THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"A 57-year-old man on immunotherapy for metastatic melanoma presenting with fatigue"

Dr. Doycheva does not have any relevant financial relationships with any commercial interests.

OBJECTIVES

- Review endocrine toxicities of immune checkpoint inhibitors
- Discuss potential causes of hyponatremia in secondary adrenal insufficiency
- Review treatment of overly corrected hyponatremia

HPI

- 57yo man with a h/o metastatic melanoma presents to the ED on 9/9/2020 with marked fatigue for the last 2 weeks and watery diarrhea with 5-6 BM/day for the last 5 days. Denies fever, chills, nausea, vomiting, abdominal pain, headache, visual disturbances. Has lost 3-4 lbs for the last month.
- Evaluated at an OSH 2 days prior to current presentation due to similar symptoms. Labs at that time were significant for Na 123, received 2 L 0.9% NaCl and was discharged home with salt tablets that he never took. Symptoms persisted and he called his oncologist who referred him to the ED.

Oncologic history

- Diagnosed with melanoma of R the ring finger in July 2019, R axilla LN biopsy was positive for metastatic melanoma (stage III C, pT4bN1a). Underwent partial finger amputation 8/14/2019
- Started on Nivolumab 9/27/2019, after the 3rd cycle noted to have TSH 5.6, no therapy, after the 5th cycle → TSH 7.8, fT4 0.95 and started on levothyroxine 137 mcg/d for ICI-induced hypothyroidism
- CT chest on 7/2/2020 with numerous metastatic pulmonary nodules, biopsy confirmed metastatic melanoma and on 8/11/2020 therapy was changed to Nivolumab / Ipilimumab (received 2 cycles, last 9/1/2020)

Other history and medications

- Past Medical History: hyperlipidemia
- Past Surgical History: 4th R finger amputation
- Medications: none
- FH: melanoma in father and sister; CRC in mother; negative for thyroid disease

Physical exam

- PE: T 97.5, HR 84 bpm; BP 109/68, O2 Sat 93%, Wt 84 kg, BMI 26
- In no acute distress, HEENT: EOMI, dry mucous membranes; No thyromegaly; Lungs: CTA, CVD: RRR, No hepatosplenomegaly, no pedal edema

- What is the differential diagnosis?
- What tests should I order?

Labs

- **LABS**

	9/1/20	9/9/20
Sodium	132	119
Potassium	5.2	3.9
Chloride	99	88
Bicarbonate	24	24
BUN	6	4
Creatinine	0.9	0.8
Calcium	9.4	9.2
Albumin	3.8	3.9
Glucose	89	168

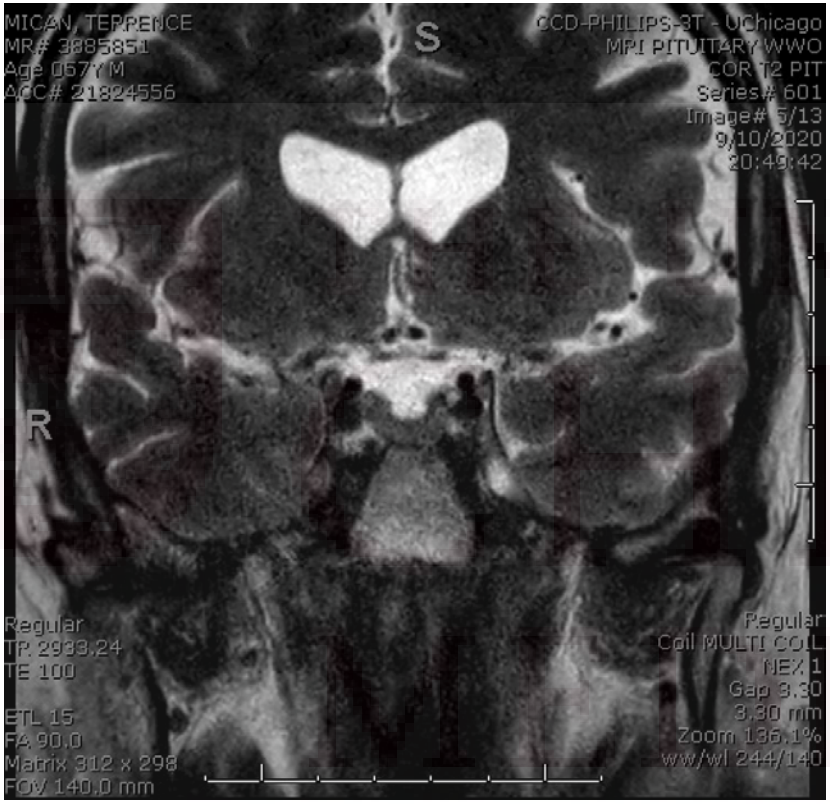
	9/9/20
Cortisol	<0.2
ACTH	<3.0
Aldosterone	5.1
Renin	<0.6
Ser osmolality	257
Urine Na	73
Urine osmolality	418
fT4	1.02
TSH	1.14

