Endocrinopathies with Immune Checkpoint Inhibitors; a 36F with Metastatic Melanoma

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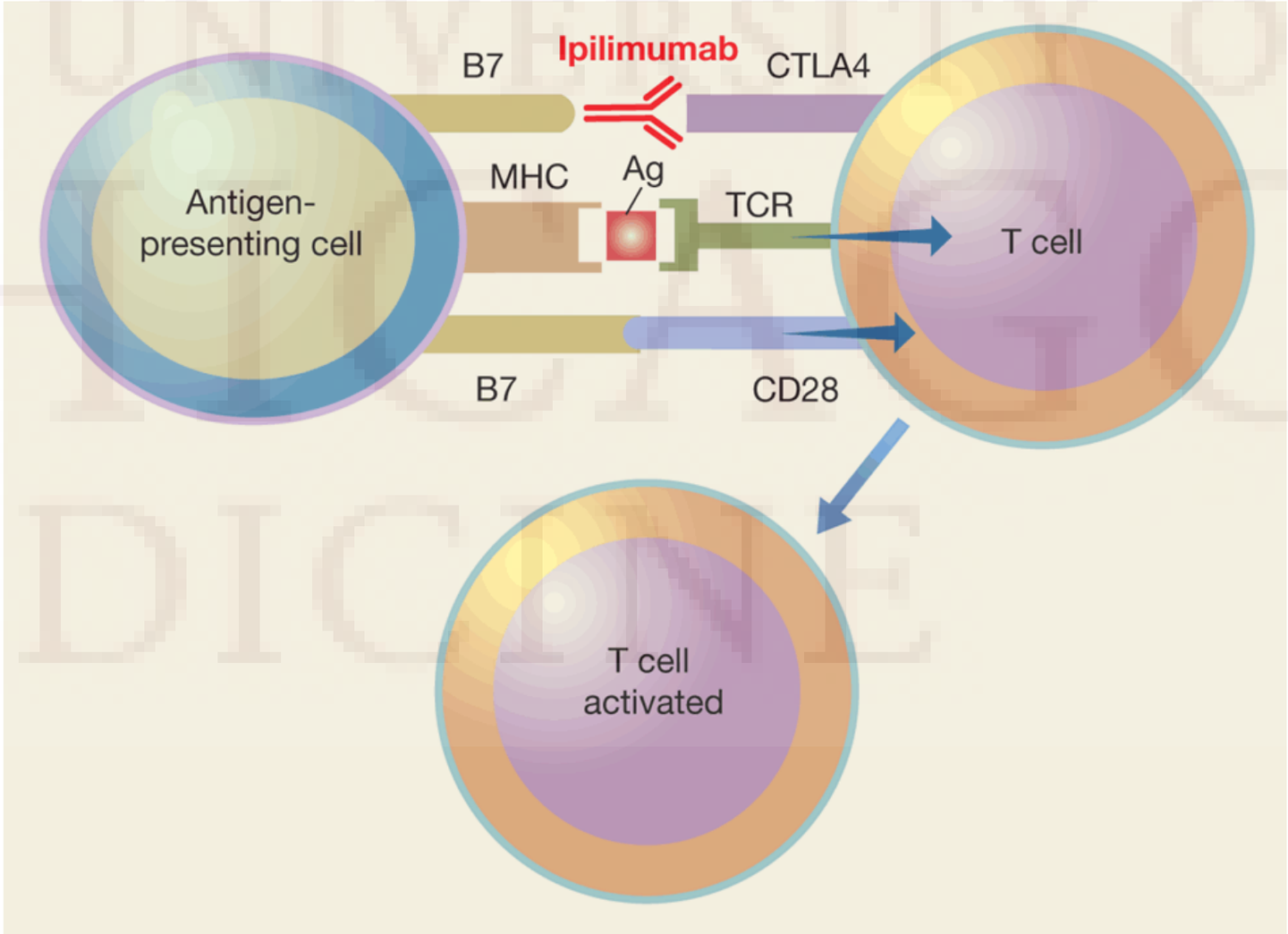
- 35 yo F with no significant PMH
- Hx of 2 moles on her L posterior arm for many years
- One of her moles "fell off" and bled then “grew back, was really hard”
- Biopsy: nodular melanoma
- Depth of 2.2mm, presence of ulceration, mitotic rate of 12/mm2, and 1/3 sentinel lymph nodes positive
- Late April 2016 CT c/a/p w & MRI Brain wwo: No metastatic disease
- 5/11/16 : Underwent left complete Level 3 axillary lymph node dissection (0/28)
- Diagnosed with stage IIIB malignant melanoma metastatic to L axillary sentinal LN
- Recs: ipilimumab (anti-CTLA4) vs pembrolizumab (anti-PD-1)

