Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immune Checkpoint Inhibitor Endocrinopathies- Diagnosis and Treatment

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Disclosures

- No Disclosures
- I will not be discussing non-FDA approved indications during my presentation.

Outline

- Immune related endocrinopathies
- Diagnosis and management:
  - Hypophysitis
  - Adrenal Insufficiency
  - Thyroid Dysfunction
  - Diabetes Mellitus
  - Parathyroiditis
- Monitoring Guidelines for immune check point inhibitors

Immune related endocrinopathies

Pituitary

- Hypophysitis,
- Isolated ACTH Deficiency
- Diabetes Insipidus

Thyroid

- Thyroiditis
- Hypothyroidism
- Graves Disease

Adrenal

- Adrenalitis

Endocrine pancreas

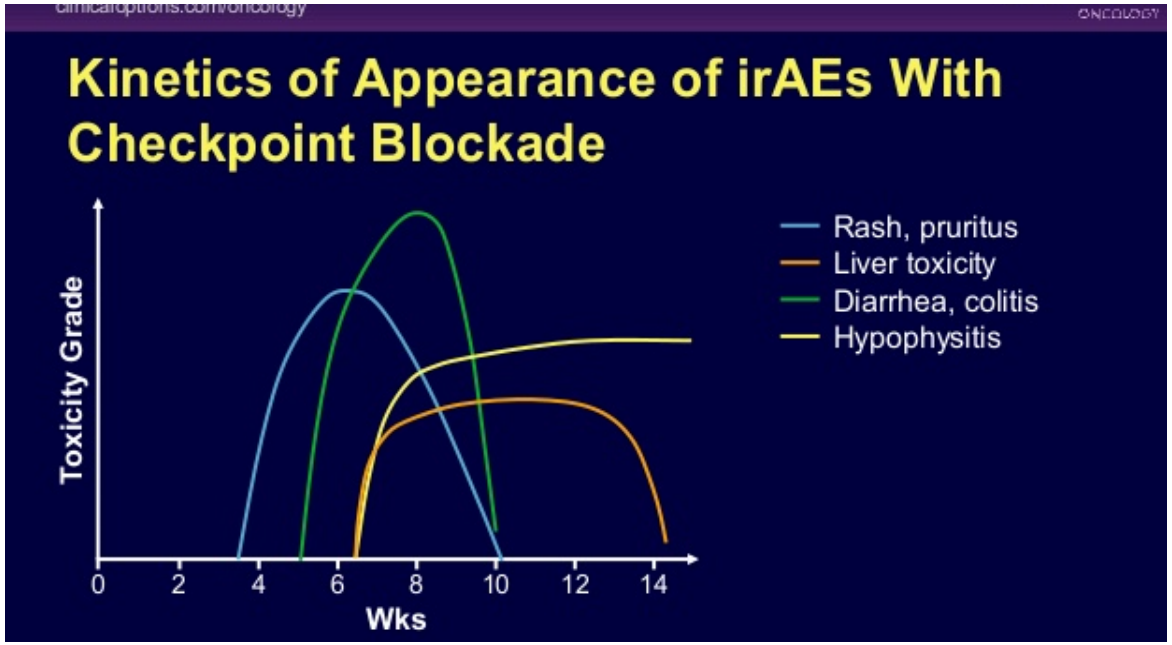
- Type 1 diabetes

Parathyroid

- Hypoparathyroidism

Hypophysitis

- Time of onset: usually 8-10 weeks
- Clinical Presentation: headache (94.1%) and fatigue (58.8%) most common symptoms.
- Hormone axis involved:
  - Central hypothyroidism
  - Hypogonadism, low prolactin,
  - Secondary adrenal insufficiency,
  - Growth hormone deficiency
  - Diabetes Insipidus