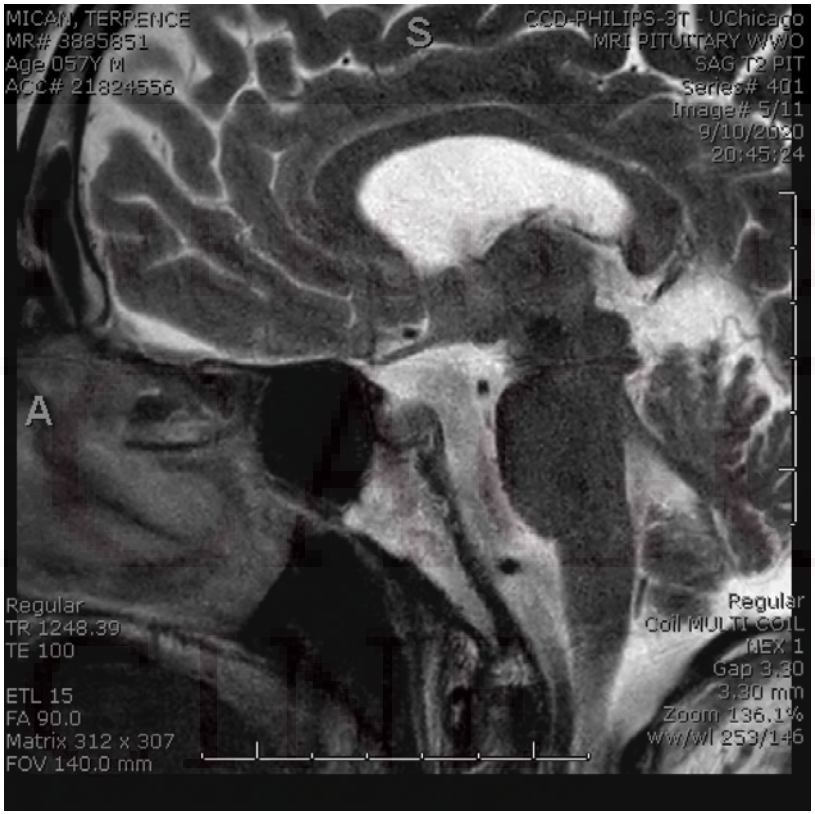
- What is the diagnosis?
- Do we need additional tests?
- What treatment: dose, IV or po?

Our recommendations

- Hydrocortsione 50 mg IV once, received 1 L NS in the ED
- Continue with hydrocortisone 40 mg AM and 20 mg in the afternoon starting the following day
- Monitor Na q 6 h
- Obtain pituitary MRI

