Checkpoint Inhibitor Induced Endocrine Disorders

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SPED Semiannual Convention 2019
5/25/2019

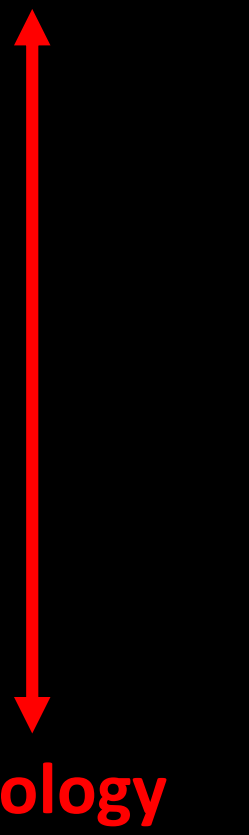
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Disclosures

- Nothing to Disclose

Endocrinology and Cancer – a management spectrum

- Primary endocrine tumors
  - Hormone secreting or non-secreting
- Glands resected/damaged by cancer/treatment
  - Hypothyroidism, hypoparathyroidism, adrenal insufficiency, etc.
- Endocrine Effects of Cancer Therapy
  - Fertility, hyperglycemia, hyperlipidemia, hypothyroidism, bone health
- Paraneoplastic Syndromes from non-endocrine cancers
  - Hypercalcemia of malignancy, SIADH, Cushing's syndrome



Endocrinologist’s role for a cancer patient

- Patient’s focus is usually cancer & treatment not their endocrine disorder
- Depends on overall goals of cancer care
- Improve quality of life without excessive burden of treatment
- Improve patient safety
- Take time/burden of management off of oncology team
- Keep in clinical trials

Targeted therapies – the future of oncology

- Modern treatments are less cytotoxic
- Targets are more specific
  - Mutated signaling pathways – often growth pathways
  - CAR-T therapy
  - Immunotherapy
- Clinical trials can be designed based on mutation/expression not tumor type
- New paradigm of side effects, not what oncologists have traditionally managed

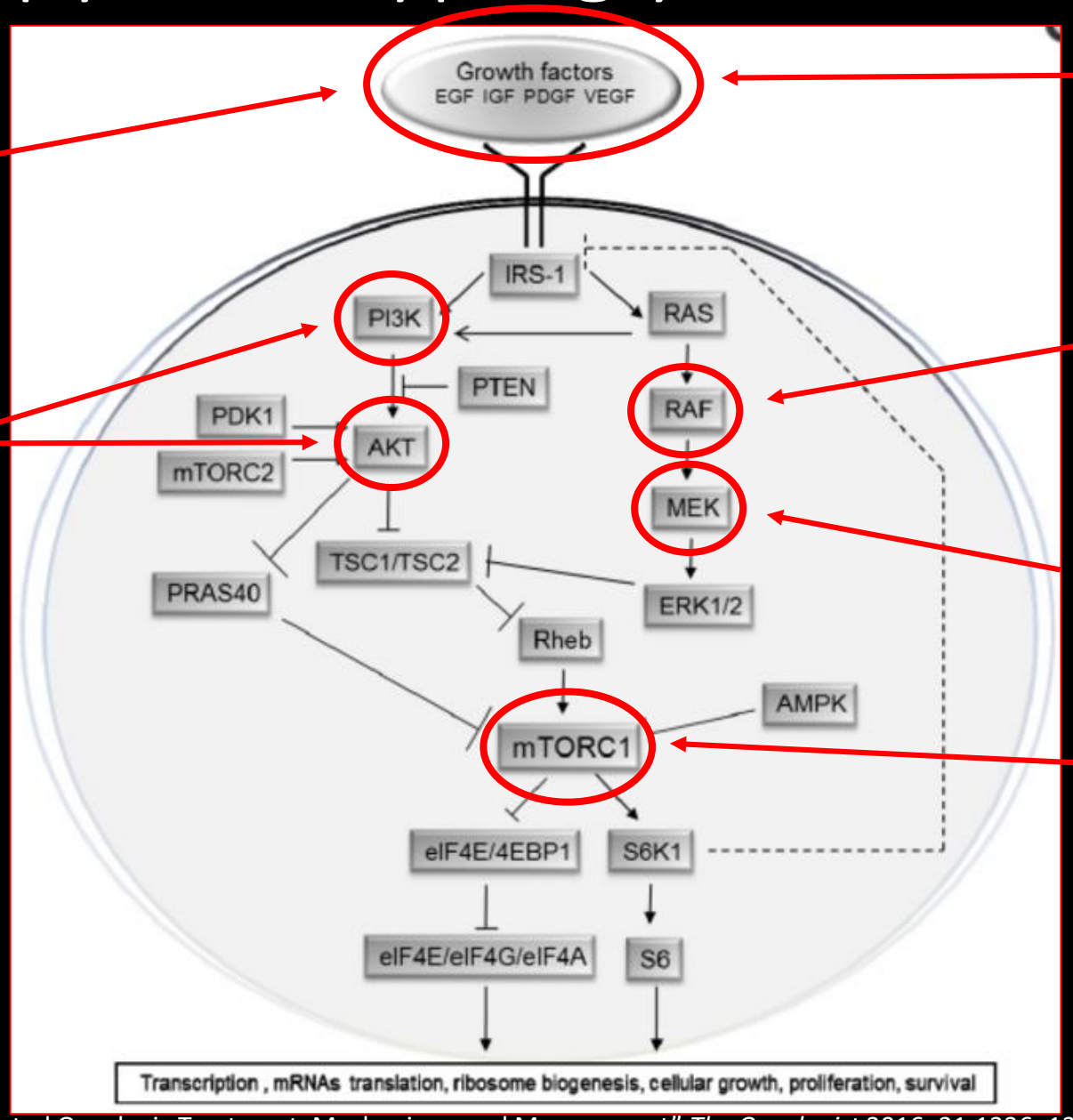
Oncology treatments with endocrine effects

- Steroids - hyperglycemia
- Cytotoxic chemotherapy – hypogonadism
- Radiation – hypothyroidism, hypogonadism
- mTOR inhibitors – hyperglycemia and lipid disorders
- Tyrosine Kinase Inhibitors – hyperglycemia and thyroid disorders
- Other medications– bexarotene, abiraterone
- Checkpoint inhibitors
  - Endocrine system is prone to autoimmune attacks

Targeted Therapy and Hyperglycemia

IGF receptor Ab
Multiple in studies with hyperglycemia rates ranging from 10-100%

PI3K/AKT Kinase inhibitors
Multiple in studies with hyperglycemia rates ranging from 2-93%



EGFR
Gefitinib – 5%
Rociletinib – 46%

BRAF
Vemurafenib – none
Dabrafenib – 49-50%

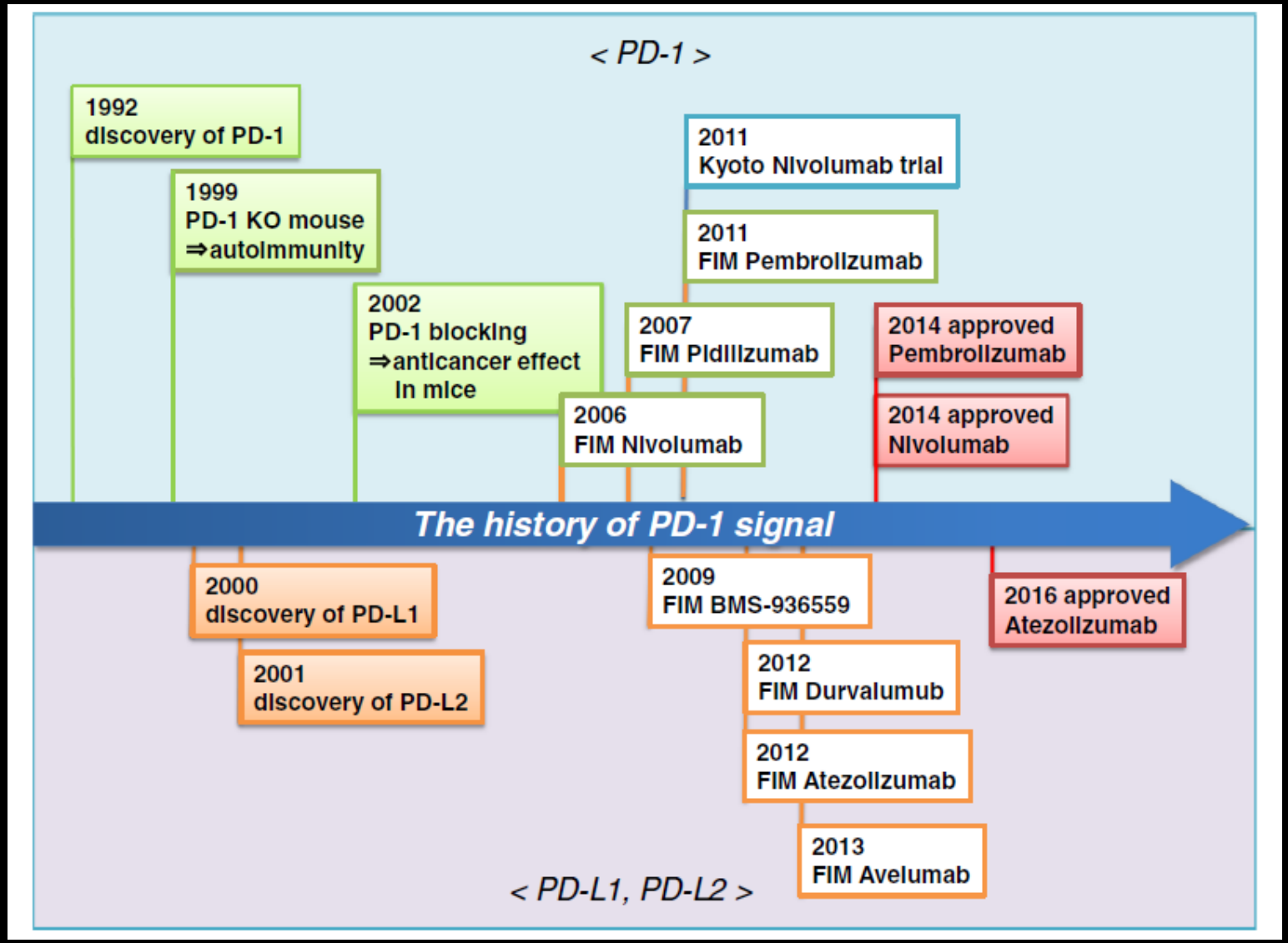
MEK
Selumentinib - none
Trametinib - none

