

University of Texas Southwestern Medical Center
Department of Internal Medicine Grand Rounds
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Title: *Immune Checkpoint Inhibitor related Endocrinopathies*

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This is to acknowledge that Sadia Ali, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Ali will not be discussing off label uses in this presentation.

Purpose and overview:

Immune checkpoint inhibitors have revolutionized cancer care and are now successfully used to treat several types cancers. Their side effect profile is distinct from the traditional chemotherapy regimens, and include immune related adverse events. With their increased use, the frequency of these events is growing and has necessitated the development of a new form of multidisciplinary care. Immune related endocrinopathies can significantly affect patients' outcome and require rapid recognition and treatment. The purpose of this talk is to identify and manage the most commonly encountered endocrinopathies associated with immune checkpoint inhibitors.

At the conclusion of this lecture, the listener should be able to:

- 1) Understand the mechanism of action of immune checkpoint inhibitors;
- 2) Identify common endocrinopathies caused by immune checkpoint inhibitors;
- 3) Understand how to manage common Endocrinopathies including: hypophysitis, thyroid dysfunction and diabetes mellitus.

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What are immune checkpoint inhibitors?

Figure 1: Mechanism of Action of immune checkpoint inhibitors.

Immune checkpoint blockade increases antitumor immunity by blocking intrinsic down-regulators of immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1). Several immune checkpoint-directed antibodies have increased overall survival for patients with various cancers and are approved by the Food and Drug Administration.

CTLA-4 is expressed on the surface of most activated T lymphocytes during initial activation phase in lymphatic tissue by dendritic cells and other APCs. Its main action is inhibitory, regulating homeostasis and peripheral immune tolerance, by inhibiting activation of T lymphocytes through negative signaling.

PD-1 is another co-inhibitory membrane receptor expressed on T-cells activated during the effector phase in peripheral tissues. The binding of PD-1 to PD-L1 and PD-L2 ligands that are expressed in tumor cells and tissue macrophages causes an inhibition of T-lymphocyte facilitating immune tolerance, thus preventing tumor rejection by the immune system.

Immune check point inhibitors are monoclonal antibodies that block these immune checkpoint proteins CTLA-4, PD -1 and PD-L1 leading to stimulation and proliferation of activated T-lymphocytes against tumor cells. The first immune checkpoint inhibitor approved by the FDA in 2011 was the CTLA-4 inhibitor, ipilimumab. Since then six checkpoint inhibitors have been approved for clinical practice across multiple tumor types.

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*		
Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high micro-satellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high micro-satellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