MRI of our patient



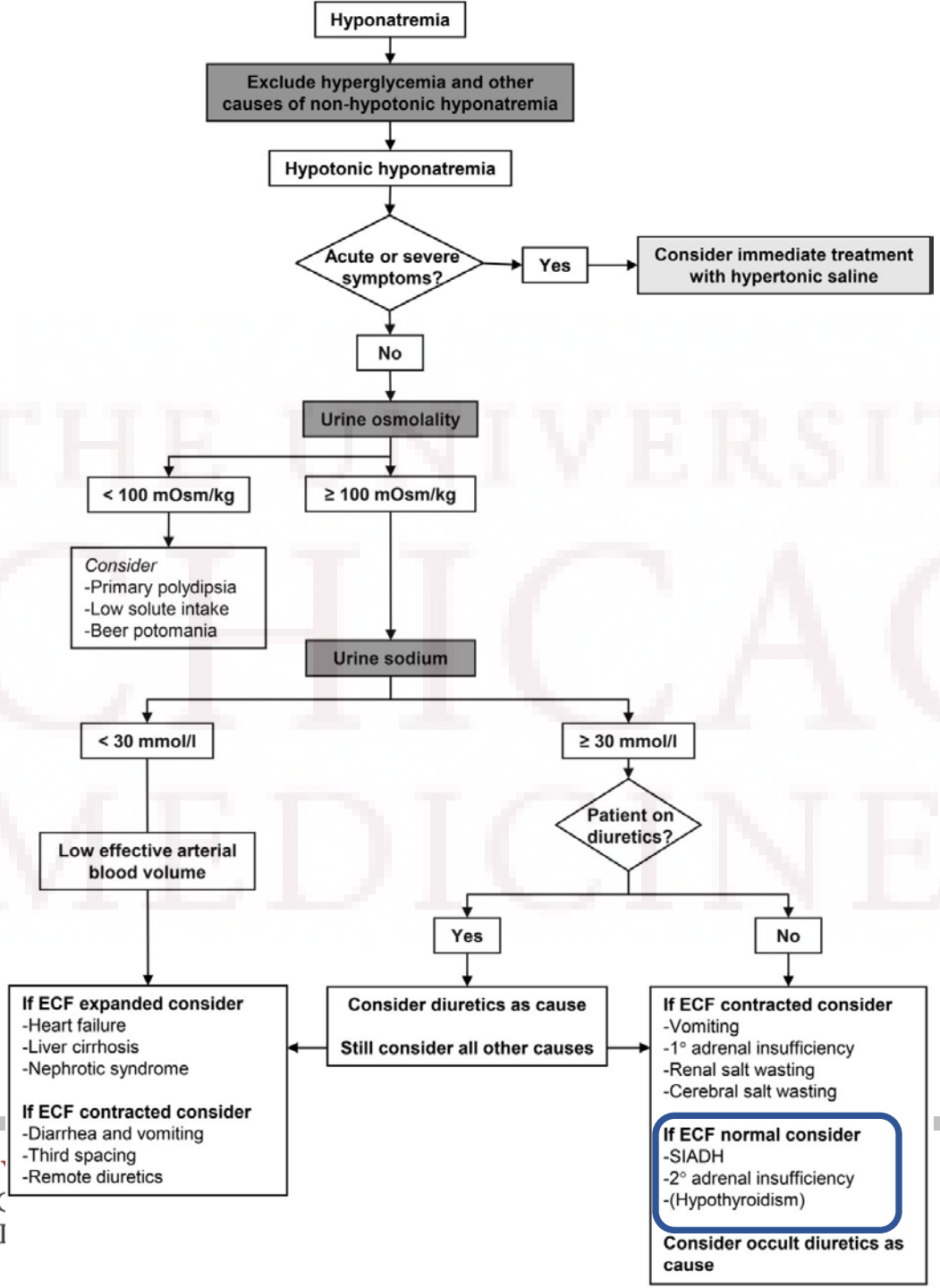


No discernable pituitary abnormality.

Labs

	9/1	9/9 11am	9/9 5pm	9/9 11pm
Sodium	132	119	121	118
Potassium	5.2	3.9	4.1	4.2
Chloride	99	88	90	89
Co2	24	24	24	18
BUN	6	4	5	6
Creatinine	0.9	0.8	0.8	0.8
Ser Osmolality		257		

What is the etiology of hyponatremia?


Hyponatremia
Exclude hyperglycemia and other causes of non-hypotonic hyponatremia
Hypotonic hyponatremia
Acute or severe symptoms?
Yes
Consider immediate treatment with hypertonic saline
No
Urine osmolality
< 100 mOsm/kg
≥ 100 mOsm/kg
Consider
-Primary polydipsia
-Low solute intake
-Beer potomania
Urine sodium
< 30 mmol/l
≥ 30 mmol/l
Low effective arterial blood volume
Patient on diuretics?
Yes
No
If ECF expanded consider
-Heart failure
-Liver cirrhosis
-Nephrotic syndrome
If ECF contracted consider
-Diarrhea and vomiting
-Third spacing
-Remote diuretics
Consider diuretics as cause
Still consider all other causes
If ECF contracted consider
-Vomiting
-1° adrenal insufficiency
-Renal salt wasting
-Cerebral salt wasting
If ECF normal consider
-SIADH
-2° adrenal insufficiency
-(Hypothyroidism)
Consider occult diuretics as cause

Hyponatremia in secondary adrenal insufficiency (SAI)

- Vasopressin secretion is tonically inhibited by glucocorticoids
- SAI is associated with increased vasopressin release despite plasma hypoosmolality → inappropriate antidiuresis
- Glucocorticoid deficiency could also modify renal sensitivity to vasopressin thus amplifying the inability to exclude a free water load
- Hydrocortisone replacement rapidly corrects hyponatremia !