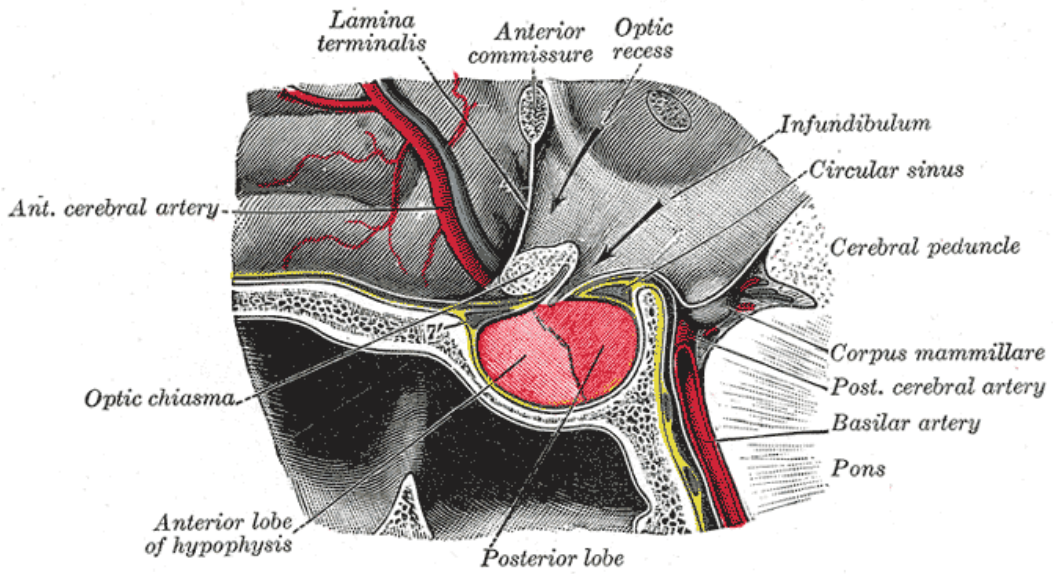


Weber et. al, J Clin Onc 2012

Hypophysitis: Diagnosis

Structural involvement:

Imaging (MRI preferred)



Hormone involvement:

- Basic metabolic panel (BMP) (low Sodium)
- Thyroid:
  - TSH - low or normal
  - FT4 - low
- Adrenal:
  - AM cortisol - low
  - ACTH - low or normal
- Gonadotrophs:
  - LH and FSH - low
  - Testosterone, estrogen - low
- Prolactin - low
- ADH: Serum & urine osmolality

Bollin et al, J Clin Oncol. 2021
Faje et al, J Clin Endocrinol Metab 2014
Min et al, Clin Cancer Res. 2015

Hypophysitis: Diagnosis

Lab abnormalities:

- Thyroid: low or normal TSH, low Free T4
- Adrenal: hyponatremia, low cortisol, low or normal ACTH
- Gonadotroph: Low testosterone/estrogen, low or nl FSH and LH
- Low Growth hormone, IGF-1, low prolactin

Radiologic changes:

-Homogenous /heterogeneous enlargement of pituitary on MRI.

Hypophysitis: Treatment

Grade 1: Mild, supportive care only needed

Grade 2: Moderate, minimal noninvasive treatment needed

Hormone replacement therapy:

- Adrenal insufficiency:
  - Corticosteroids (HC 15-30 mg/day) (initiated before thyroid replacement)
  - Stress dose education, emergency injectable
  - Medical alert bracelet /necklace
- Thyroid hormone deficiency:
  - Start levothyroxine (50-100% weight based dose)
  - Titrate based on FT4 (upper half reference range)
- Gonadotroph deficiency:
  - Testosterone replacement
  - Estrogen replacement (pre-menopausal)
- Growth hormone deficiency:
  - Not recommended with an underlying malignancy