Anti-CTLA4 mAbs

- CTLA4 is an immune checkpoint molecule expressed on T cells
- Down regulates T cell activation after T cell/APC interaction
- Ipilimumab (Yervoy) & tremelimumab are mAbs directed against CTLA4
  - Blocks it to promote anti tumor immunity



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Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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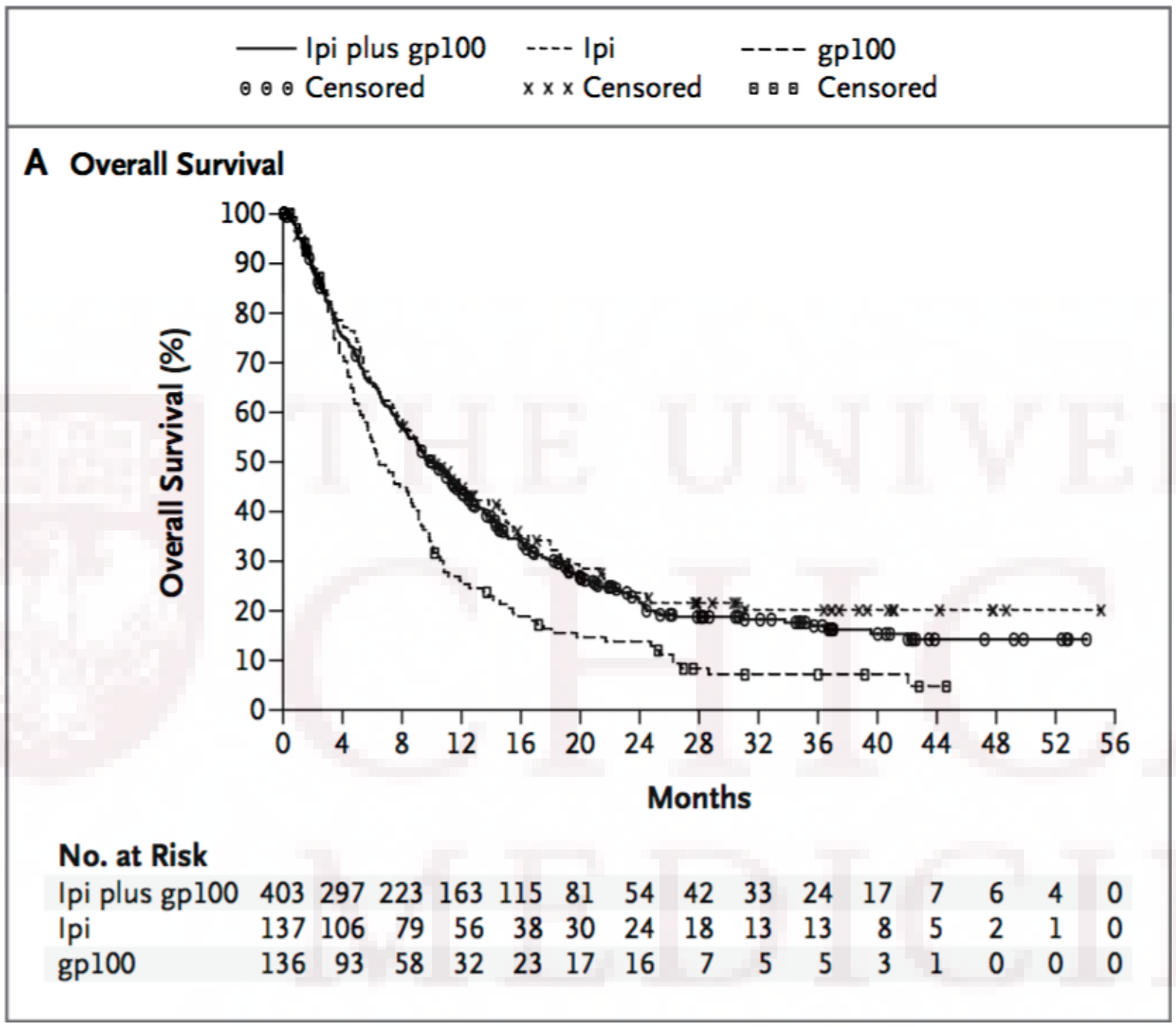
- Randomized Phase 3 study in which ipilimumab with or without gp100 was given compared to gp100 alone as control
- Standard of care for metastatic melanoma is enrollment in clinical trial

