C, et al. JAMA Oncol, 2020

# Development of irAEs may be associated with improved OS in advanced NSCLC

- Cohort study using Alberta Immunotherapy Database evaluating association between “clinically meaningful” irAEs and OS in 803 patients with advanced NSCLC receiving ICIs
- Clinically meaningful irAEs (mandating delay or discontinuation of ICI therapy and/or steroids) occurred in 37% of patients
- Nearly 1/3 of all clinically meaningful irAEs resulted in hospitalization (>50% pneumonitis)
- Adjusting for established prognostic factors, developing irAE remained independently associated with longer OS




**Developing clinically meaningful irAE associated with longer median OS (23.7 vs 9.8 months; *P* < 0.001)**

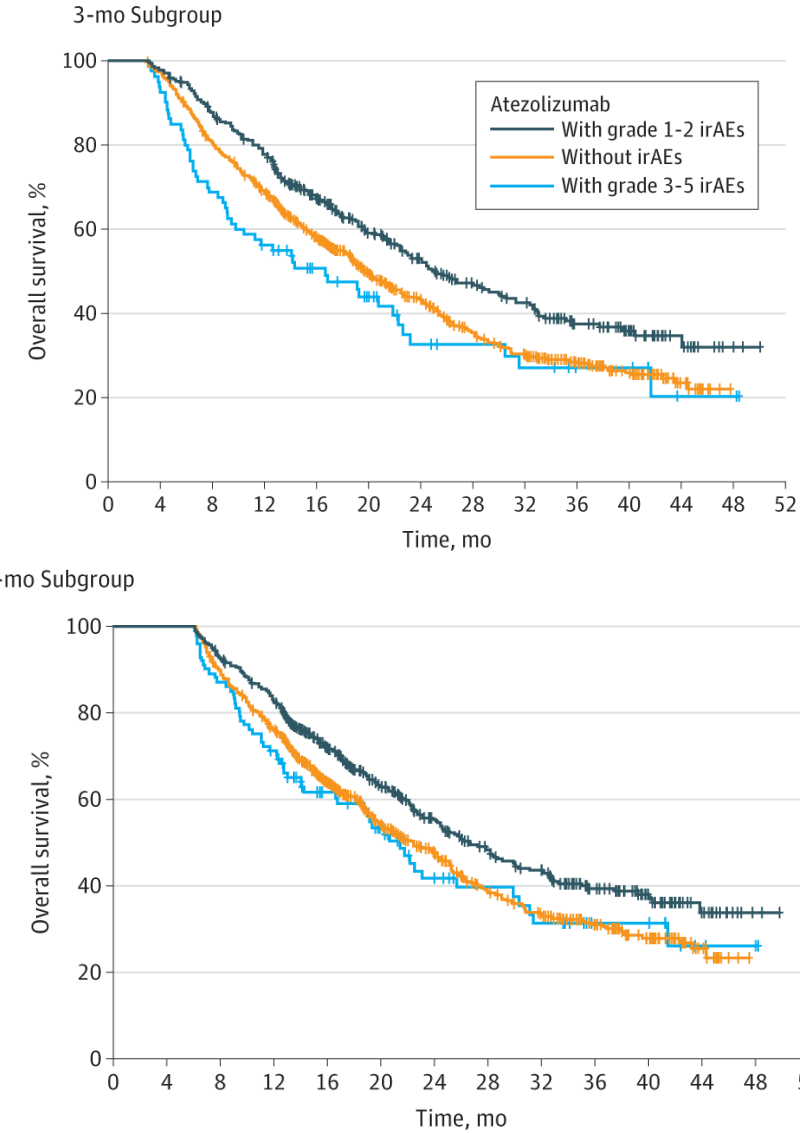



**For patients with clinically meaningful irAE, no association with median OS was seen between those hospitalized and those treated as outpatients (20.8 vs 25.6 months; *P* = 0.33)**

Cook, S, et al. JAMA Netw Open, 2024

# However – irAE severity may impact survival

- Pooled data from IMpower130, IMpower132, and IMpower150 to evaluate association between irAEs and atezolizumab efficacy
- Patients in atezo arm with grade 3-5 irAEs had shorter OS than those with grade 1-2 irAEs or no irAEs
- High grade irAEs may indicate presence of T cells that are more responsive to ICIs, yet can also be life threatening, require treatment discontinuation or immunosuppression, which may antagonize the effect of ICIs