mTOR
Everolimus – 7-93%
Temsirolimus – 7-76 %

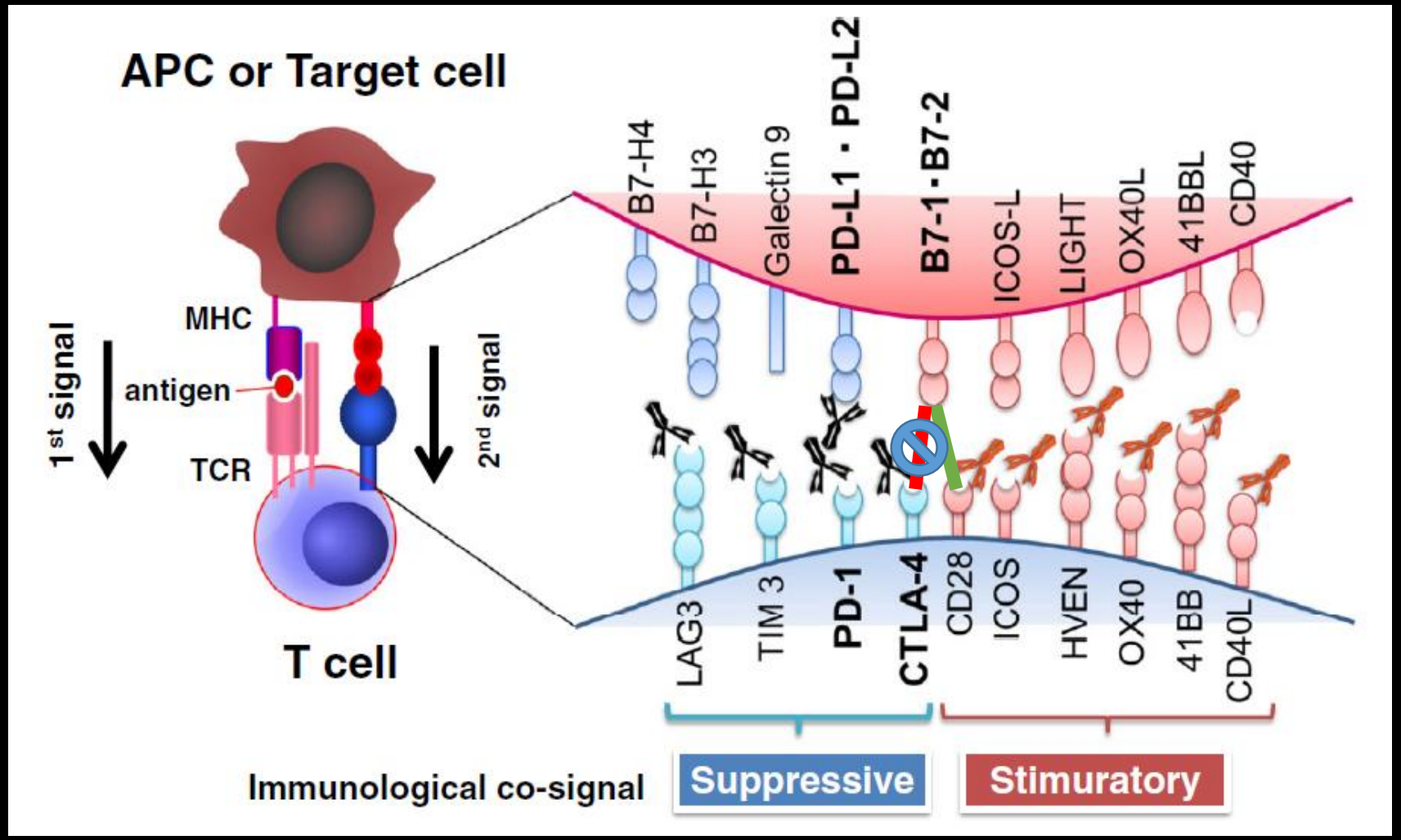
Goldman J. et al "Hyperglycemia Associated with Targeted Oncologic Treatment: Mechanisms and Management" *The Oncologist* 2016; 21:1326–1336
Populo H, et al "the mTOR Signalling Pathway in Human Cancer" *Int J Mol Sci.* 2012; 13(2):1886-1918

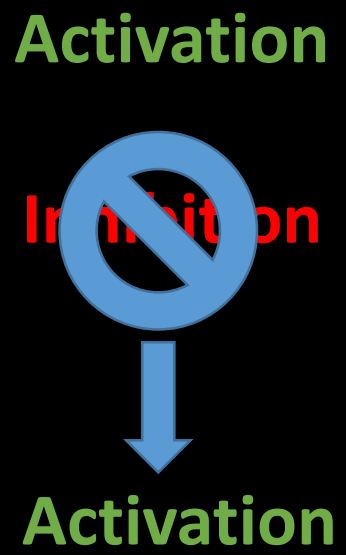
Background

- Checkpoint inhibitors introduced as cancer therapy in 2011
- CTLA-4 inhibitors followed by PD-1 inhibitors in 2014



Iwai et al. Journal of Biomedical Science (2017) 24:26 DOI 10.1186/s12929-017-0329-9





- T-cell needs co-stimulation to activate. Suppressive signals prevent auto-immunity
- By inhibiting this signal we can increase response to cancer “neoantigens”

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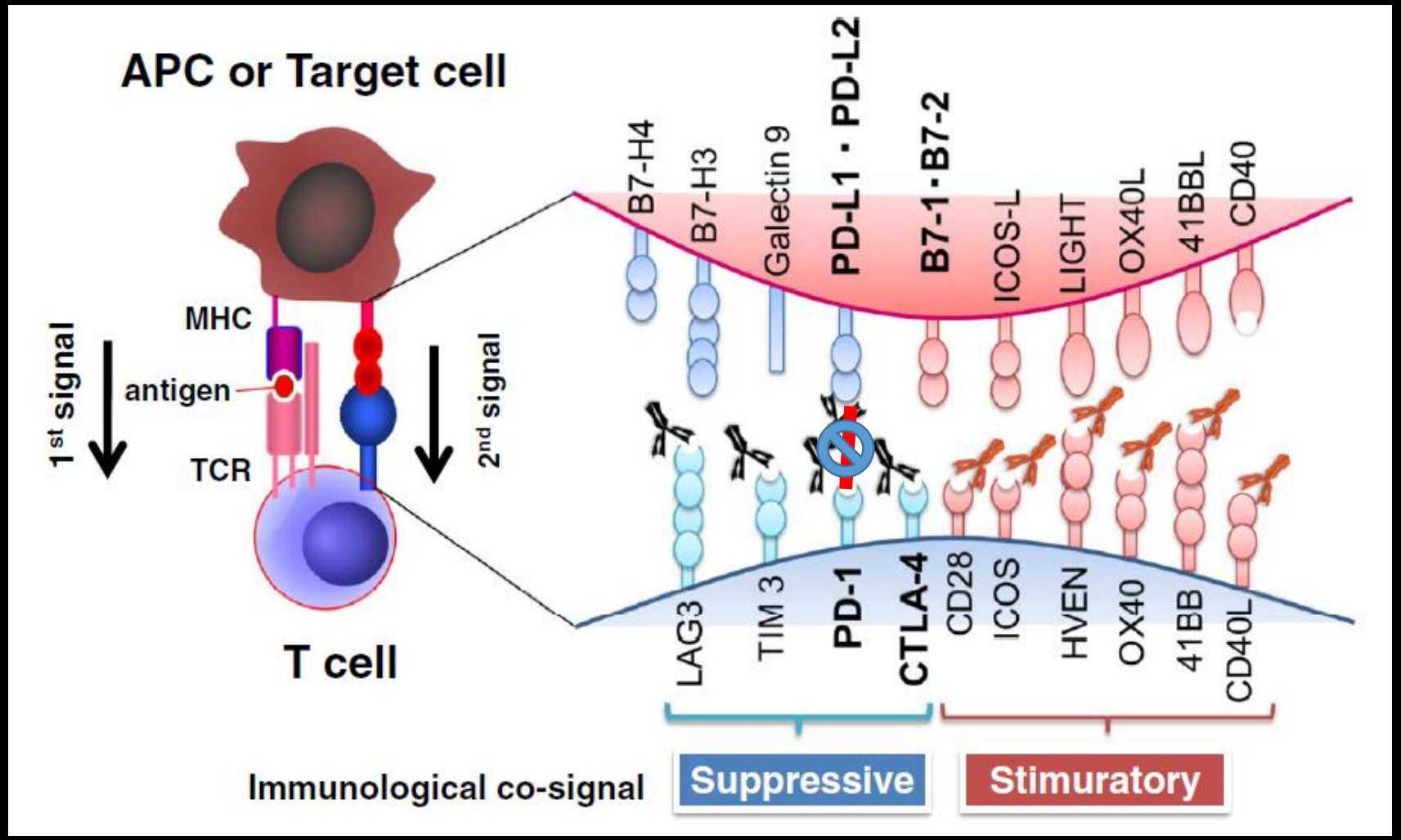

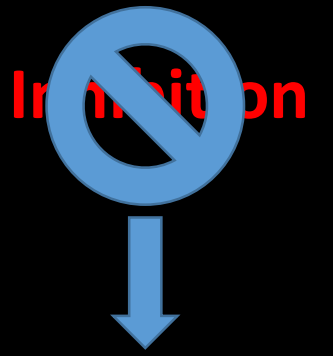

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CTLA-4 vs PD-1/PD-L1

- CTLA-4 functions early in T-cell activation
  - Expressed on dendritic/antigen presenting cells in lymph nodes
- PD-1/L1 functions in the tumor microenvironment
  - PD-L1 expressed on tumor cells
  - Can stain pathology of target tissues to predict possible effectiveness of therapy
  - PD-1 expressed on T-cells
- Different sites of activation lead to different side effect profiles

Hargadon et al. “Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors” International Immunopharmacology (2018) 62:29-39 DOI 10.1016/j.intimp.2018.06.001

Currently Available agents

- CTLA-4
  - **Ipilimumab** (**Yervoy**) – FDA approved: malignant melanoma
  - Tremelimumab – In studies for melanoma and mesothelioma (orphan)
- PD-1
  - **Pembrolizumab** (**Keytruda**) – NSCLC, Head and Neck SCC, Hodgkin's lymphoma
  - **Nivolumab** (**Opdivo**) – melanoma, NSCLC, RCC, Hodgkin's lymphoma, urothelial, H&N SCC
  - Cemiplimab – metastatic cutaneous squamous cell cancer
- PD-L1
  - Durvalumab – Urothelial and NSCLC
  - Atezolizumab – Urothelial and NSCLC
  - Avelumab – Merkel cell carcinoma

What increases the risk of side effects?