Labs

	9/1	9/9 11am	9/9 5pm	9/9 11pm	9/10 4am	9/10 8am	9/10 10 am	9/10 5pm
Sodium	132	119	121	118	128	132	127	135
Potassium	5.2	3.9	4.1	4.2	4.7	4.4	4.4	4.4
Chloride	99	88	90	89	98	100	99	104
Co2	24	24	24	18	22	23	21	21
BUN	6	4	5	6	5	5	5	6
Creatinine	0.9	0.8	0.8	0.8	0.8	0.8	0.7	0.8
Ser Osmolality		257					273	

24 Urine output 3.5L

The most common thresholds for correction of hyponatremia are:

1) <10-12 mEq/L in the first 24h and < 18 mEq in the first 48h

2) < 8 mEq/L in any 24h period

My patient's Na corrected 14 mEq/L in 24h, but no symptoms. Should I do something?

Labs

	9/1	9/9 11am	9/9 5pm	9/9 11pm	9/10 4am	9/10 8am	9/10 10 am	9/10 5pm	9/10 11pm	9/11 4 am
Sodium	132	119	121	118	128	132	127	135	133	138
Potassium	5.2	3.9	4.1	4.2	4.7	4.4	4.4	4.4	4.3	4.1
Chloride	99	88	90	89	98	100	99	104	102	104
Co2	24	24	24	18	22	23	21	21	23	23
BUN	6	4	5	6	5	5	5	6	6	6
Creatinine	0.9	0.8	0.8	0.8	0.8	0.8	0.7	0.8	0.8	0.8
Ser Osmolality		257					273			

Given D5W 6 ml/kg

Day #2

Patient's wife reports he seemed mildly confused on the phone that morning and he feels his mind is not clear

No change in physical exam, no change in mental status, no dysarthria or ocular abnormalities

How to treat now?
What to do with steroid dose?

Follow up management: day #2

- DDAVP 1 mcg sc every 6 h (for 2 doses) + D5W 250 cc once and then 83 cc/h
- Decreased the dose of hydrocortisone to 20 mg +10 mg

Labs

	9/11 8am	9/11 12pm	9/11 3pm	9/11 7pm	9/11 10 pm	9/12 4am	9/12 12 pm
Sodium	138	135	138	138	138	136	131
Potassium	4.4	4.1	4.2	3.7	4.0	3.7	4.2
Chloride	105	103	104	105	104	101	96
Co2	22	23	24	16	25	24	25
BUN	6	5	5	8	9	9	9
Creatinine	0.8	0.8	0.8	0.9	0.9	0.9	0.8

MRI brain 9/11
no acute abnormalities

	9/9	9/10	9/12
Urine osmolality	418	< 100	360
Urine Na	73	<30	54

Risk factors for osmotic demyelination syndrome: causes of autocorrection

- Administration of saline in true volume depletion
- Administration of steroids in AI
- Discontinuation of drugs that cause SIADH
- Spontaneous resolution of SIADH
- Treatment with vasopressin receptor antagonists

Recommendations of ASN for relowering overly rapid corrected hyponatremia

- Consider in patients with severe hyponatremia (<120 at presentation) of chronic (>48h) or unknown duration
- Goal is to bring Na just under the correction limit
- The best option is coadministration of desmopressin and D5W. Desmopressin is given at a dose of 2-4 mcg IV or SC every 6-8h. D5W is administered at 3 ml/h → ↓ Na ~1 mEq/L per hour
- Once target is achieved, consider stopping D5W, but continuing desmopressin to prevent further correction

Which strategy is the best?