Socinsky MA, et al. JAMA Oncol, 2023

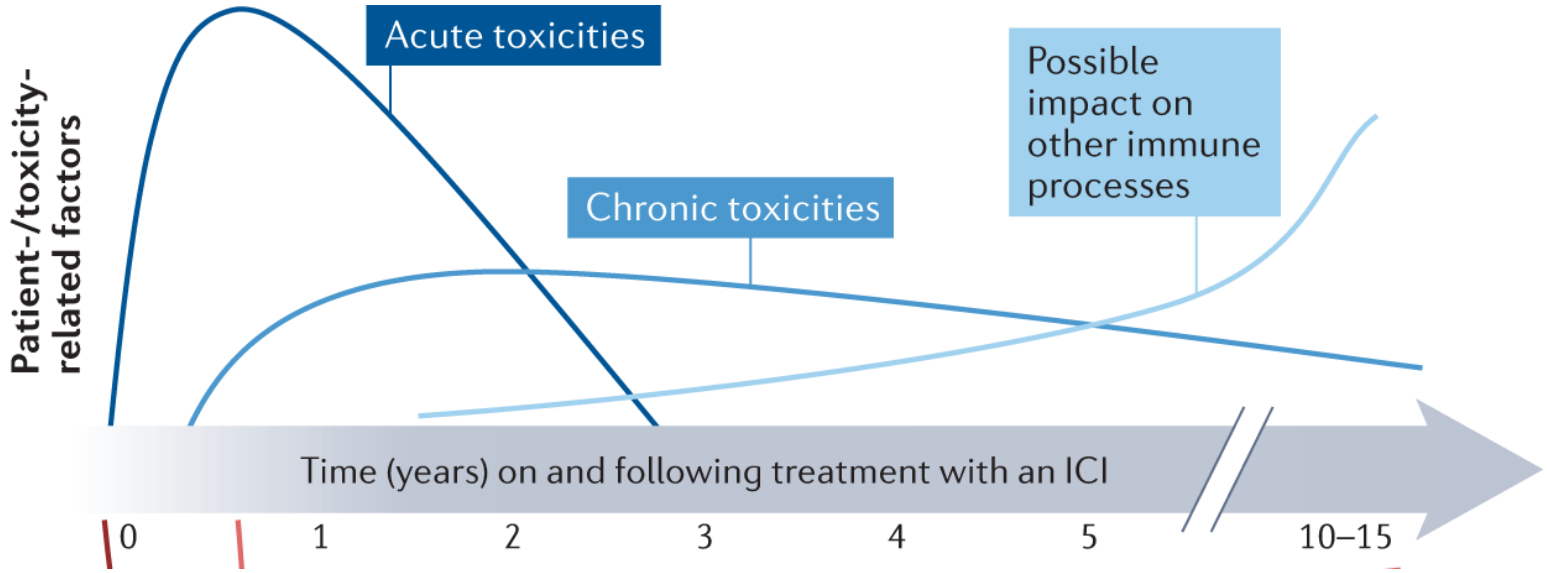
# With expanding indications for ICIs in NSCLC, including neoadjuvant and adjuvant settings, need to better understand and manage chronic irAEs

- Chronic irAEs can be defined as persisting >12 weeks after discontinuation of ICI

- Ongoing irAEs in up to 40% of patients, with endocrinopathies, arthritis, xerostomia, neurotoxicities and ocular events more likely to become chronic toxicities

- ICIs may also affect other immune-mediated processes such as atherosclerosis or neuroinflammation

- <u>Need for studies focusing on IO survivorship and the development of dedicated survivorship programs</u>




Johnson DB, et al. Nat Rev Clin Oncol, 2022

# Key Takeaways

- Predicting which patients will develop irAEs remains challenging, and a variety of biomarkers are under investigation
- ICIs are reasonable in some patients with well-managed and/or inactive AID, however risk of AID flare may be up to 50%
- About 1 in 3 patients will have recurrence of the same irAE after ICI rechallenge, but recurrent or new irAEs are typically grade 1-2 and manageable with standard treatment algorithms
- Recent studies suggest that development of irAEs is associated with improved OS in advanced lung cancer
- With expanding indications for ICIs in NSCLC, critical need for studies focusing on survivorship and development of dedicated survivorship programs