- Combination ipilimimumab/nivolumab has been studied in melanoma
  - Increased efficacy but increased rates of adverse effects
  - 59% for combo vs 28% for ipilimumab and 21% for nivolumab
- Side effects are dose dependent – dose can vary significantly
  - Ipilimumab – 3 mg/kg for metastatic disease
  - 10 mg/kg for adjuvant (curative treatment)
  - 1 mg/kg with nivolumab for renal cell or colorectal cancer
- Other drugs are being studied as “co-stimulators’
  - Modulate the immune system to promote activation
  - Unclear what the effect these drugs have on adverse effects
- Can also combine with conventional chemotherapy or radiation

Barroso-Sousa R, et al “Incidence of Endocrine Dysfunction Following the Use of a Different Immune Checkpoint Inhibitor Regimens A Systematic Review and Meta-analysis” *JAMA Concol*. 2018;4(2):173-182

Case 1

- 63 y/o man with a history of chronic myelomonocytic leukemia
- He was enrolled in a clinical trial of nivolumab + azacitidine
- He presented after 5 months of treatment with progressive headache and 1 month of fatigue, cold intolerance, and low libido
- Given symptoms his chemotherapy was canceled and he was admitted for further evaluation

- Note: Fatigue is a side effect in ~50% of patients treated with CPIs

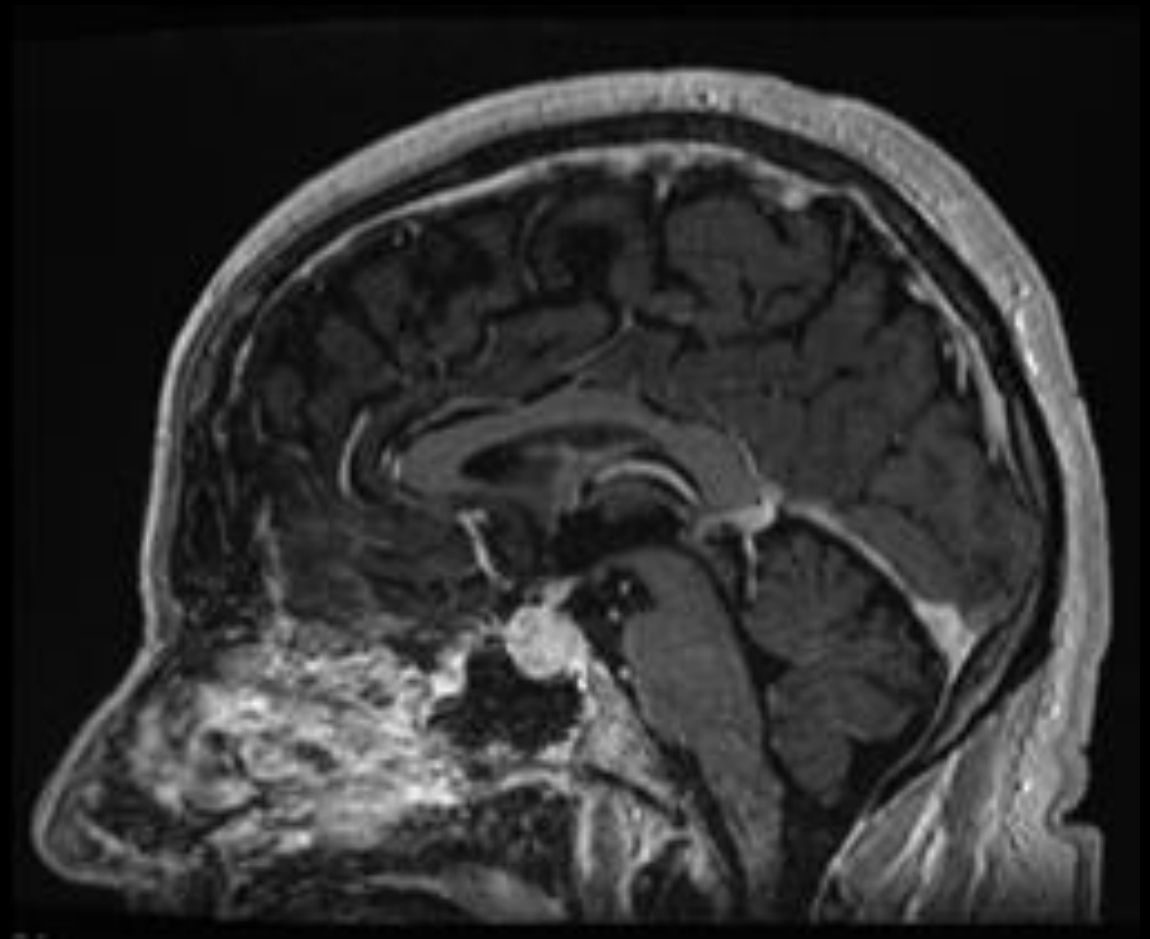
Labs – Drawn at 10:23 AM

- ACTH 21
- Cortisol 4.1
- TSH 0.38
- Free T4: 0.24
- Total Testosterone: <20
- LH: <0.7
- FSH: 4
- Prolactin: 2.2
- Urine SG: 1.017

Hospital course

- Started on empiric hydrocortisone
- Given borderline cortisol level and rarity of hypophysitis with nivolumab he was scheduled for a low dose (1 mcg) ACTH stimulation test
- MRI of the pituitary ordered

MRI



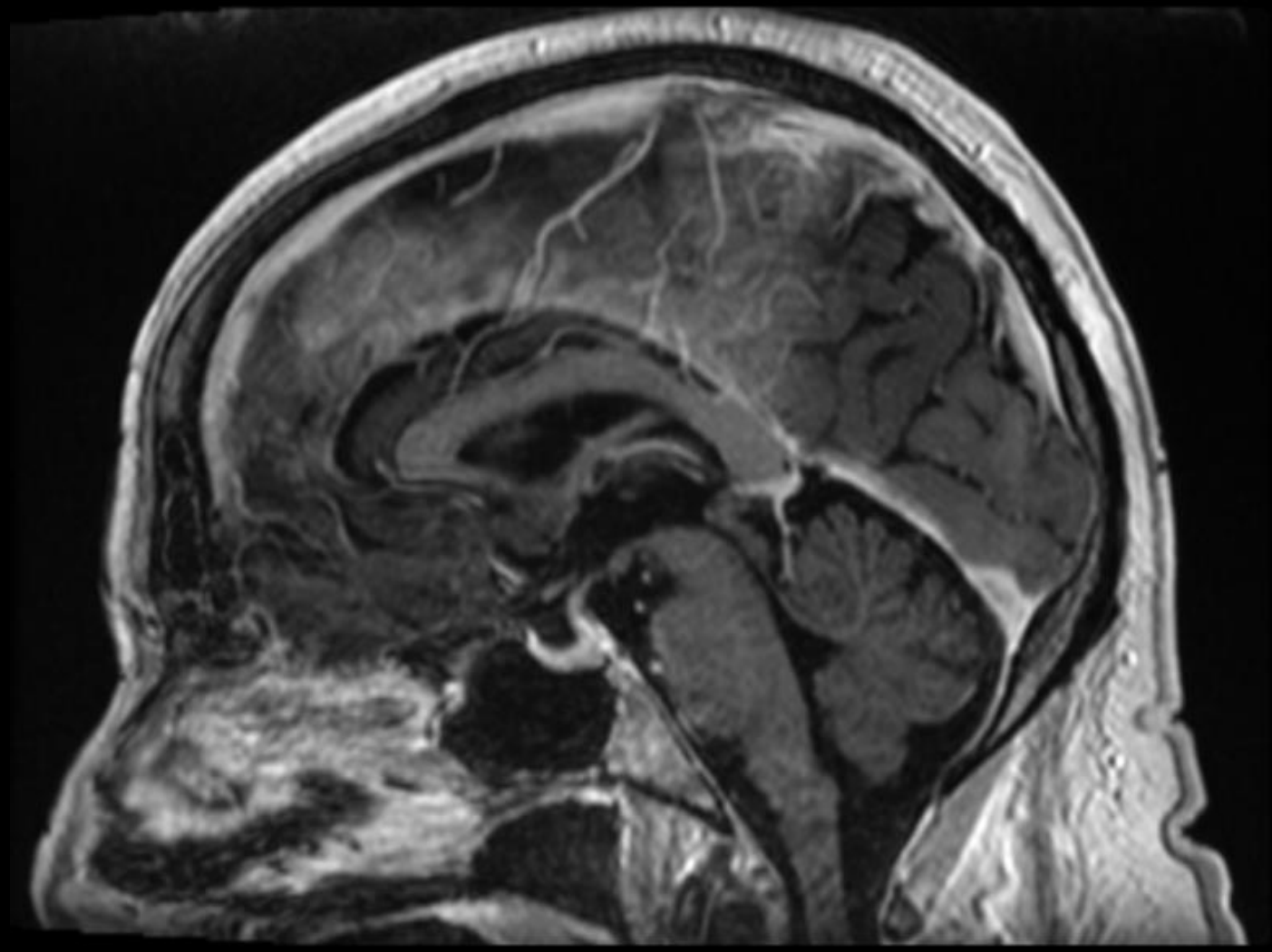
- New enlargement of pituitary compared to prior CT scan
- Heterogeneous enhancement with preserved posterior bright spot

Hospital Course

- Significant symptomatic improvement with hydrocortisone.
- Hydrocortisone held overnight and ACTH stimulation test
  - cortisol: 2.0 -> 11.0
- Kept on maintenance dose hydrocortisone
- Levothyroxine added
- Testosterone deferred for outpatient management

Follow-up

- Repeat ACTH levels fell to undetectable
- Low cortisol when hydrocortisone held
- Kept on levothyroxine given continued illness
- MRI enlargement persisted for 2 months but resolved by month 3
- Proceeded to SCT
- Eventually developed primary hypogonadism



Checkpoint Inhibitor Induced Hypophysitis

- Form of lymphocytic hypophysitis
  - Now becoming a leading cause of a rare condition
- Presents with acute hypopheseal/pituitary inflammation and anterior pituitary deficiencies
- In severe cases can have optic nerve compression
- Can lead to permanent deficiencies
- Difficult to classify in initial studies
  - Hypophysitis vs adrenal insufficiency vs hypothyroidism vs low TSH