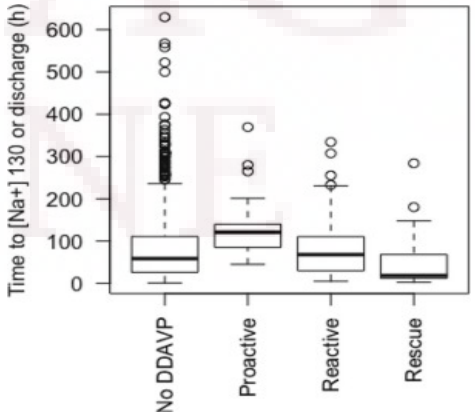
- Retrospective study of 1450 admissions for hyponatremia investigated 3 strategies:

- proactive (desmopressin and hypertonic saline);

- reactive: desmopressin at the onset of rapid correction or increased urine output;

- rescue: desmopressin and hypotonic fluids after overly corrected

Proactive therapy was associated with prolonged hospitalization,
Reactive strategy was the most commonly used and effective,
while the rescue group only 6.5% met the correction limit of 8 mEq/L/24h



Currently approved immune checkpoint inhibitors

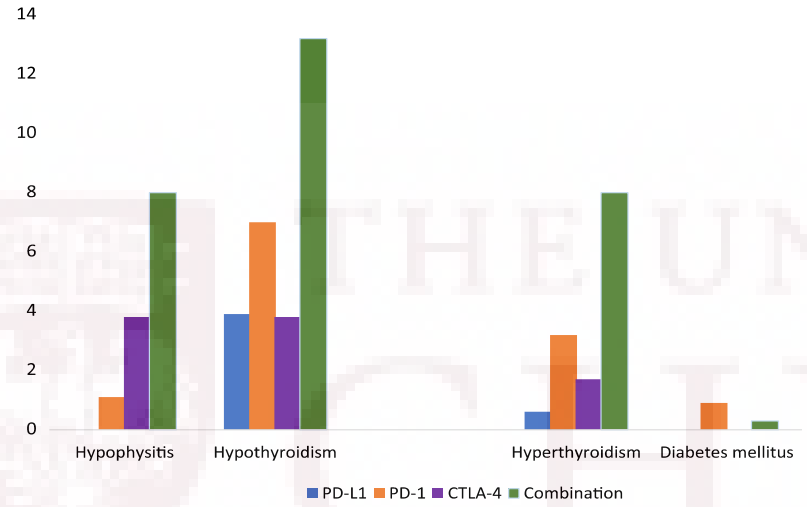
FDA-Approved Cancer Immune Checkpoint Inhibitors

Agent	Target	Cancer Indication(s)
PD-1/PD-L1		
Nivolumab	PD-1	Melanoma; NSCLC; metastatic SCLC; intermediate/advanced RCC; HCC; cHL; HNSCC; and urothelial and MSI-H/dMMR cancers
Pembrolizumab	PD-1	Melanoma; NSCLC; SCLC; HNSCC; cHL; PMBCL; and urothelial, MSI-H/dMMR, gastric, esophageal, cervical, hepatocellular, and Merkel cell, and renal cancers
Cemiplimab	PD-1	Metastatic or locally advanced cSCC
Atezolizumab	PD-L1	Urothelial carcinoma; NSCLC; TNBC; SCLC
Avelumab	PD-L1	Urothelial, renal, and Merkel cell cancers
Durvalumab	PD-L1	Urothelial carcinoma; stage III NSCLC
CTLA-4		
Ipilimumab	CTLA-4	Melanoma; RCC; MSI-H/dMMR cancer

NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; cSCC: cutaneous squamous cell carcinoma; HNSCC: head and neck squamous cell cancer; TNBC: triple-negative breast cancer; cHL: classical Hodgkin lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; MSI-H: microsatellite instability-high cancer; dMMR: mismatch repair deficient; CRC: colorectal cancer; RCC: renal cell carcinoma; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; B-CLL; B-cell chronic lymphocytic leukemia

Please see prescribing information for each agent for full indications, notes and stipulations for use. Indications accurate as of September 11, 2019.

Incidence of endocrinopathies with different ICI regimens



Overall incidence of hypothyroidism 6.6% (95% CI 5.5-7.8%), from 3.8% with ipilimumab to 13.2% with combination