Figure 2: Immune checkpoint blocking antibodies approved by the FDA

Immune related adverse events

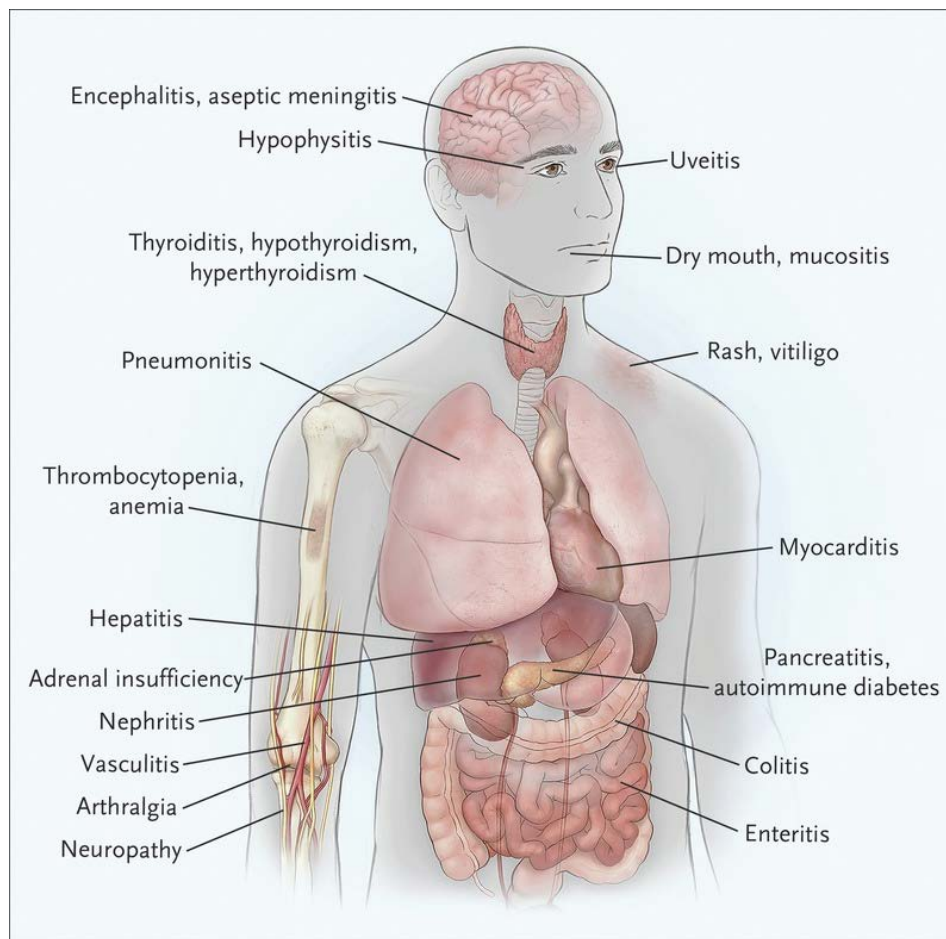


Figure 3: Immune related adverse events

By increasing the activity of the immune system, immune checkpoint blockade can have inflammatory side effects, which are often termed immune-related adverse events. Although any organ system can be affected, immune-related adverse events most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver. Less often, the central nervous system and cardiovascular, pulmonary, musculoskeletal, and hematologic systems are involved.

Immune-related adverse events usually develop within the first few weeks to months after treatment initiation. However, these can present at any time, including after cessation of immune checkpoint blockade therapy, and may wax and wane over time.

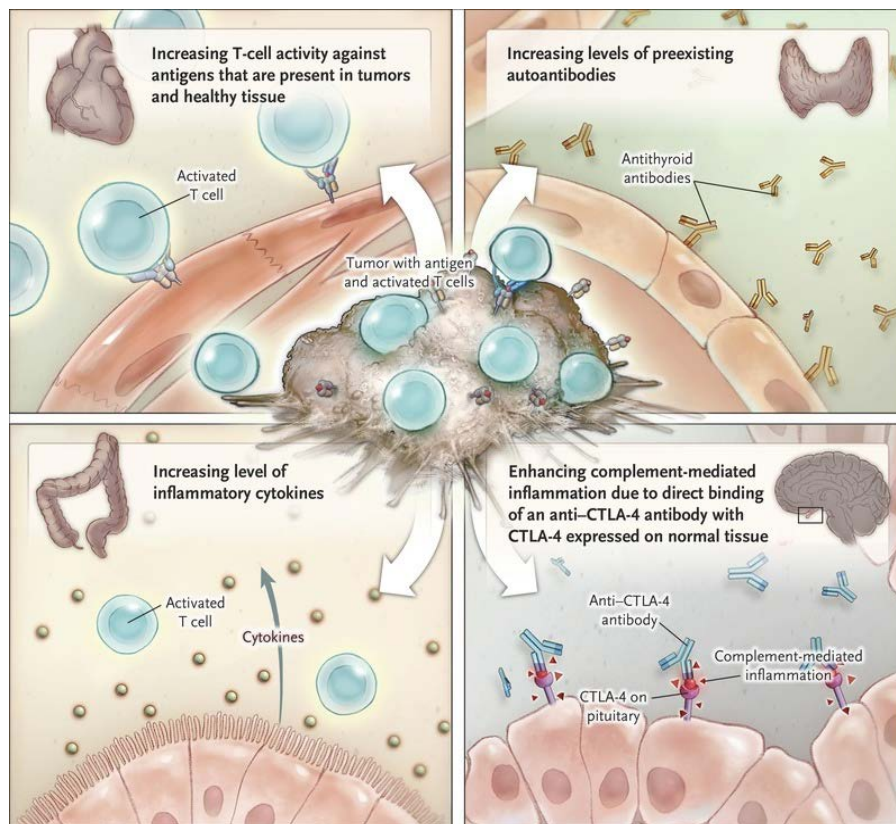


Figure 4: Proposed mechanism of immune related adverse events.

Patients treated with anti-CTLA-4 therapy have immune related adverse events that differ from those in patients treated with anti-PD-1, and the effects of anti CTLA-4 are generally more severe. For example, colitis and hypophysitis seem to be more common with anti-CTLA-4 therapy, whereas pneumonitis and thyroiditis appear to be more common with anti-PD-1 therapy.