Cancer adverse effect grading

- Common Terminology Criteria for Adverse Effects
  - Published by US Health & Human Services, NIH, NCI
  - Grades adverse effects on a 1-5 scale

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fasting glucose > 160 mg/dL	Fasting glucose 161-250 mg/dL	Fasting glucose 251-500 mg/dL	Fasting glucose > 500 mg/dL	Death

Primarily assesses **symptoms/lab abnormalities**
Immunotherapy induces an autoimmune attack which causes a **syndrome**

CTCAE v4.0

Immune-related adverse events (irAEs)

- Induction of autoimmunity due to decreased self tolerance
  - Normal proteins become antigens
  - Analogues of many autoimmune diseases have been reported
- Most treated with holding treatment and courses of steroids
  - Colitis
  - Arthritis
  - Dermatitis
- Endocrine irAEs tend to persist despite steroids
- Need a new way to define/describe these events

irAE Guidelines

- Published by American Society of Clinical Oncology in Feb 2018 to address these toxicities
- Grades developed for each known condition
  - Many are based more on symptoms than lab cutoffs
  - All expert consensus based – very little evidence
- General recommendations
  - Grade 1: continue with monitoring
  - Grade 2: hold treatment and follow until grade 1 or less. Consider steroids
  - Grade 3: hold treatment and start high dose steroids
  - Grade 4: permanently stop treatment and start high dose steroids
- General recommendations **DON'T** apply to endocrine conditions

Brahmer J, et al. "Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline" *J Clin Oncol* 36:1714-1768

Hypophysitis Grading

Grading	Management
G1: Asymptomatic or mild symptoms	Considering holding ICPi until patient is stabilized on replacement hormones Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight) Testosterone or estrogen therapy as needed in those without contraindications Endocrine consultation Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis Follow FT4 for thyroid hormone replacement titration (TSH is not accurate)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks

Brahmer J, et al. "Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline" *J Clin Oncol* 36:1714-1768

What about preexisting autoimmune disease?

- Often excluded from trials
- Some studies do suggest there is an increased risk of additional irAEs
- But is this a reason to hold treatment?
- No clear guidelines

Presentation – ipilimumab induced hypophysitis

- Series of 98 patients at Harvard
  - Headache 71%
  - Fatigue 62%
  - Nausea 39%
  - Dizziness 11 %
  - Altered mental status 9%
  - Myalgias 6%
- Timing of onset median 9.8 weeks (7.3-12.6)
- Radiographic pituitary enlargement in 88%
- Some pituitary deficiency in 93% at time of diagnosis
  - Gonadal 82%, Thyroid 78%, Adrenal 57%, low prolactin 51 %, IGF-1 17%, high prolactin 10%, Diabetes Insipidus 0%

Faje et al. “High-Dose Glucocorticoids for the Treatmetn of Ipilimumab Induced Hypophysitis is Associated with reduced Survival in Patients with Melanoma” Cancer(2018) 62:29-39 DOI 10.1016/j.intimp.2018.06.001

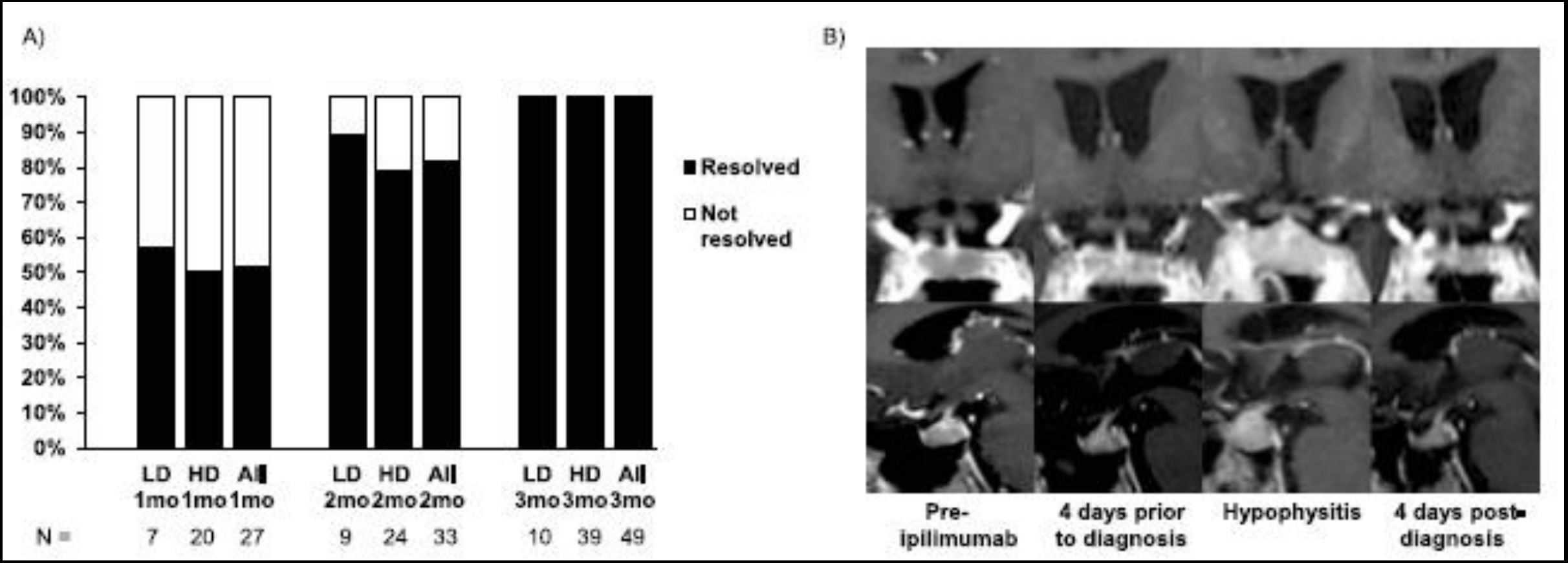
Workup

- ACTH & cortisol (ideally AM)
- TSH & free T4
- LH, FSH, & estradiol/Testosterone
- Serum sodium and urine SG/Osm if symptoms of DI present (rare)
- MRI pituitary
- Can assess prolactin, GH/IGF-1 but don’t provide much guidance

- ACTH stimulation test not recommended as part of initial workup: use with caution

Diagnosis

- MRI is time critical



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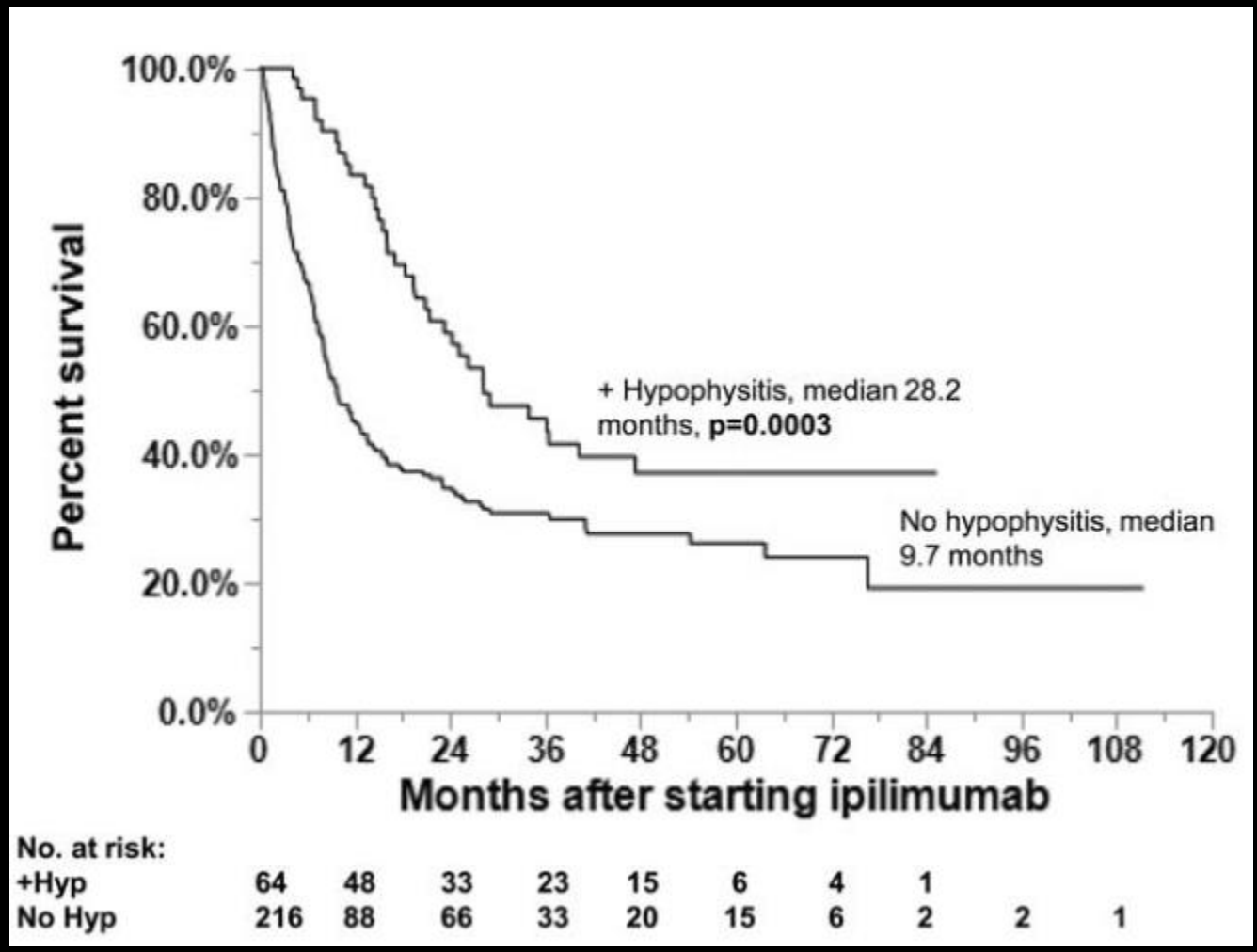
Incidence

- Meta-analysis of studies estimated:
  - Combination therapy: 6.4%
  - CTLA-4: 3.2%
  - PD-1: 0.4%
  - PD-L1: <0.1
- However, varies greatly by study and dose
  - Up to 18% in one study – using 10 mg/kg dose
- Underestimated in early studies?