- gp100 is a cancer vaccine that induces immune responses but has limited anti tumor activity



676 patients enrolled:

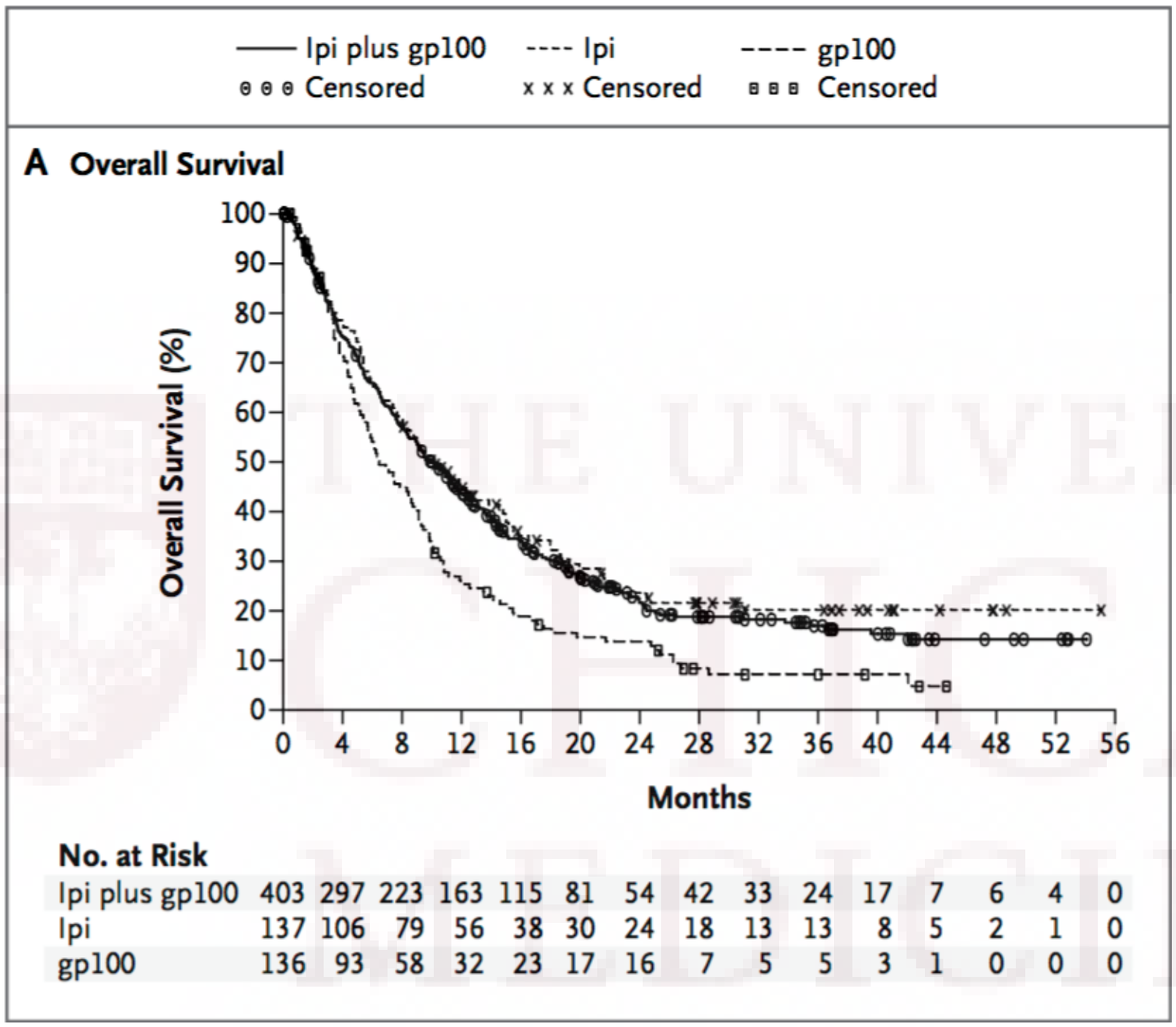
-403 randomly assigned to receive ipi + gp100