Although we do not know why organ-specific toxic effects differ between these two targets, reports of hypophysitis have identified the expression of CTLA-4 on normal pituitary cells, which may contribute to the toxicity of anti-CTLA-4 therapy. Also, thyroid disorders can occur in patients receiving anti-PD-1 therapy who have anti-thyroid antibodies.

Another possibility is that PD-1 may be involved in maintaining self-tolerance, the process that keeps the immune system from attacking the person it was designed to protect. In addition, cytokines may be involved in the pathophysiology of immune-related adverse events. One study identified elevated levels of interleukin-17 in patients with ipilimumab-induced colitis.

Generally speaking, immune-related adverse events result from excessive immunity against normal organs. A majority of immune-related adverse events are effectively treated by:

- 1) delaying or stopping the checkpoint inhibitor and/or
- 2) inducing temporary immunosuppression with agents such as oral glucocorticoids or additional immunosuppressants in more severe cases.

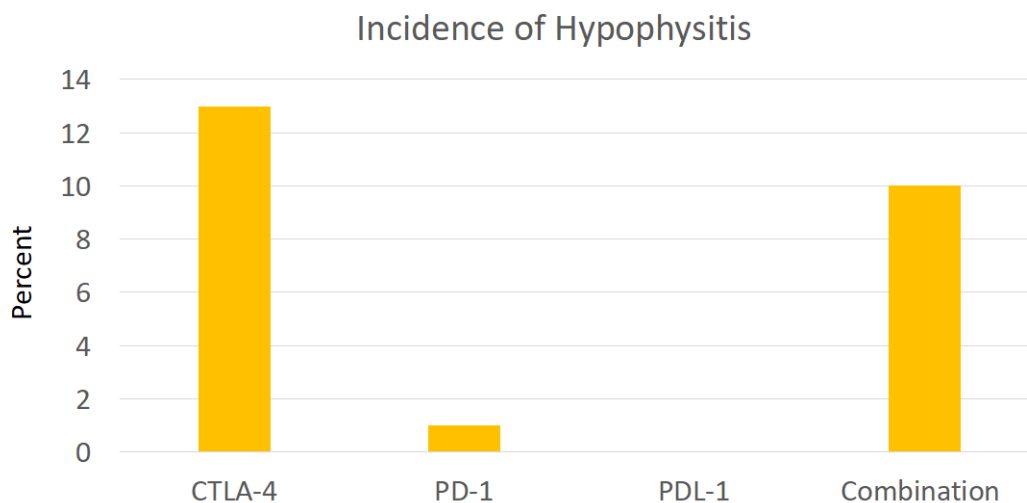
Multidisciplinary collaboration can often be helpful in treating patients with immune-related adverse events.

Endocrine specific adverse events:

Endocrine immune related adverse events include hypophysitis, primary or secondary thyroid disease, primary adrenal insufficiency, diabetes mellitus type 1 and rarely hypoparathyroidism.

Hypophysitis:

Incidence and Prevalence:



More frequent in men and older age (>60 yrs)

Pathogenesis: Although the precise mechanism for hypophysitis is not completely understood it is thought to be related to development of a process of immunological activation at the level of the pituitary gland.

- 1) Pituitary auto antibodies: Expression of CTLA-4 protein has been found on pituitary cells. Binding to CTLA-4 antibodies or Ipilimumab IgG is thought to lead to activation of classical complement pathway which then destroys pituitary cells.
- 2) Direct activation of T-cells results destruction of pituitary cells and inflammation and production of cytokines in response to cognate antigen.

Clinical presentation:

Hypophysitis generally appears between 6-10 weeks after starting treatment.

The clinical manifestations of hypophysitis are related to

- 1) Structural changes associated with the enlargement of pituitary
- 2) Hormonal disturbances that occur as a result of pituitary inflammation.

Clinical manifestations can be nonspecific and be related to the underlying malignancy or non-endocrine related adverse events. These include:

- Headache
- Hypotension
- Hypoglycemia
- Nausea
- Weakness
- Anorexia
- Diarrhea.

Lab abnormalities can include

- Hyponatremia
- Low AM cortisol, ACTH
- Low free T4, TSH
- Low prolactin, testosterone in men, and estrogen in premenopausal age group for women.

Imaging:

MRI of the pituitary gland may show mild to moderate diffuse pituitary enlargement. Chiasmatic compression was not seen in most studies.

A normal pituitary gland on MRI does not rule out hypophysitis and management should be based on clinical presentation and evaluation of pituitary hormone levels.