Barroso-Sousa R, et al. “Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens A systematic Review and Meta-analysis” *Jama Oncol*. 2018;4(2):173-182

Outcomes

- As with many other CPI toxicities, there is an association with improved outcomes
- Includes patients who got high and low doses of steorids



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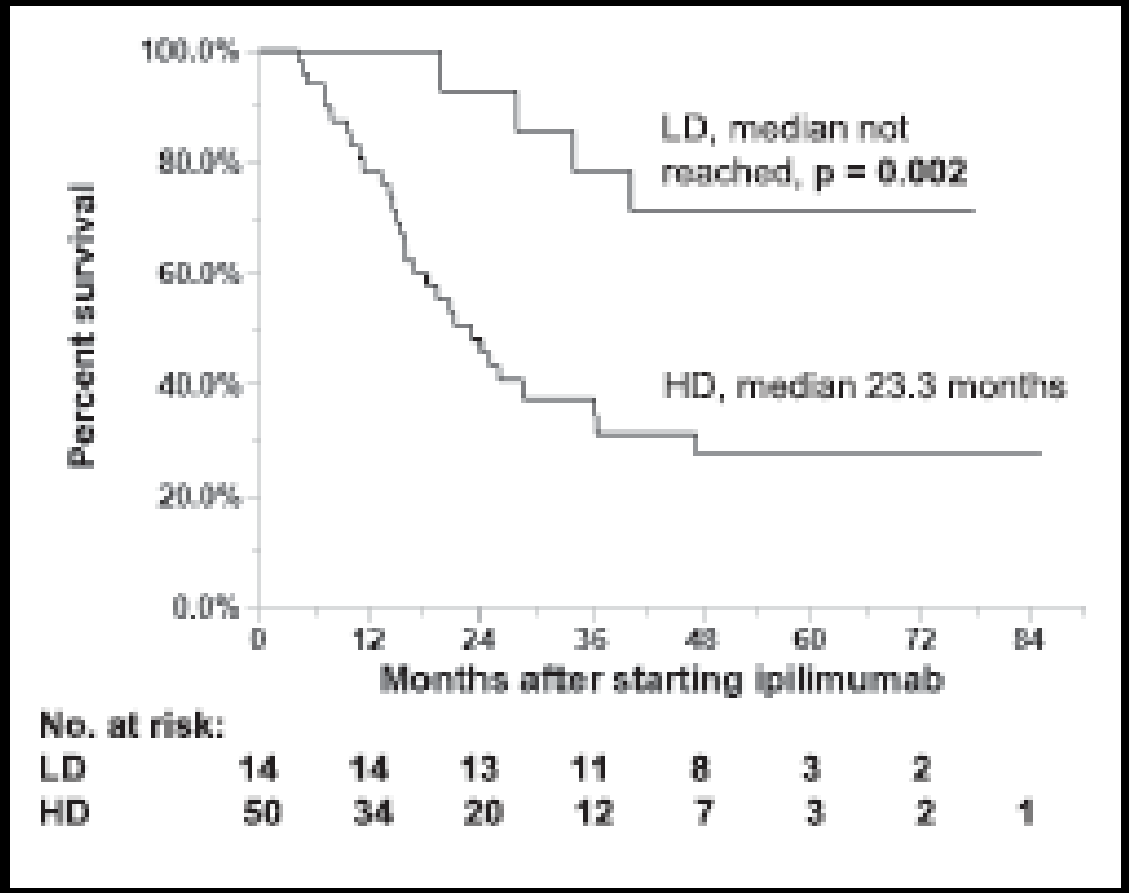
Treatment

- Not a clear benefit to high dose steroids
  - Recommended for severe headache, vision changes, or signs of optic nerve compression
  - Studies have not found an improvement in recovery of pituitary function
  - No randomized data
- Suggestion in the data that those given high dose steroids had worse survival



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Min L, et al “Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study” *Clin Cancer Res.* 2015 Feb 15;21(4):749-55

Should you hold treatment?

- Evidence suggests that holding checkpoint inhibitors also does not improve recovery of pituitary deficiencies
- Potential therapeutic benefit, given better outcomes in patients with toxicity
- Once on stable replacement hydrocortisone/levothyroxine and headache resolves ok to restart
- “damage is done”
- Still at risk of other irAEs

Min L, et al “Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study” *Clin Cancer Res.* 2015 Feb 15;21(4):749-55

Clinical Course/Recovery

- From same set of 98 patients
- 97% still had some pituitary deficiency:
  - 96% adrenal (57% at diagnosis)
  - 46% gonadal (82% at diagnosis)
  - 45% thyroid (78% at diagnosis)
  - 29 % low prolactin (51% at diagnosis)
  - 25 % high prolactin (10% at diagnosis)
  - 6 % growth hormone/IGF-1 (10% at diagnosis)
  - 0 % diabetes insipidus (0% at diagnosis)

Checked less frequently

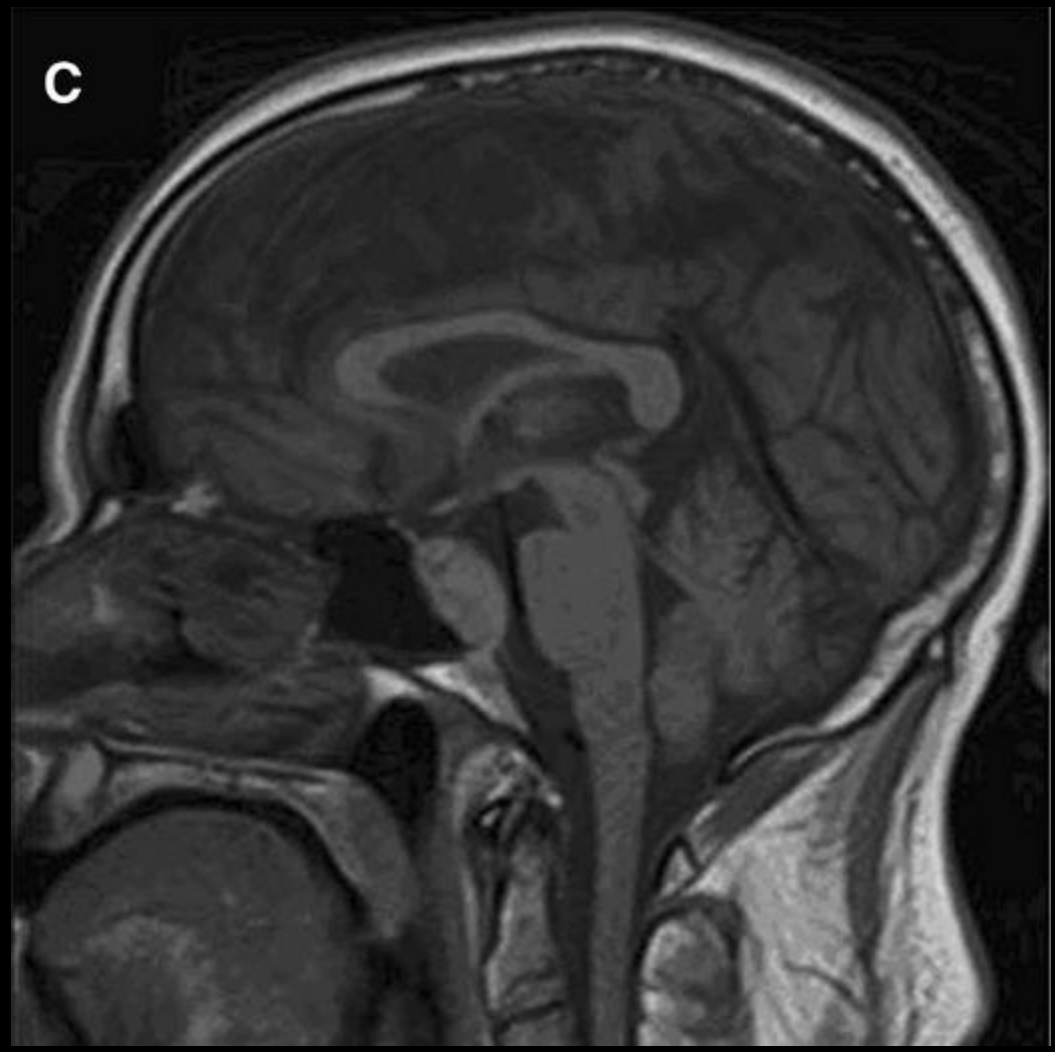
Faje et al. “High-Dose Glucocorticoids for the Treatmetn of Ipilimumab Induced Hypophysitis is Associated with reduced Survival in Patients with Melanoma” Cancer(2018) 62:29-39 DOI 10.1016/j.intimp.2018.06.001

Clinical Course/Recovery

- Continued need for steroids, need to convince oncology team that replacement hydrocortisone won’t interfere with immunotherapy
- Recovery of ACTH is unlikely
- Monitoring for recovery of thyroid and gonadal function
- Unclear if there is a difference between hypophysitis induced by CTLA-4 and PD-1/L1 inhibitors
- GH treatment typically not recommended in patients with active malignancy

Pitfalls in diagnosis

- Misinterpretation of labs
  - Inappropriate timing of cortisol
  - Low TSH – high dose steroids
  - Low T4 – euthyroid sick
- Steroids
  - For other irAEs
- Metastatic disease to pituitary
  - Primarily presents in the posterior pituitary with diabetes insipidus as most common symptom 42%



He W, et al. “Metastatic involvement of the pituitary gland: a systematic review with pooled individual patent data analysis” *Pituitary* (2015) 18:159-168

Case 2 – example of challenges

- 72 year old man with history of prostate cancer
- On levothyroxine for 23 years after total thyroidectomy for goiter
- On a treatment regimen of
  - Leuprolide acetate (Lupron) – suppresses LH/FSH/testosterone
  - Abiraterone (Zytiga) – prescribed with prednisone 5 mg twice daily
  - Apalutamide (Erleada) – can induce/worsen hypothyroidism
  - Ipilimumab
- Developed fatigue while on ipilimumab, had headache for 1 week
- Referred for MRI but declined due to travel arrangements

Case 2

Component	Latest Ref Rng & Units	10/8/2018	10/31/2018	11/11/2018	12/10/2018	12/31/2018	1/23/2019	2/10/2019	3/4/2019	3/25/2019
TSH	0.27 - 4.20 mcunit/mL	2.47		3.59	3.18	3.00	0.43	0.04 (L)	0.76	1.48
T4 Free	0.93 - 1.70 ng/dL		1.37	1.04	1.34	1.24	1.15	0.96	0.71 (L)	0.79 (L)
T3 Total	80 - 200 ng/dL		161	139		157	130	124	136	92
ACTH	7 - 63 pg/mL				122 (H)	148 (H)	40	3 (L)	2 (L)	1 (L)
Testoster Tot	193 - 740 ng/dL							<3 (L)		

MRI done on return 2 months later did not show hypophysitis

Does he have hypophysitis?