-137 ipi alone

-136 gp100 alone (control group)

NEJM 2010;363:711-723

Ipilimumab dose: 3mg/kg x 4 doses



NEJM 2010;363:711-723

676 patients enrolled:

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-137 ipi alone

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Overall median survival was 10 months among patients receiving ipi + gp100 (95% CI, 8.5-11.5), as compared to 6.4 mos among patients receiving gp100 alone (95% CI, 5.5-8.7).

Ipilimumab for Metastatic Melanoma Treatment

- 2011 US FDA approves ipilimumab for advanced melanoma
- Survival benefit results were not obtained with tremelimumab
- Approved dose is 3mg/kg IV infusion Q3wks for 4 doses total; maintenance therapy can continue for some patients
- Toxicity profile worsens in a dose dependent manner

Immune Related Adverse Events (IRAEs)

- In a pooled analysis of 325 patients treated with 10mg/kg ipilimumab Q3 weeks for 4 doses IRAEs were observed in 72.3%

- IRAEs: colitis/diarrhea, dermatitis, hepatitis, endocrinopathies

Endocrine-Immune Related Adverse Events (E-IRAEs)

- E-IRAEs: hypopituitarism (caused by hypophysitis), thyroid disease, abnormalities in TFTs, primary adrenal insufficiency
- Incidence of anti-CTLA4 hypophysitis was dose dependent
  - 1-3mg/kg occurred in 1.8-3.3% cases
  - >3mg/kg occurred from 4.9-17% of cases
- Primary adrenal insufficiency has been reported (0.3-1.5%)

Presentation of anti-CTLA4 Hypophisitis

- Nonspecific symptoms: fatigue, weakness, headache, nausea, vertigo, behavior change, visual impairments such as diplopia, confusion, memory loss, loss of libido, anorexia, insomnia, hallucinations, temperature intolerance, subjective f/c

- Average onset: 6-12 weeks after initiation of therapy

- Levels of ACTH, cortisol, TSH, FT4, GH, prolactin, IGF-1, FSH, LH & testosterones (in males) are variably altered

- Most cases: MRI reveals enlargement of pituitary gland (60-100%), & thickening of the stalk