Treatment:

Severe Hypophysitis: headache and Na < 125 mg/dl

1) High Dose Steroids

- Dexamethasone 4mg Q6hr or methylprednisolone/prednisone 1-2 mg/kg/day)

2) Fluid Resuscitation:

- D5 or Normal Saline (hypoglycemia, hyponatremia, hypotension)
- AVOID hypotonic fluids, e.g. D5W, D5 0.5% NaCl

3) Correct metabolic abnormalities: severe hyperkalemia

- IV bicarb, rectal polystyrene resin, IV glucose and insulin

Mild and Moderate Hypophysitis

Hormone replacement therapy is the mainstay of treatment.

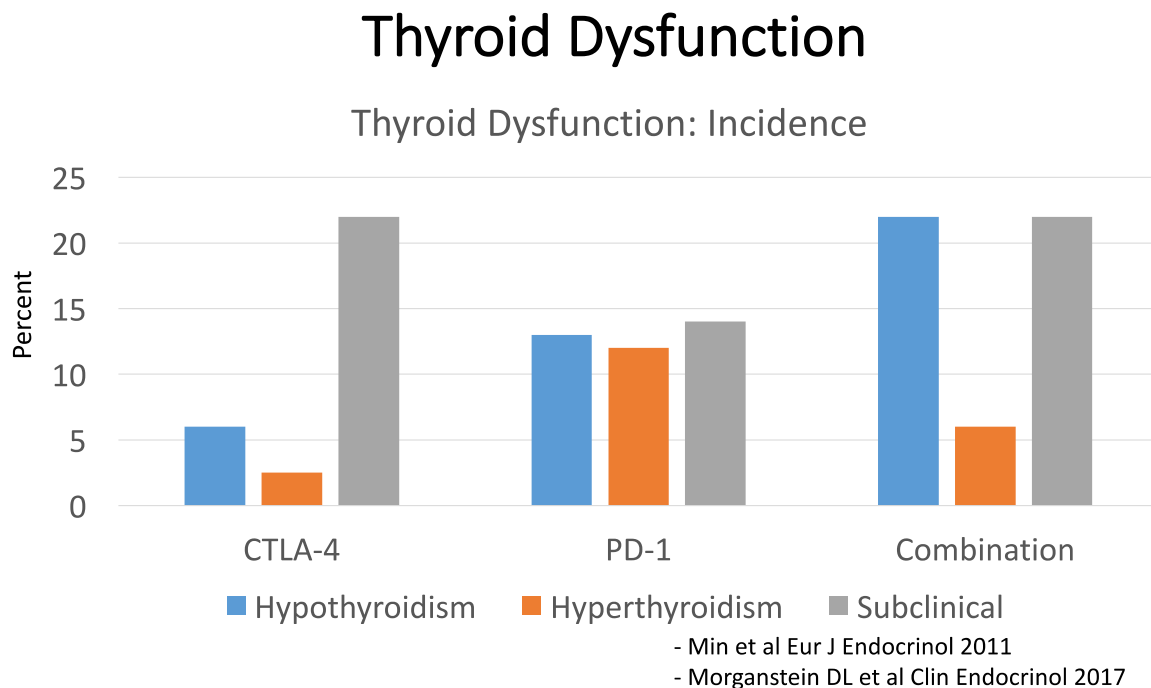
- 1) Secondary adrenal insufficiency: hydrocortisone can be started on replacement dose 20-30 mg per daily divided into 2 doses through the day. Patients are educated about sick day rules to double dose of steroids.
- 2) Thyroid axis: start levothyroxine to be titrated based on FT4 lab values.
- 3) Gonadal axis: Testosterone replacement can be considered as outpatient for male patients for hypogonadism.
- 4) Growth hormone therapy is not instituted as it is not indicated due to underlying malignancy.

Some authors have found an association between Ipilimumab induced hypophysitis and a better tumor response in patients with metastatic melanoma. Hypophysitis was accompanied by a greater survival 21.4 versus 9.7 months in these patients compared to those who did not develop it. Because steroid use and management of hypophysitis has also not shown to negatively influence the therapeutic benefit of immune checkpoint inhibitors.

Thyroid Dysfunction:

Thyroid dysfunction includes thyroiditis with transient thyrotoxicosis, hypothyroidism which could be transient or long standing and subclinical disease (both hypo and hyperthyroidism) in an isolated or sequential way in the same patient over time. Rare cases of hyperthyroidism associated with Graves disease have been reported.