Summary

- Checkpoint inhibitor induced hypophysitis is seen most commonly with ipilimumab
  - More common with higher doses
  - Much less common with PD-1/ PD-L1 inhibitors
- Onset around 9 weeks, but can vary
- Residual deficiencies common, particularly ACTH
- No clear benefit and possible harm to high dose steroids
  - Use only if clearly indicated
- CTLA-4 inhibitors falling out of favor recently – more focus on PD1/L1

Case 3

- 54 y/o man with a longstanding cheek mole which became ulcerated
- Diagnosed as melanoma, resected without evidence of disease at margins
- 1 year later new lung nodule noted on chest x-ray
- Referred for CT: 1.6 cm R lower lobe nodule. CT guided biopsy confirms metastatic melanoma
- Diagnosed with type 2 diabetes and hypertriglyceridemia during this time

Case 3

- Enrolled in a clinical trial using epacadostat (IDO1) and durvalumab (anti PD-L1) every 2 weeks.
- On enrollment he had blood glucose of 290, had discontinued his diabetes medications, told to restart.
- 1 month later presents for cycle 3 with blood glucose 422 mg/dL
- Referred for urgent evaluation

Diabetes history

- Diagnosed ~1 year ago when he had high blood glucose and triglycerides at PCPs office
- Started on saxagliptin/metformin XR 5/1000 mg combination and vascepa 2 capsules twice daily
- Reports on this his blood glucose trended down to low to mid 100s, rarely 200s
- Ran out of medication the past week, he was taking twice daily instead of daily and ran out early
- Ate a carbohydrate heavy dinner (with beers) the night before

In office

- Repeat finger stick glucose: 299 mg/dL
- Point of care hemoglobin A1c: 8.2%
- Asymptomatic, feels these BG are out of the ordinary but they have been this high off of treatment in the past
- Last blood glucose on prior visit: 182 mg/dL

Labs

137	101	14	422
4.3	24	0.7	

BG spontaneously decreased to 260
Insulin: 18.4 mIU/mL (2-29.1)
C-peptide: 2.6 ng/mL (0.9-7.1)

Case 3

- No outside records available
- Given insulin in clinic for acute hyperglycemia, new prescription for maximum dose saxagliptin and metformin
- Told to start today, contact us if BG don’t normalize
- Warned about DKA symptoms
- Blood sugars improved the following day and received his scheduled treatment

10 days later

- Presented to local ED with persistent nausea vomiting
- Bicarbonate: 9 mEq/L
- Anion Gap: 34
- 4 + urine ketones
- Given fluids, IV insulin and 10 units of glargine
- Discharged home with metformin and glipizide (didn’t fill)

2 days later

- Returned to local Emergency Department
- Bicarbonate: 5 mEq/L
- Kept on insulin drip and discharged home with Determir 10 units twice daily
- Returned for follow-up 1 week later
- C-peptide: <0.1 ng/mL
- Anti-GAD65: 0.12 nmol/L (<0.02)
- Anti-IA-2: negative
- Repeat C-peptide 10 months later: <0.1

Checkpoint inhibitor induced diabetes

- No clear diagnostic criteria or guidelines
- Variable presentation, time of onset, antibody status, HLA haplotypes
- Tentative criteria
  - New onset or acutely progressive diabetes
  - Presentation with DKA is highly suggestive but not required
  - Clinical evidence of insulin deficiency/dependence

DKA

15 4/25/2016 0853	14 5/6/2016 1003	13 5/20/2016 0856	12 6/6/2016 0815	11 6/21/2016 1345	10 7/6/2016 1404	9 7/20/2016 0727	8 8/1/2016 1324	7 8/12/2016 1448	6 9/6/2016 0944
98 *	93 *	99 *	93 *	113 * ▲	103 *	91 *	100 * ▲	117 * ▲	285 * ▲

Early Reports of diabetes related to PD-1

- Initial case series reported in 2015
  - 5 patients with acute onset diabetes
  - 3/5 had positive antibodies, all had high risk HLA haplotypes
- Theorized due to prior studies on NOD mice
- Early cases missed? Hyperglycemia categorized by CTCAE as an AE but no criteria for diabetes.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fasting glucose > 160 mg/dL	Fasting glucose 161-250 mg/dL	Fasting glucose 251-500 mg/dL	Fasting glucose > 500 mg/dL	Death

- No clear cases of DM on CTLA-4 monotherapy

Hughes J, et al. Diabetes Care 2015 vol 38
CTCAE v4.0

MD Anderson Data

- Patients referred to the Endocrinology service at MD Anderson with new onset or progressive hyperglycemia on ICIs
- Included if they were felt to meet criteria by treating endocrinologist
- Cases independently reviewed by 2 other endocrinologists in the practice and excluded if there was not agreement
- 32 cases
- Collected between 4/2014 and 6/2018
- 8.9 months median follow-up

Patient Demographics	n=32
Median age at presentation (range)	62 (32-83)
Male (%)	23 (72)
Caucasian (%)	26 (81)
Median BMI at presentation (range)	25.7 (19.9-36.2)
Cancer Type (%) • Melanoma • Renal cell carcinoma • Lung • Prostate cancer • Other	 14 (44) 5 (16) 3 (9) 2 (6) 8 (25)
ICI Type • Anti PD-1 monotherapy • Anti PD-L1 monotherapy • Combination immunotherapy • Immunotherapy + systemic chemotherapy	 17 (53) 0 13 (41) 2 (6)

Other Cancer Types: glioblastoma, rectal, angiosarcoma, esophageal, hepatic, ovarian, parotid, adenocarcinoma with unknown primary

Onset of Diabetes – Our patients

- Median time to onset of diabetes: 12.3 weeks (range 1-67.3)
- Trend towards more rapid onset in patients with combination therapy
  - Median 14.3 weeks on single agent vs 6 weeks on dual immunotherapy (p= 0.07)
- All patients require insulin at diagnosis
- 77% reported some symptoms of diabetes prior to diagnosis
- At 31 patients: 3962 patients received PD-1/PD-L1 inhibitors: 0.78%
- Similar to series by Stamatouli et al (27 pts): 0.9%

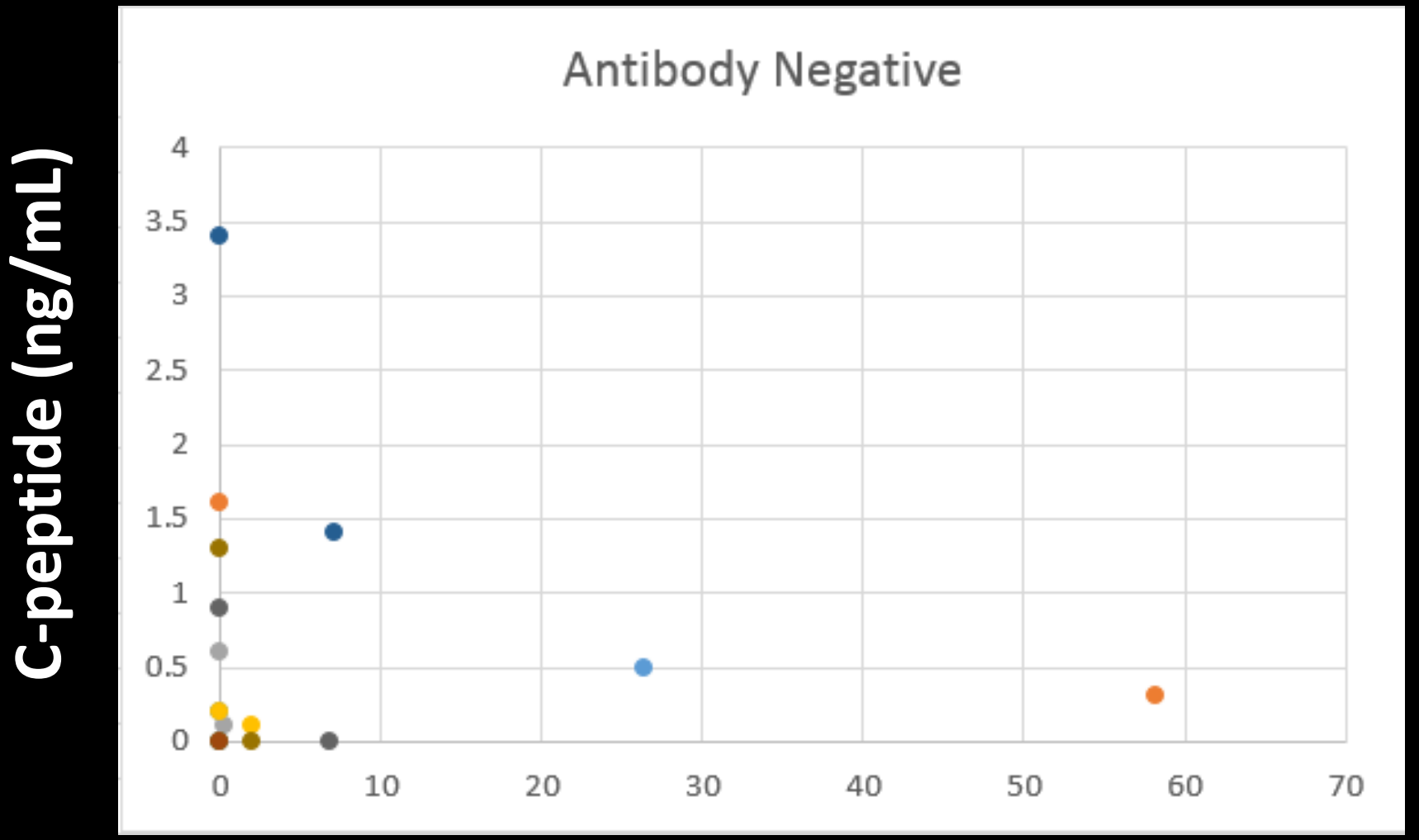
Stamatouli A, et al “Collateral Damage: Insulin-Dependent Diabetes Induced with Checkpoint Inhibitors” *Diabetes* 2018;67:1471-1480