  - Height in sagittal view increases from 3.4 - 6mm to 7.7 - 11.8mm

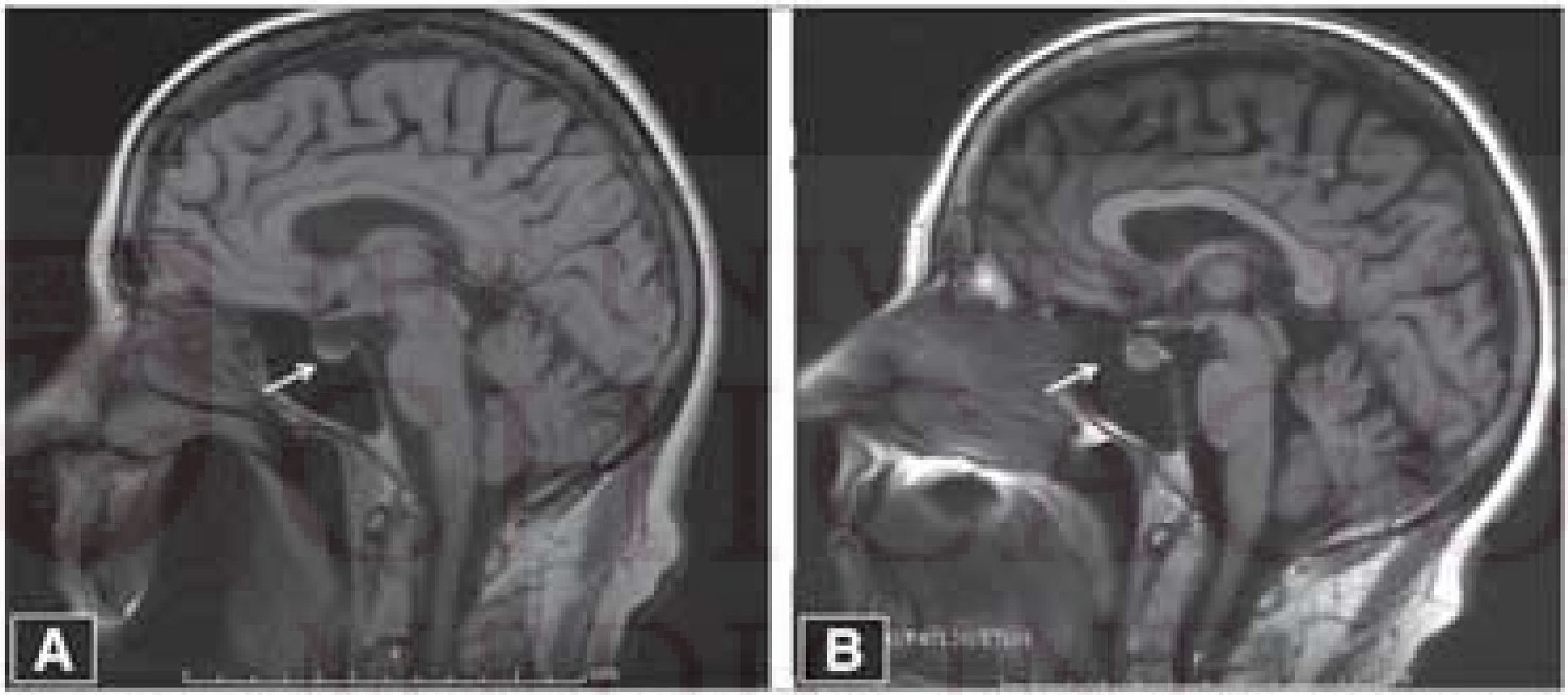


Figure 2: MRI Findings in a Patient With Ipilimumab-Induced Hypophysitis — These MRI images show the pituitary gland before therapy **(A)** and after four cycles of induction **(B)**.

Clinical Approach to Pt with Hypophysitis

- Pituitary MRI and pituitary function assessment
- If anti-CTLA4 hypophysitis is confirmed, the drug should be held and IV glucocorticoids should be given for a few days
- Followed by oral glucocorticoids with tapering to replacement doses
- Once hypophysitis resolves with treatment and adequate hormone replacement has been tailored anticancer treatment can be resumed with close monitoring of pituitary function

Treatment of anti-CTLA4-mAb Hypophisitis

- Most Pts experience resolution of symptoms a few days after withdrawal of the drug and the start of high dose glucocorticoids, LT4 & sex hormone replacement

- Time time needed for resolution of symptoms & duration of replacement therapy may be longer or even lifelong (considering limited survival of Pts)