Bollin et al, J Clin Oncol. 2021
Min L et al Clin Cancer Res 2015

Hypophysitis : Treatment

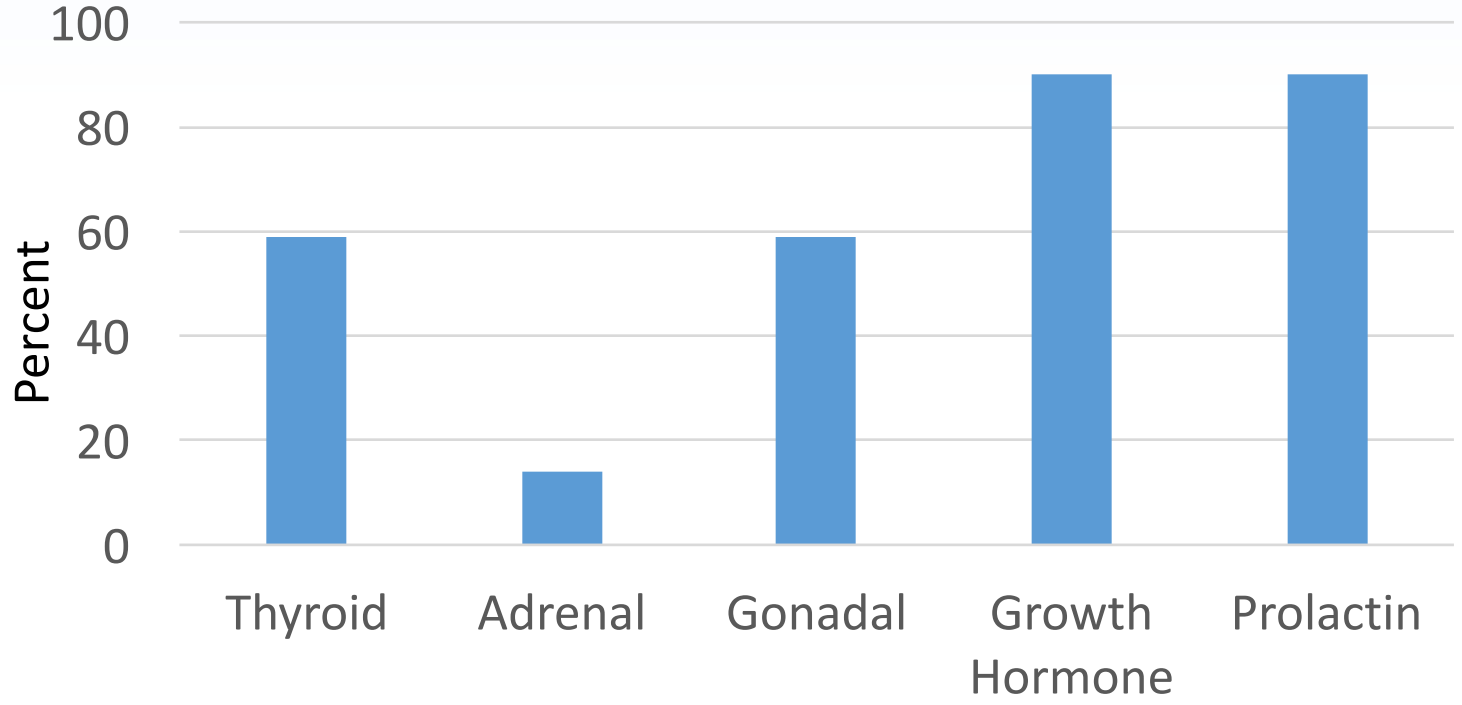
Grade 3: Severe Not imminently life threatening , hospitalization required

Grade 4: Life threatening consequences/ urgent intervention indicated

- **Stop immune checkpoint inhibitor**
- **Hospitalize or make an ED referral**
- High dose steroids:
  - Hydrocortisone (HC) 50-100 mgQ4-6 hrs (taper to physiologic dose over 5-7 days)
  - Oral pulse dose prednisone 1-2 mg/kg/day tapered over 1-2 weeks (swelling on MRI, optic chiasm involvement)
- Fluid resuscitation:
  - D5 Normal Saline or NS (to correct hypoglycemia, hyponatremia, hypotension)
  - AVOID hypotonic fluids
- Correct metabolic abnormalities (i.e. severe hyperkalemia)

Bollin et al, J Clin Oncol. 2021
Min L et al Clin Cancer Res 2015

Hormonal Function Recovery by Axis Involvement



- MRI alterations resolve in < 40 days after treatment
- Pituitary enlargement > 60 days after diagnosis may indicate a secondary (metastatic) involvement of pituitary