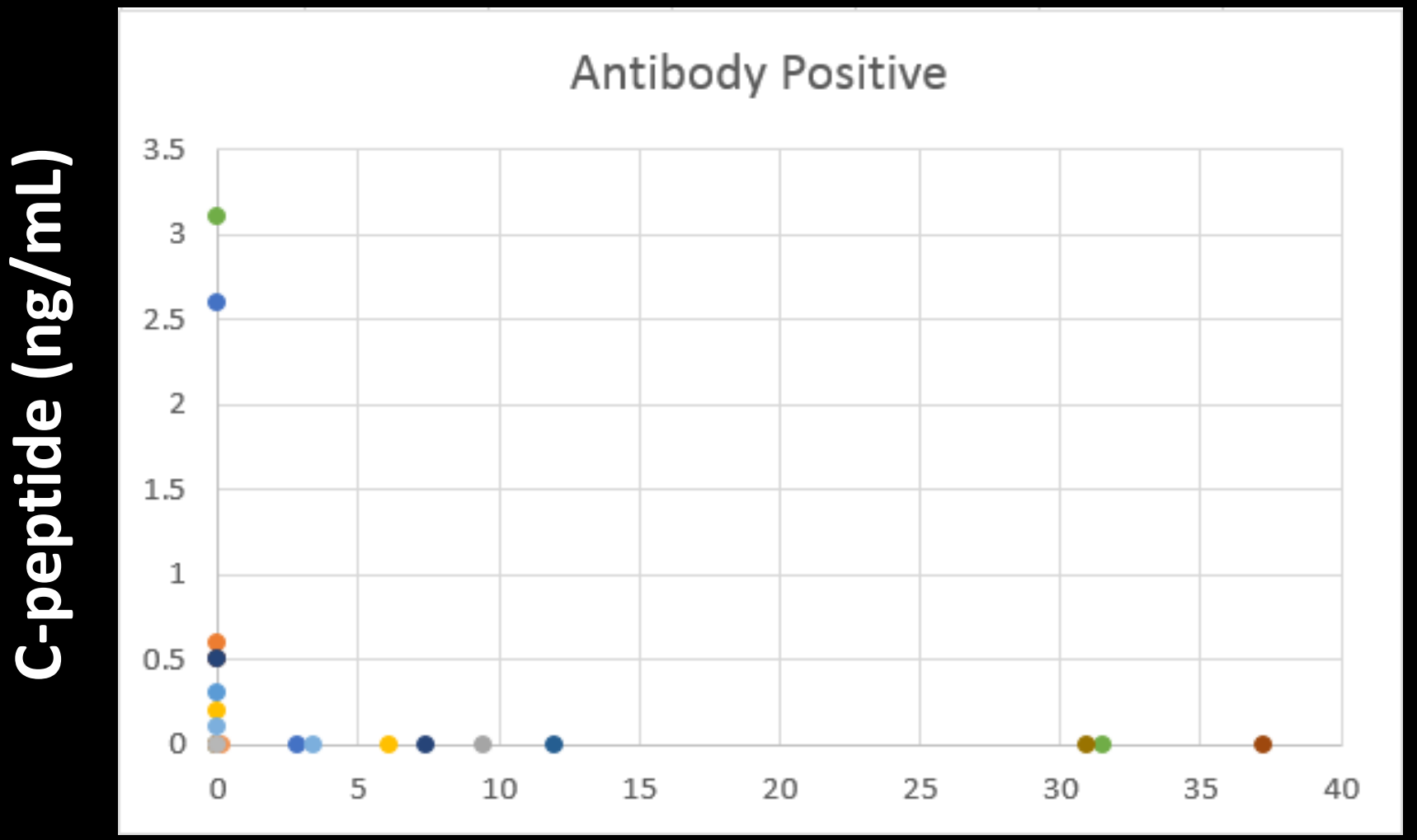
DKA – Our patients

- Overall 20 of 32 patients presented with DKA (62.5%)
- Rate depended on severity of hyperglycemia on presentation
  - CTCAE Grade 3 (BG 250-500 mg/dL)
    - 2 out 7 (28%) presented with DKA
  - CTCAE Grade 4 (BG > 500 mg/dL)
    - 18 of 25 (72%) presented with DKA
- One case of euglycemic DKA in a patient started on SGLT-2 inhibitors by his PCP for worsening hyperglycemia which delayed diagnosis
- Amylase/Lipase checked on presentation in 19/32 patients (59%)
  - Positive in 6/19 (32%)

C-peptide Levels

- C-peptide levels were assessed in 31 patients (97%)
  - Undetectable (<0.1) in 12 (39%)
  - Low (<0.9 ng/mL) but detectable in 13 (42%)
  - In normal range (0.9-7.1 ng/mL) in 6 (19%)
- Many drawn while acutely hyperglycemic on presentation
- Follow-up c-peptide levels assessed in 20 patients
  - Undetectable in 14 (70%)
  - Low but detectable in 6 (30%)
  - 18/20 had a decline in value
- All patients with Ab had undetectable f/u c-peptide


Antibody Negative
C-peptide (ng/mL)
Time (weeks)
4
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
40
50
60
70


Antibody Positive
C-peptide (ng/mL)
3.5
3
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
30
35
40
Time (weeks)

Presentation

- Can be very rapid after detection of hyperglycemia
- Often, not detected at visits and DKA can be presenting symptom
- Early identification can prevent progression to DKA, but must intervene immediately
- Some patients have more gradual onset and preceding mild hyperglycemia

	20 3/16/2016 1326	19 4/5/2016 0724	18 4/19/2016 0832	17 5/3/2016 0846
CHEM PROFILE				
Glucose Level	95 *	120 * ▲	156 * ▲	445 * !!

Grading

Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value > 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology

- Groups all diabetes together – type 1 and type 2

Brahmer J, et al. “Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline” *J Clin Oncol* 36:1714-1768

Management

- Basal/bolus insulin
- No clear evidence of recovery in any cases
  - Can restart treatment when patient is stable
- No data on starting steroids specifically for diabetes
  - No suggestive data from studies on Type 1 Diabetes
  - Multiple cases of patients developing diabetes with low c-peptide while on steroids for other irAEs

Monitoring recommendations

- Glucose at each treatment cycle for the first 12 weeks then every 3-6 weeks thereafter
- Education of oncology teams is critical
  - Patient awareness of symptoms of hyperglycemia
- Immediate initiation of insulin for patients with any concern for new onset hyperglycemia while on PD-1/L1 inhibitors
- Time of onset can vary widely, including after treatment

Case 4

- 34 year old man from South Korea with history of chronic hepatitis B and metastatic HCC
- Prior treatment with surgery/ablations and a clinical trial using sorafenib with an experimental anti-endoglin antibody
- Due to progression enrolled in a clinical trial using nivolumab and mogamulizumab (anti-CCR4)
- A1c 4.9% on screening labs for his trial

Case 4

- Presented for clearance for cycle 4 after 9 weeks
- New onset hyperglycemia to 208 mg/dL
- Lipase elevated to 1034
- No acidosis or anion gap
- CT showed interval response with no pancreatitis noted
- Follow-up 1 day later
  - Some increase in chronic myalgias but otherwise no reported complaints
  - Elevated lipase and glucose noted, felt likely related but not an exclusion criteria by study design (both grade 2 AEs)

Case 4

- That evening presented to local ED with progressive nausea and abdominal pain
- BG now elevated to 439
- Acidotic with CO_2 of 15, anion gap of 34
- Hemoglobin A1c: 5.3%
- Treated for DKA and discharged on basal/bolus insulin
- Follow-up c-peptide levels 1 and 3 months later <0.1 ng/mL

Can we predict who will develop?

- Antibodies
  - Present in around 50% of patients
- HLA typing
  - 17 of 27 patients in case series by Stamtouli et al had testing performed
  - 9 of 17 patients (53%) had a high risk HLA haplotype
- At present time – would patients decline therapy?
  - Potentially more options in the future

Stamatouli A, et al “Collateral Damage: Insulin-Dependent Diabetes Induced with Checkpoint Inhibitors” *Diabetes* 2018;67:1471-1480

Antibody Positivity – our patients

- At least 1 antibody assessed in 94% of patients

Antibody	Assessed (% of total)	Positive (% of tested)
GAD65	30 (94)	15 (50)
Insulin	26 (81)	2 (8)
Islet Cell	23 (72)	1 (4)
Zinc Transporter 8	4 (12.5)	0

- No significant difference in time to onset of DM

Summary

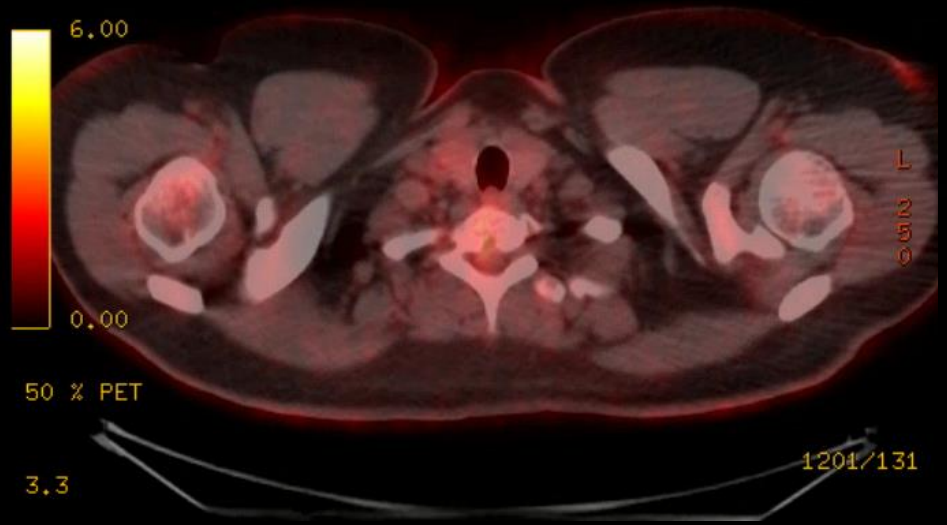
- Checkpoint inhibitors can cause a rapid onset hyperglycemia
- Onset can be at any time, including after treatment finished
- So far only clearly reported with PD-1/PD-L1 inhibitors (pembrolizumab, nivolumab)
- Over half of patients present in DKA
- Insulin should be started immediately if there is any concern for CPI induced diabetes
  - C-peptide and antibodies can guide therapy but are not diagnostic
- No clear cases of recovery, need insulin long-term
- Those with high risk HLA haplotypes may be at higher risk