Thyroid Side Effects by anti-CTLA4 mAbs

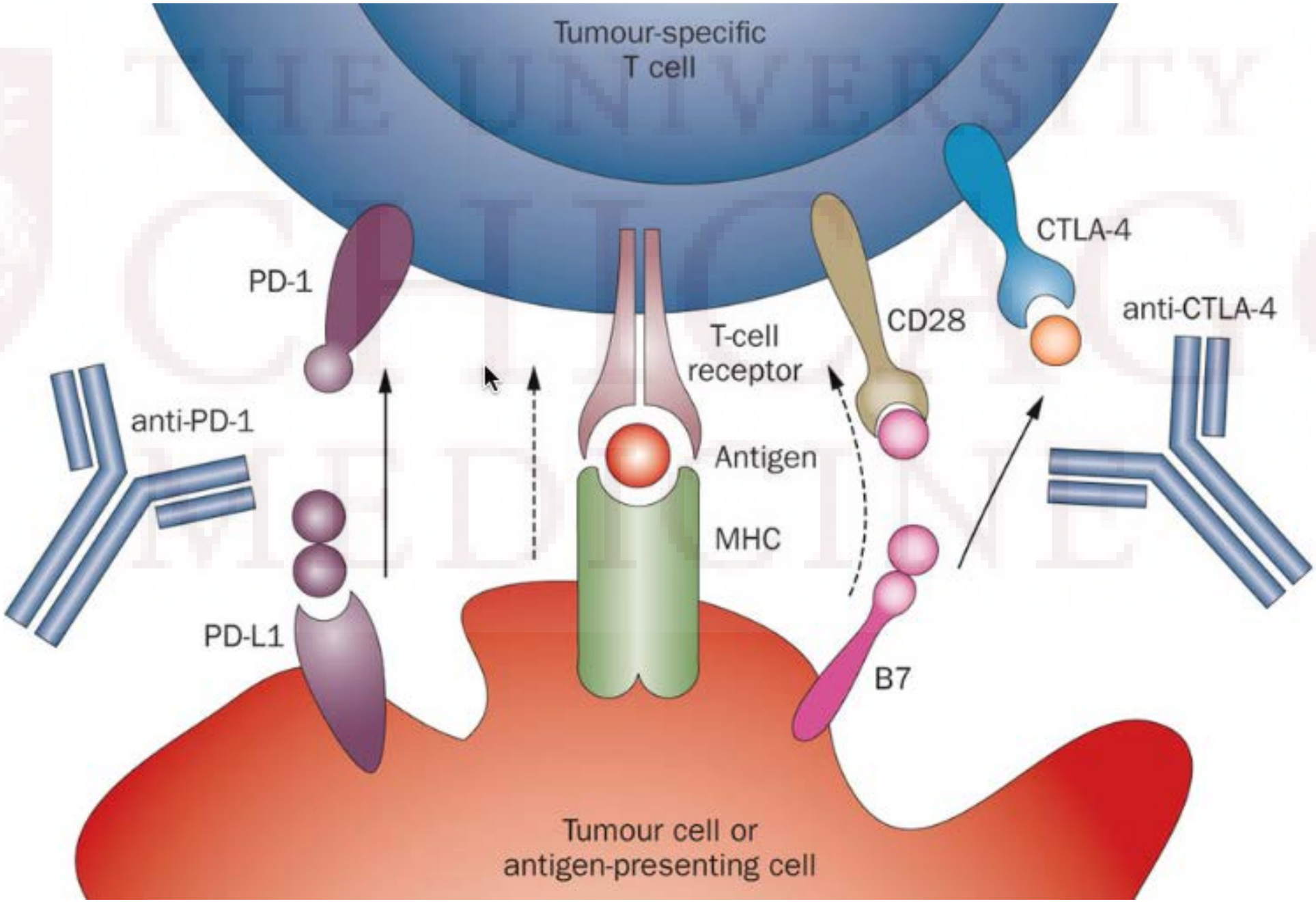
- Second most frequent endocrine organ involved in anti-CTLA4-mAb toxicity
- Incidence is 0-4%
- Presents as thyroiditis usually associated with antithyroglobulin & anti-TPO Ab positivity & hypothyroidism, or transient hyperthyroidism
- Most cases have a subclinical course, may be transient or may evolve into permanent hypothyroidism
- Rare cases of Graves opthalmopathy have been reported with elevation of TSH receptor antibodies but normal thyroid function

Mechanism of CTLA-4 mAb Induced Hypophysitis?

- Pathogenesis is attributable to autoimmunity, however, the exact mechanism remains to be clarified

- anti-CTLA-4 mAbs may act by depleting T reg cells vs antibodies directed against the pituitary gland (presence of pituitary antibodies remains to be shown)

Other Immune Checkpoint Inhibitors: anti-PD-1 mAbs



PD-1 mAbs

- PD-1 is another immune checkpoint inhibitory receptor expressed on activated T cells to inhibit T cell activation and proliferation, thereby promoting immunological self tolerance