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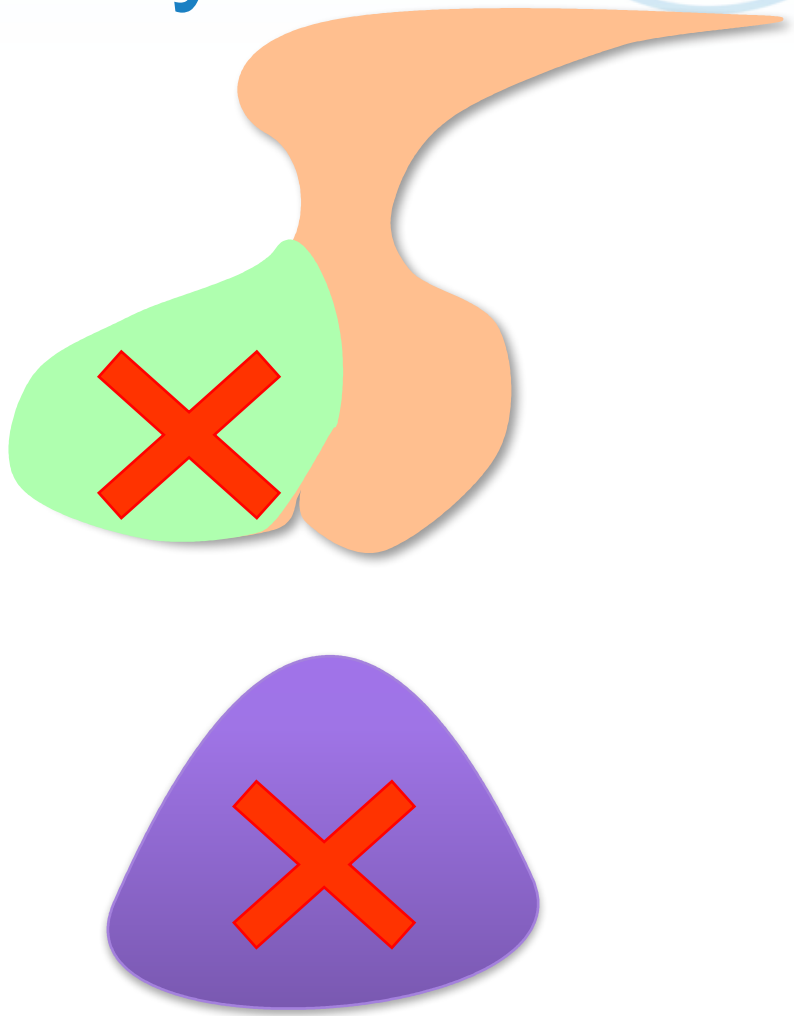
Faje et al JCEM 2014, Albarel et al Eur J endocrinol 2015, Min et al 2015 Clinical Cancer Research

Adrenal Insufficiency

- 1° adrenal insufficiency : Adrenal gland
  Cause: Adrenalitis

- 2° adrenal insufficiency: Pituitary gland or hypothalamus
  Cause: hypophysitis, Isolated ACTH deficiency

- Clinical presentation:
  signs/symptoms: fatigue, weight loss, hypotension



Laboratory Findings

Primary and Secondary AI

- ↓Na, ↓glucose and ketosis
- Acidosis is often present, ↑BUN if dehydrated
- ↓ cortisol
- ↓ DHEAS
- ↑Ca (due to dehydration), lymphocytosis, eosinophilia

Primary AI only

- ↑↑ ACTH
- ↑ K
- ↑ Renin
- ↓Aldosterone

Secondary AI only

- ↓ or "inappropriately normal" ACTH
- ↓CRH
- [↓other pituitary hormones]

Diagnostic Approach

- Morning serum cortisol
  - <3 mcg/dL = AI
  - 3-15 mcg/dL = indeterminate
  - >15 mcg/dL = normal
  - DHEAS is >80 ug/dl, AI is very unlikely

- ACTH
  - Primary AI, ACTH > ULN
  - Secondary AI, ACTH is low or “inappropriately normal”

- Aldosterone and renin
  - ↓Aldosterone are ↑renin in primary AI

	Primary AI	Secondary AI
Cortisol	Low	low
ACTH	High	Low or normal

- Cosyntropin stimulation test : confirm diagnosis in most cases
  - Cortisol baseline, 30 and 60 minute later
  - Maximum cortisol stimulation to ≥ 18 mcg/dL is a normal result.