Incidence:



Time of onset:

Median time of onset is 2 months but can be delayed up to 2-3 years after treatment initiation.

Pathogenesis:

Thyroid problems appear to occur as a result of immunological activation at the thyroid level which manifests as autoimmune /destructive thyroiditis induced by immunological and inflammatory mechanisms.

A large majority of these patients were positive for anti-thyroglobulin and anti-thyroid peroxidase antibodies.

Clinical presentation:

Clinical picture of thyrotoxicosis is usually mild and transient. TSH levels are low and free T4 is elevated. Patients may present with fatigue, anxiety, diarrhea and palpitations. Majority of patients after transient thyrotoxicosis develop hypothyroidism. Asthenia and fatigue are the main reported symptoms. Labs are consistent with low free T4 and elevated TSH for primary hypothyroidism and low free T4 and normal to low TSH in secondary hypothyroidism (from hypophysitis).

Management:

Thyroiditis with transient thyrotoxicosis can be managed symptomatically with beta blockers. Corticosteroids are sometimes used if being used for other irAEs. Given the pathogenesis treatment with anti-thyroid drugs usually does not help unless thyroid stimulating immunoglobulins are positive.

For symptomatic subclinical hypothyroidism and frank hypothyroidism with TSH > 8-10 and low free T4 hormone replacement therapy with levothyroxine is instituted and titrated based on labs for TSH and free T4.

It is important not to rely on TSH for secondary hypothyroidism caused by hypophysitis.

Autoimmune Diabetes:

Immunotherapy has also been associated with autoimmune diabetes mellitus.

This side effect is uncommon and has been reported with anti- PD-1 use and combined therapy but not with CTLA-4 alone. The incidence is < 1%.

It may appear after a treatment period ranging from 1 week to upto 4 years.

Patients present with hyperglycemia and occasionally with diabetic ketoacidosis. Hormone replacement therapy with basal and bolus insulin is instituted.

Proposed pathogenic mechanism is infiltration of pancreatic islets with activated of T lymphocytes accompanied by production of anti- GAD and anti IA2 antibodies.

Primary Adrenal Insufficiency/ Adrenitis:

Primary adrenal insufficiency is uncommon. Incidence varies from 0.3 to 1.5%.

Before establishing its diagnosis, it is important to rule out metastatic infiltration of both adrenal glands as the cause for primary adrenal insufficiency. A bilateral reversible enlargement of the adrenal glands has been reported.

It can present clinically with fatigue, diarrhea, chronic hyponatremia and hypotension. Laboratory findings are consistent with low cortisol, low DHEA-S, high ACTH.

Hormone replacement therapy is instituted with corticosteroids and mineralocorticoids which controls symptoms, restores metabolic abnormalities and allows continued immunotherapy treatment. Dose for corticosteroids (hydrocortisone 20-30 mg/day divided in two doses) is usually sufficient.

Principal of Immunotherapy re-challenge: NCCN guidelines

Hypophysitis: Manifested by deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: immunotherapy may continue while replacement endocrine therapy is regulated.

Hypophysitis accompanied by symptoms of pituitary swelling (eg headache, vision disturbance, and /or neurologic dysfunction): hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms are controlled on steroid dose less than 10mg/day.

Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling graves-like disease, consider holding immunotherapy and resuming after work up is complete and there is evidence of improvement in symptoms and TFTs.

Primary Adrenal Insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue.

DM Type 1 with DKA: Consider resuming once DKA has been corrected and glucose levels have been stabilized.

Table 2. Ten Questions Relevant to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Blockade.

Questions about Immune-Related Adverse Events	Comments
Why do they occur?	The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.
How are they generally treated?	No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.
When do they occur?	Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.
Why do they occur in some patients and not others?	The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.
Are they associated with the efficacy of immune checkpoint blockade?	Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.
Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?	Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.
Are there unintended effects of immunosuppression to treat adverse events?	Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.
Is it safe to restart treatment after a major adverse event?	Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti-CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti-PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.
Is it necessary to restart treatment after resolution of an adverse event?	Retrospective data suggest that patients who have had a favorable response to immune checkpoint blockade and then discontinue treatment because of immune-related adverse events generally maintain responses. Prospective data are needed to address whether restarting immunotherapy is necessary.
Is it safe to treat patients at potentially increased risk for such adverse events?	Patients at increased risk for immune-related adverse events (e.g., preexisting autoimmune disease) may still benefit from immune checkpoint blockade. Age alone should not be used to exclude patients from treatment, since benefit appears to be similar regardless of age.

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