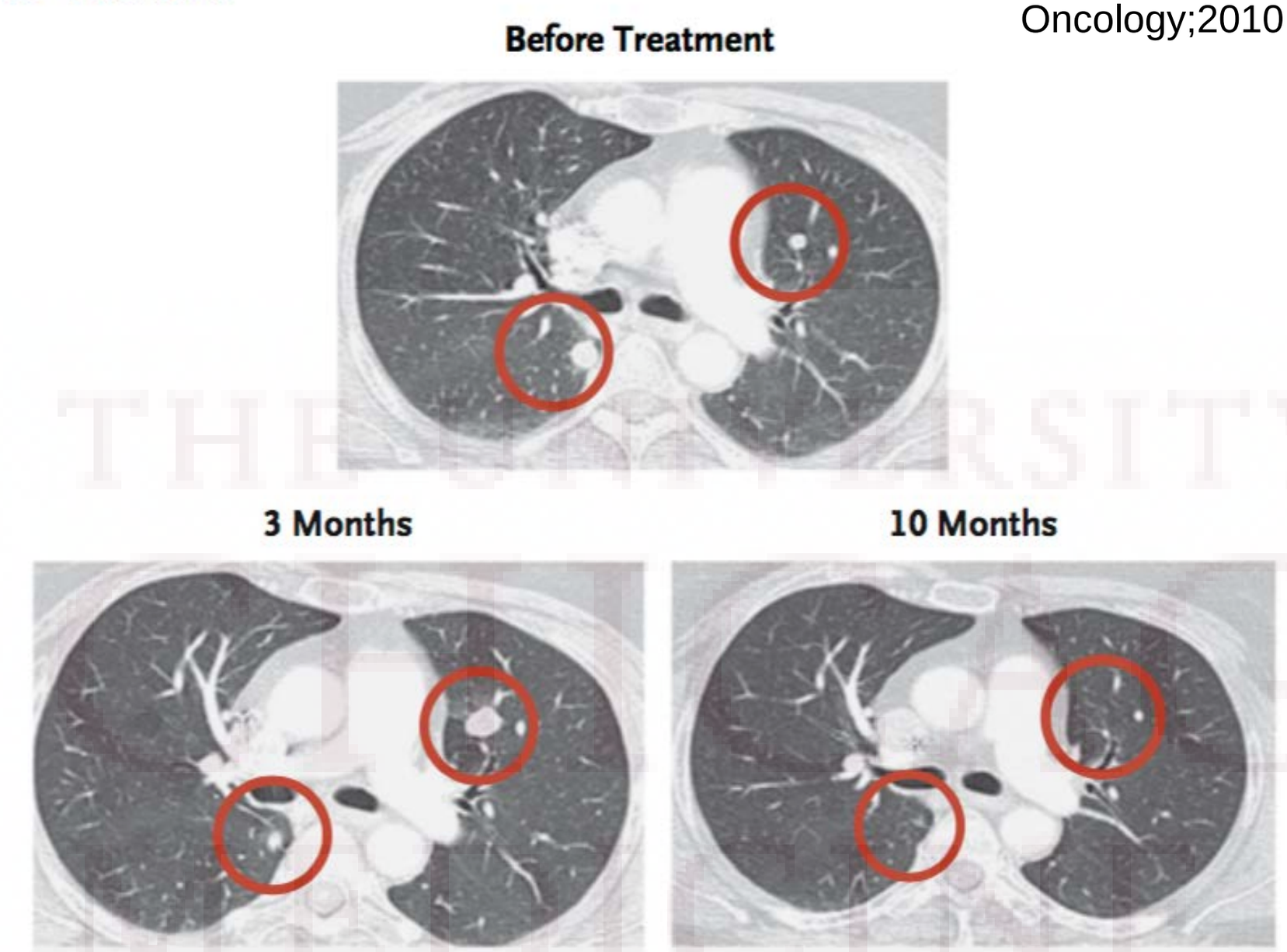
- Highly expressed on T cells from patients with tumors causing tumor related immune suppression

- Pharmacological interference with anti-PD-1 and anti-PD-1L increases anti tumor immunity & enhances immunity *in vitro*

- PD-1 inhibitors: Pembrolizumab (Keytruda) & Nivolumab (Opdivo)

- mAbs blocking PD-1 have been shown to be beneficial in different types of cancers (H&N cancer, ovarian, bladder, Hodgkin's lymphoma, melanoma, RCC, non-small cell lung cancer)

Oncology;2010:24(14):1280-1288



- Complete response in a patient with melanoma who received 3mg/kg of anti-PD-L1 antibody

- Circles indicate an initial increase in the size of pulmonary nodules at 6 weeks and 3 months, followed by complete regression at 10 months (immune related pattern of response)

Anti-PD-L1 Endocrine Side Effects

- Phase I study of 207 patients with advanced cancers
- No Pt developed hypophysitis
- Endocrine side effects developed in Pts receiving higher doses of drug (3-10mg/kg)
  - 6 Pts (3%) developed hypothyroidism
  - 2 Pts (1%) developed autoimmune thyroiditis
  - 3 Pts (1.5%) developed adrenal insufficiency
- In one retrospective study in Pts receiving Ipilimumab incidence of thyroiditis/hypothyroidism was reported at 6% whereas it was 22% in group receiving both ipilimumab & nivolumab

Table 2 Previous History of Thyroid Disease, Thyroglobulin (Tg), Anti-Tg, Anti-TPO, and TSI Titers at Initial Thyroid Dysfunction (Thyroiditis) and the Change (denoted by ») in the Hypothyroid Phase, Available Thyroid Imaging, Status of Hypothyroidism after 6 Months, and Tumor Response.