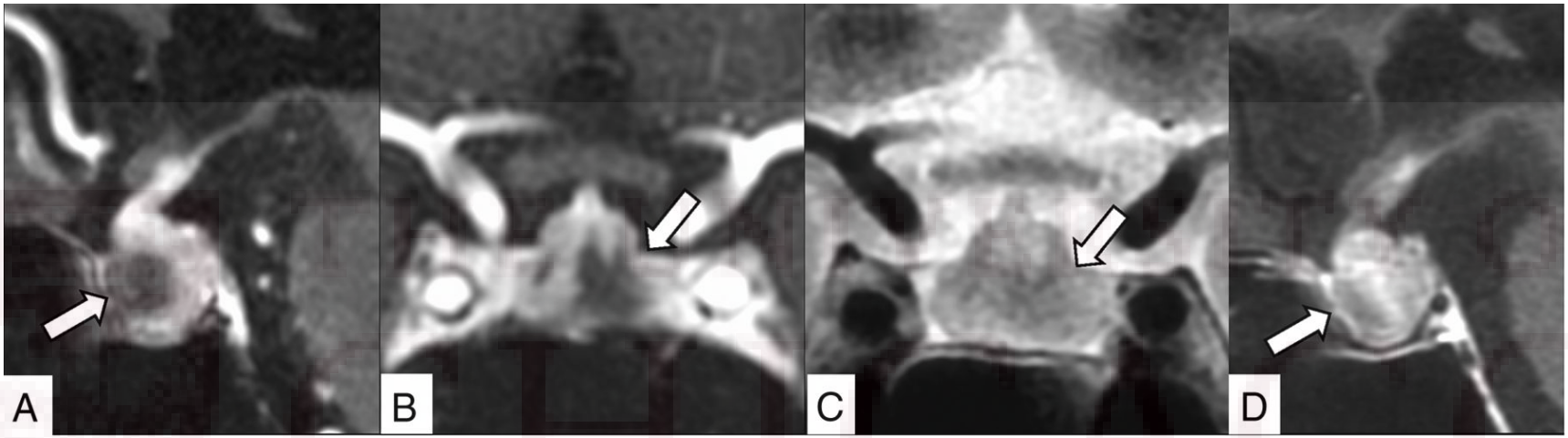
Overall incidence of hyperthyroidism 2.9 (95% CI 2.4-3.7%) up to 8% with combination. Higher risk with PD-1 than with PD-L1 (OR 5.36) and with pembrolizumab (3.8%) vs nivolumab (2.5%), p=0.04

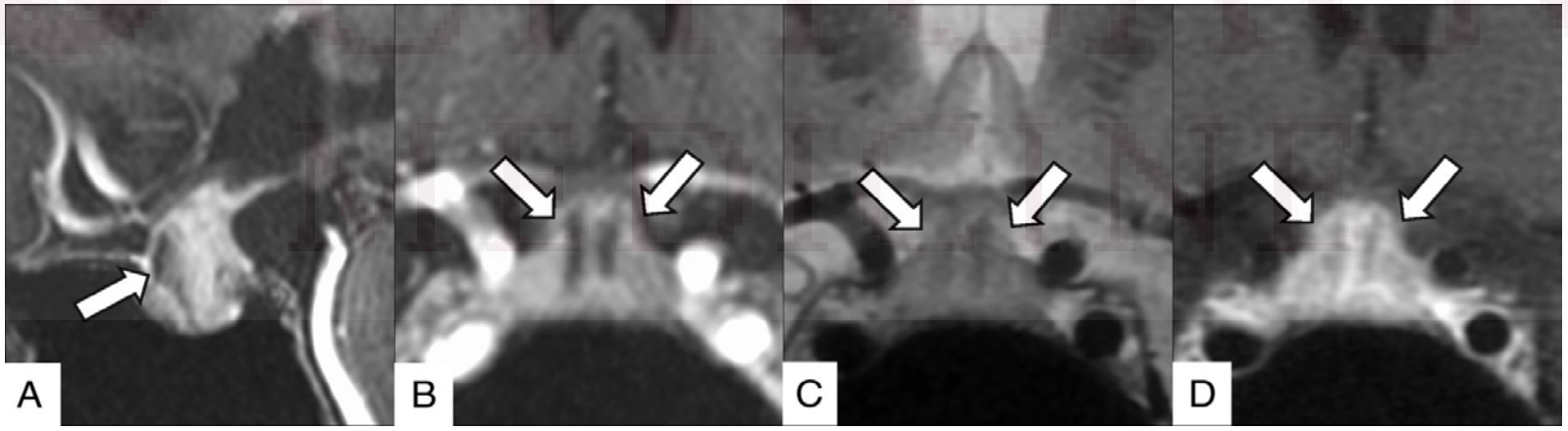
Incidence of hypophysitis was greatest with combination therapy 6.4%, 3.2 % CTLA-4, 0.4% with PD-1 inhibitors, and <0.1% with PD-L1 inhibitors