Case 5

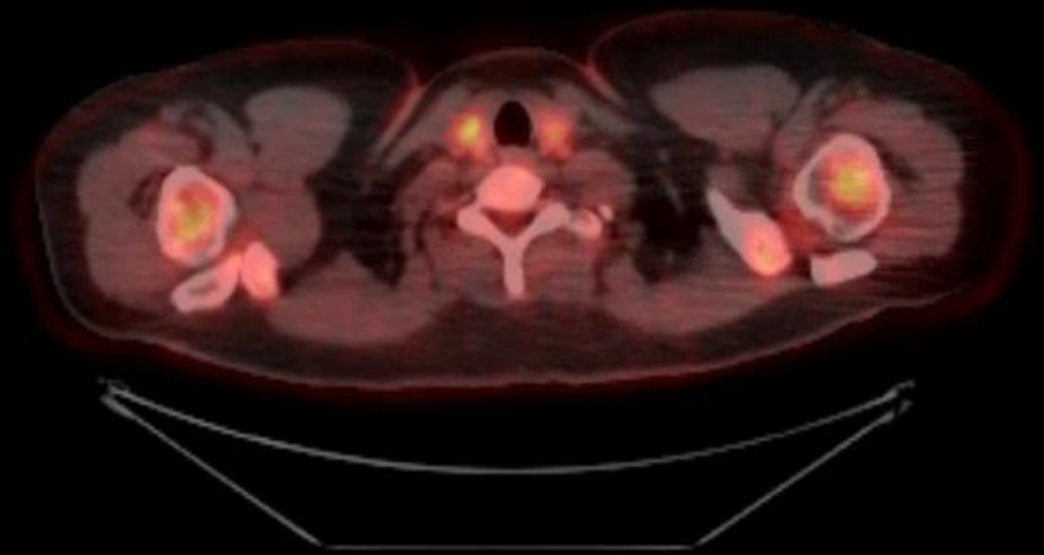
- 41 y/o man with a history of metastatic alveolar soft part sarcoma
- On dual checkpoint inhibitors with durvalumab (PD-1 inhibitor) and tremelimumab (CTLA-4 inhibitor)
- Previously had colitis, treated with high dose steroids, now resolved and restarted on treatment
- No prior history of thyroid disease

Case 5

11/2016



3/14/2017



	2/16/2017 1121	3/14/2017 0725	4/12/2017 0727	5/9/2017 1048	5/18/2017 0740	5/23/2017 0841	6/21/2017 0946
TSH	3.05	0.29	0.01	<0.01	0.10	2.12	119.90
T3 Total							21 *
T3 Free		4.6 *	3.5 *	4.1 *	2.7 *	1.6 *	0.9 *
T4 Free	1.15	1.70	2.21	1.83	1.00	0.67	0.14

Case 5

- No symptoms at all phases of hyper/hypothyroidism
- Now on 1.54 mcg/kg/day with stable levels
- Able to continue therapy with continued cancer response

Thyroiditis Presentation

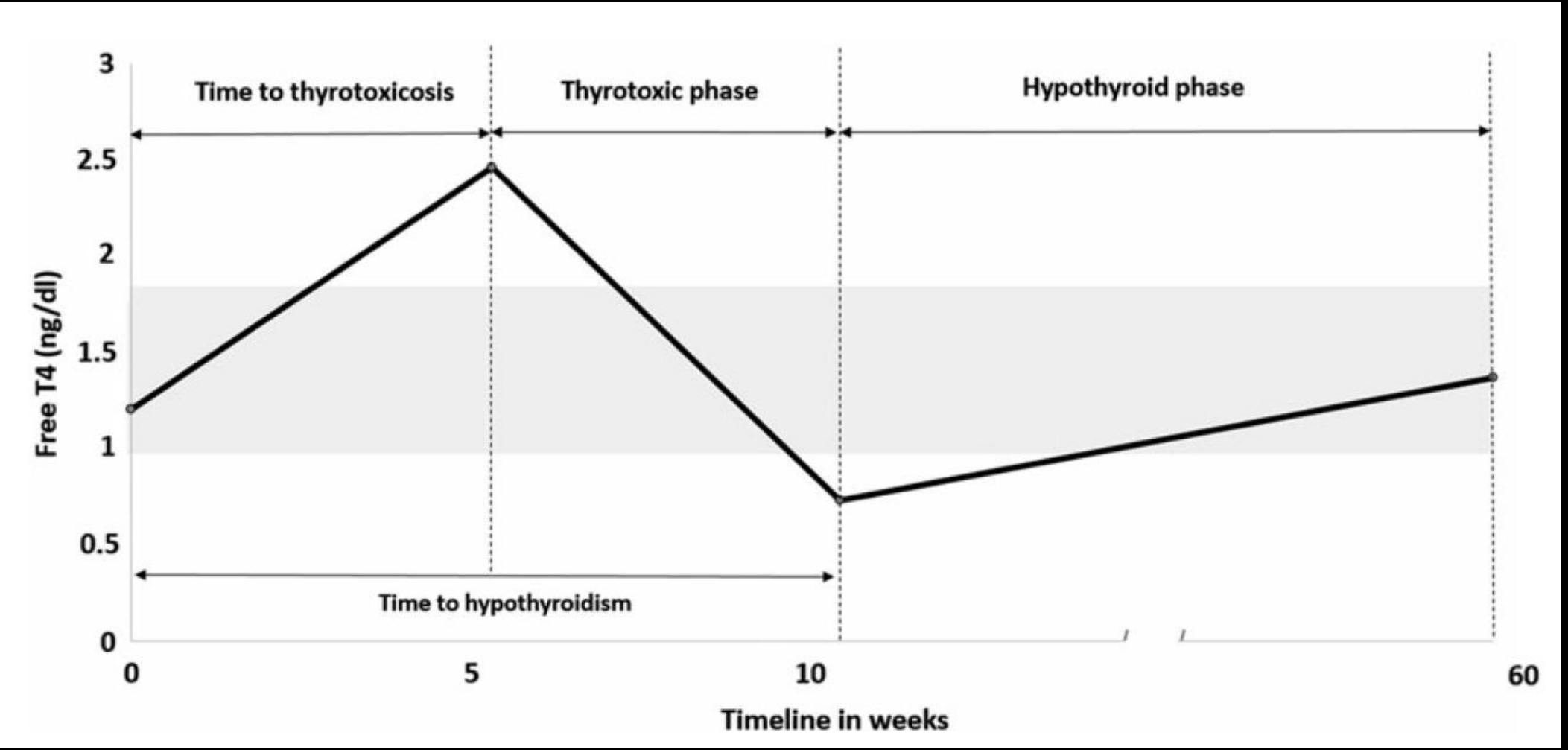
- Has been difficult to define in studies
  - Hyperthyroidism vs Hypothyroidism vs Thyroiditis
- In our experience at MD Anderson:
  - Majority of patients present with a brief hyperthyroid phase
  - Most of these patients are minimally symptomatic
  - In most, there is a rapid progression to overt hypothyroidism
  - Most will require relatively high replacement levothyroxine (1 - 1.6 mcg/kg/day)
  - All thyroiditis has been painless

MD Anderson Experience

- 56 (8.5%) of 657 patients treated with CPIs over the study period (Nov 2014 – July 2016)
  - 4 hypothyroidism without evidence of thyroiditis
  - 2 Graves' disease
  - 6 underlying thyroid disorder before therapy
  - 1 lack of baseline labs
- 43 of 56 (77%) showed some evidence of thyrotoxicosis
  - 37 (86%) of these developed hypothyroidism
- Symptoms present during thyrotoxic phase in 33%, in hypothyroid phase in 14%
- Only 1 case on CTLA-4 monotherapy (tremelimumab)

Iyer P, et al "Immune-Related Thyroiditis with Immune Checkpoint Inhibitors" *Thyroid* 2918 Oct;28(10):1243-1251

Time Course of Thyroiditis



Iyer P, et al "Immune-Related Thyroiditis with Immune Checkpoint Inhibitors" *Thyroid* 2918 Oct;28(10):1243-1251

Grading - hypothyroidism

4.1 Thyroid

4.1.1 Primary hypothyroidism

Definition: Elevated TSH, normal or low FT4

Diagnostic work-up

TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients

Grading	Management
G1: TSH < 10 mIU/L and asymptomatic	Should continue ICPi with close follow-up and monitoring of TSH, FT4
G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2

Brahmer J, et al. "Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline" *J Clin Oncol* 36:1714-1768

Grading - hyperthyroidism

4.1.2 Hyperthyroidism

Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine

Diagnostic work-up

Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients

Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy)

Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism

Grading	Management
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until symptoms return to baseline Consider endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).

Imaging

- Not usually needed
- Studies have shown findings consistent with thyroiditis in most cases
  - 11 patients underwent ultrasounds – 7 had findings consistent with thyroiditis
  - 7 patients underwent nuclear medicine studies – all consistent with thyroiditis
- Iodine/Technetium uptake can be helpful in cases where diagnosis is unclear
  - Prolonged hyperthyroid phase or any findings concerning for Graves'
  - Cancer patients often have relatively high iodine exposure from repeated CT scans with iodine contrast

Iyer P, et al "Immune-Related Thyroiditis with Immune Checkpoint Inhibitors" *Thyroid* 2918 Oct;28(10):1243-1251

Treatment

- Supportive through hyperthyroid phase – beta blockers
- No clear indication for methimazole unless there is evidence of increased thyroid hormone synthesis (Graves)
- Consider prednisone and empiric methimazole/PTU for severe/life threatening
- Average levothyroxine requirement 1.2 mcg/kg/day
- Aggressive/early dosing of levothyroxine recommended
- Steroids don’t seem to have much effect on outcomes
- Recovery is unclear – most patients not assessed

Ma C, et al “The impact of high-dose glucocorticoids on the outcome of immune checkpoing inhibitor-related thyroid disorders” Published online ahead of print cancerimmunolres.aacrjournals/org DOI: 10.1158/2326-066.CIR-18-0613

Other Rare Conditions

- Primary Adrenal Insufficiency
- Hypoparathyroidism
- Autoimmune insulin resistance
- Autoimmune lipodistrophy

Summary

- Checkpoint inhibitors function by removing safeguards on the immune system to trigger an attack against cancer “neoantigens”
- This lowers the threshold for immune self tolerance and can induce autoimmune syndromes
- Endocrine autoimmune syndromes tend to be less responsive to steroids and cause permanent hormone deficiencies
- In general, treatment can be restarted once the patient is stable on hormone replacement
- Knowledge of these syndromes by oncologists and endocrinologists can improve patient safety

MDA Oncologic Endocrinology Fellowship Program

- First of its kind; established in 2012
- Develop expertise in evaluation & management of endocrine neoplasias
- Understand the research developments in thyroid cancer & other endocrine neoplasias
- Expand the understanding of managing endocrine complications of cancer patients

Program Director: Mimi Hu, MD (mhu@mdanderson.org)

Thank You!

- cjbest@mdanderson.org