Diagnostic Approach (2)

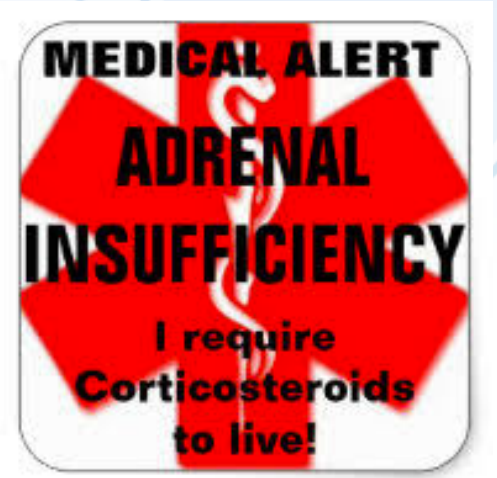
- **Cosyntropin (ACTH) Stimulation Test**
  - Serum cortisol is measured before, 30 min and 60 min after IV/IM administration of 250 mcg of ACTH (cosyntropin)
  - Baseline cortisol < 3 mg/dl or < 18 mg/dl at 30 min or 60 min post cosyntropin → AI
- US, CT, or MRI of the abdomen
  - can help define the size of the adrenal glands
- Pituirary/brain MRI
  - If unexplained secondary/tertiary AI

Treatment: Acute AI

- Treatment must be immediate and vigorous
- Obtain labs before therapy: electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma renin activity
- If the pt's condition permits, perform a cosyntropin stim test
- Fluid resuscitation: IV D5 in 0.9% saline
- Treat metabolic abnormalities: severe hyperkalemia
- Glucocorticoid replacement*
  - Hydrocortisone IV bolus, followed by smaller doses every 6 hrs

*Mineralocorticoid therapy is not required because high doses of glucocorticoids (except for dexamethasone) provide sufficient cross reactivity with mineralocorticoid receptor

Treatment: Chronic AI



- Glucocorticoid replacement:
  - Hydrocortisone is preferred
  - 10-15 mg in the morning and 5 mg in early afternoon
  - Monitor well-being of patient
  - Absence of signs of glucocorticoid excess
- Mineralocorticoid replacement (primary AI only): Fludrocortisone
  - 0.05-0.2 mg daily
  - Normal electrolytes
  - Renin near the upper limit of normal range
  - Absence of edema and hypertension
  - Absence of postural hypotension

Endocrine Society Practice Guidelines 2016 JCEM

Long-Term Treatment of AI

Steroid	GR potency (anti-inflammatory)	MR potency (Na-retaining)	Replacement or equivalent dose (daily)	Duration of action
Hydrocortisone = cortisol	1	1	15-20 mg	8-12h
Prednisone	4-5	0.8	5 mg	18-36h
Prednisolone	4-5	0.8	5 mg	12-36h
Fludrocortisone	0	125	--	24h
Dexamethasone	25	0	0.75 mg	36-54h
Methylprednisolone	5	0.5	4 mg	18-36h
Triamcinolone	5	0	4 mg	12-36

Note: hydrocortisone is arbitrarily assigned a potency level of 1 in each of the 3 categories above. For e.g. – prednisone has 4 times glucocorticoid properties and 0.75 mineralocorticoid properties compared to hydrocortisone.

Shimmer et al, The Pharmacological Basis of Therapeutics, 12th ed, 2011
Liu et al, Allergy Asthma Clin Immunol 2013

Thyroid Dysfunction: Clinical Presentation

Hypothyroidism

Fatigue
Weakness
Constipation
Cold intolerance
Dry skin
Weight gain

Hyperthyroidism

Tachycardia
Diarrhea
Heat intolerance
Excessive diaphoresis
Weight loss

Morganstein DL et al Clin Endocrinol 2017

Thyroid Dysfunction: Diagnosis

Labs:

- Thyroid stimulating hormone (TSH)
- Free thyroxine (FT4)
- If abnormal - Check antibodies Thyroid peroxidase antibody (TPO) , thyroid stimulating antibody (TSI)

Thyroid Dysfunction : Laboratory Findings

	TSH (mIU/L)	Free T4	Antibodies (TPO,TSI)
Primary Hypothyroidism	High >10	Low	+/-
Secondary Hypothyroidism	Low or normal	Low	NA
Subclinical Hypo	4.5-10	Normal	+/-
Hyperthyroidism	Low	High	+/-

*TPO: thyroid peroxidase ntibody, TSI: thyroid stimulating antibody, thyroglobulin antibody

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ATA/AACE clinical Practice Guidelines 2012, https://doi.org/10.4158/EP12280.GL

Thyroid Dysfunction : Management

Hypothyroidism

- Hormone replacement therapy:
  - - Start levothyroxine
  - - Titrate based on TSH (goal within normal range)