ICI- induced hypophysitis

- Anti-CTLA-4 Ab are the most common cause due to the presence of “ectopic” CTLA-4 expression on adenohypophyseal cells. Leads to panhypopituitarism and is associated with pituitary enlargement on MRI (mild to moderate with homogeneous or heterogeneous enhancement).
- PD-1 blockade is characterized by isolated and severe ACTH deficiency, no mass effect symptoms, no imaging abnormalities
- Present with fatigue, headache, visual changes, hyponatremia. Usually after the 3rd or 4rd dose (8-9 weeks) after initiation of immunotherapy
- Risk factors: male, age >60yo
- SIC Toxicity: deficiency of ≥ 1 pituitary hormones (TSH or ACTH) +MRI abnormality or deficiency ≥2 pituitary hormones in the presence of headache
- Mild → replacement doses of hydrocortisone, for severe cases → high dose steroids

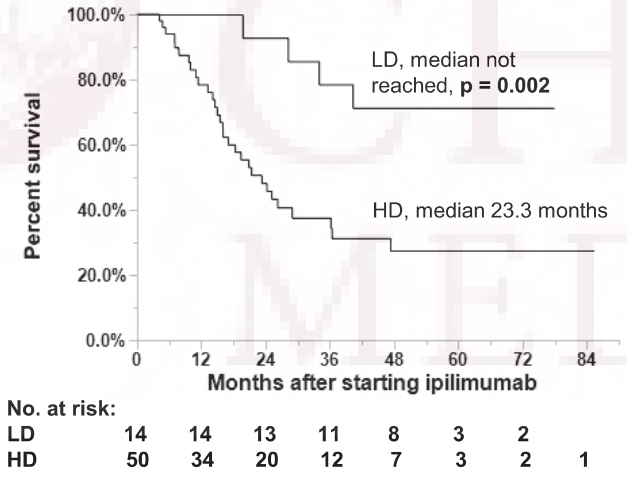
MRI findings

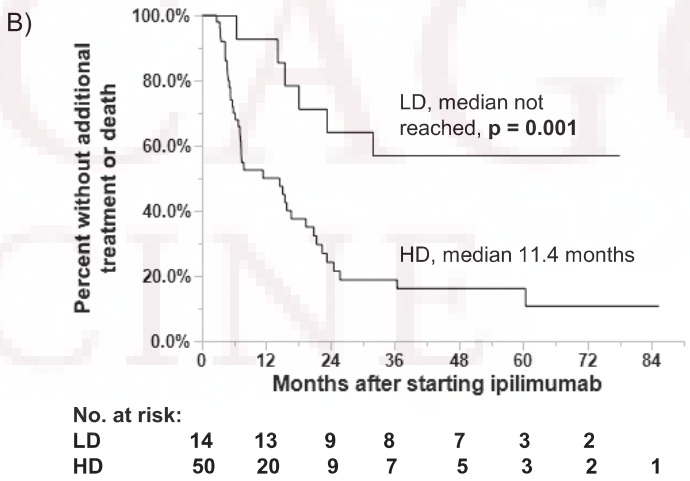