Hyperthyroidism

- Beta blockers – for symptom control
- Corticosteroids
- Thionamides (methimazole, propylthiouracil) if thyroid stimulating immunoglobulin (TSI) positive

ATA/AACE clinical Practice Guidelines 2012

Thyroid Dysfunction: Evolution

- Hyperthyroidism:
  - usually followed by hypothyroidism (burns out)
- Hypothyroidism:
  - Spontaneous recovery is unusual
  - Cases reported for recovery with high dose steroid used for other irAEs.
- Immunotherapy is rarely interrupted for thyroid dysfunction

Morganstein DL et al Clin Endocrinol 2017, Osorio JC et al Ann Oncol 2017

Diabetes Mellitus/Insulitis

Timing: highly variable, 1 week to 4 years

Clinical Presentation:

- Symptoms: Polyuria, polydipsia
- Labs: Elevated glucose, Low C-peptide, anti-beta-cell antibodies: anti-GAD, anti-IA2

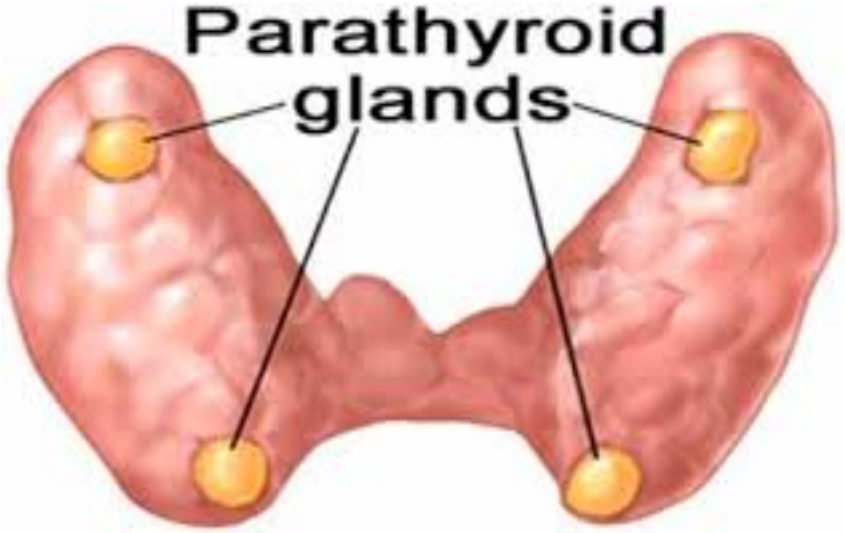
Treatment:

- Insulin Replacement therapy
- Weight based 0.4-0.6 units/kg/day
  - split 50% basal and 50% bolus
- Referral to Endocrinology

Chae YK et al Cancer Immunol Immunother 2017 Lowe JR et al J Immunother Cancer 2016

Parathyroiditis

- One case recently reported
- 73 y/o man with metastatic melanoma with severe hypocalcemia associated with hyperphosphatemia, normal albumin and PTH < 1pg/ml
- Treatment:
  - Elemental calcium divided in 3-4 doses
  - Calcitriol
  - Replace 25-OH vitamin D



Win et al Emerg Med 2017

Monitoring Guidelines for Immune Checkpoint Inhibitors

	Baseline Assessment	Evaluation for abnormal findings/symptoms
Pituitary & Adrenal	Basic metabolic panel, am cortisol, TSH, FT4	ACTH, LH, FSH, estradiol, testosterone
Thyroid	TSH, FT4	TPO, TSI Abs
Diabetes	Basic metabolic panel	HbA1c, GAD, IA-A2 Abs

Monitoring Frequency:

- On therapy: Every cycle
- After therapy: q 6-12 weeks

NCCN guidelines 2020

Principles of Immunotherapy Re-challenge

Condition	Recommendation
Hypothyroidism Hyperthyroidism	No discontinuation required Hold immunotherapy Restart after improvement of symptoms and labs
Primary adrenal insufficiency	Continue after hormone replacement instituted
Hypophysitis w/o symptomatic pituitary swelling	Continue while hormone replacement instituted
Hypophysitis w symptomatic pituitary swelling	Hold until resolution of symptoms Resume after symptoms controlled on < 10 mg daily prednisone/ equivalent
DM with DKA	Continue once DKA corrected

NCCN Guidelines version 1.2018

Thank you!

Questions