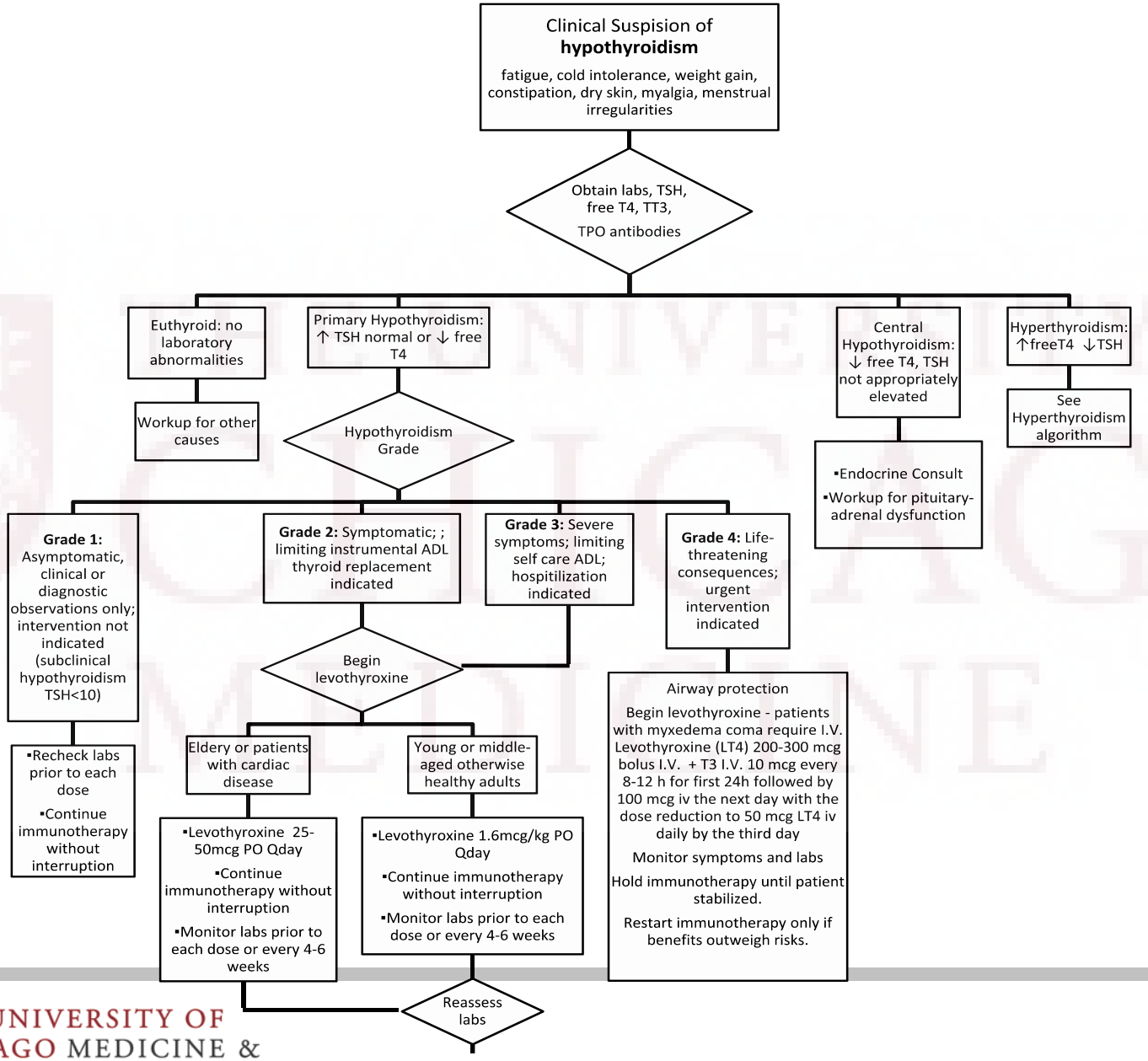
Dose of steroids in ICI-induced hypophysitis

- 98 patients with melanoma who received ipilimumab and were diagnosed with ipilimumab-induced hypophysitis. The study assessed the effect of low-dose (maximum 7.5 mg prednisone) vs high-dose steroids for treatment
- Both OS and time to treatment failure were significantly longer in low-dose (HR 0.24)





Thyroid dysfunctions

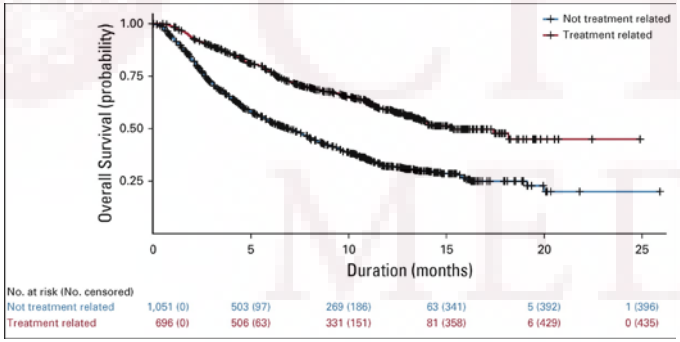


Rivero et al. The Oncologist 2020

Outpatient follow up

- Patient was noted to have progression of pulmonary metastases and nivolumab/ipilimumab was stopped and he was started on carboplatin /taxol. Remains on levothyroxine 137 mcg and hydrocortisone 20+10 mg

- In contrast, efficacy (response to treatment and OS) of PD-1 and PD-L1 has been associated with development of irAE



Maher et al, J Clin Oncol. 2019
Eggermont et al. JAMA Oncol. 2020|

Thank you!