Case #	Previous History of Thyroid Disease	Tg (1.3–31.8 ng/ml)	Anti-Tg (0–4 IU/ml)	Anti-TPO (<60 units/ml)	TSI (<123%)	Imaging at Thyroid Abnormality	Status of Hypothyroidism (at 6 months)	Tumor Response
1	Subclinical Hypothyroidism on natural thyroid	109»33	Neg	Neg	Neg	US: decreased vascularity	Resolved at 6 weeks	Yes
2	None	N/A	24» 2.4	Neg	161»96	US: heterogeneous thyroid gland	Persistent	Yes
3	None	162.6 »4	Neg	Neg	164» 99	N/A	Persistent	Yes
4	None	154 » 20	Neg	Neg	Neg	RAI: decreased uptake	Resolved at 2 months	Yes
5	None	141 »1.3	Neg	Neg	128»87	US: diffusely hypoechoic	Persistent	Yes
6	Resolved Hypothyroidism	N/A	8.6»2.1	1300>1400	N/A	N/A	Persistent	Yes
7	Hypothyroidism on LT4 25 µg daily	N/A	247»108	223 »127	N/A	N/A	Persistent	Yes
8	None	N/A	Neg	156»246	Neg	RAI: Low uptake	Persistent	Yes
9	None	61 » 0.1	Neg	580»545	219»120	US: heterogeneous thyroid	Persistent	No
10	None	N/A	344 » 61	894 »237	150» 103	US: diffusely hypoechoic gland	Persistent	Yes

Exp Clin Endocrinol Diabetes. 2017; doi: 10.1055/s0042-119528

Hypothyroidism in Pts receiving anti-PD1 agents (10 cases)

- During thyroiditis phase, 50% of Pts had elevated Tg titers, 40% had elevated anti-Tg, and 40% had elevated TSI

- Permanent hypothyroidism was noted in 80% of cases

- Hypothyroidism following initiation of immune therapy has immunologic and non-immunologic mediated mechanisms and is likely to be persistent

Mechanism of PD-1 Associated Hypothyroidism

- Immunologic phenomenon?
- Destructive thyroiditis with release of thyroid antigen and consequent secondary antibody production?
  - Initial hyperthyroid phase was notable for elevated Tg levels in all the patients who did not have anti-Tg as well as elevated anti-Tg and TSI in 40 & 50% of Pts respectively
  - Evidence of thyroiditis in Pts with available imaging
  - Subsequent normalization of Tg and disappearance of anti-thyroid antibodies support a destructive process ending in permanent hypothyroidism in most patients
  - Presence of anti-TPO was not necessary for development of hypothyroidism

Patient Course

- Started on Ipilimumab (anti-CTLA4) on 8/2/16 plan for 4 infusions (3mg/kg)
- After 3rd cycle, began to feel run down, tired, & dizzy upon waking

Labs 10/4/16 07:06am

Cortisol <0.4
TSH: 0.02
FT4: 0.61

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Oncologist started on 20mg HC Qd & 25mcg LT4 Qd

	Prior to Ipi	After 1st cycle	After 2nd cycle	After 3rd cycle	Endo Appt
	8/2/2016 0745	8/23/2016 0708	9/13/2016 0729	10/4/2016 0706	10/25/2016 0754
THYROID FUNCTION					
Triiodothyronine, ...					224
Thyroxine, Free	1.24 *	1.32 *	0.93 *	0.61 *	0.77 *
Thyroglobulin Ab					<0.4
Thyroid Perox. Ab					<0.4
Thyrotropin	1.16	1.26	0.43	0.02	0.01

Labs 10/25/16 07:54am:

cortisol: 30.4
estradiol (high sensitivity): <3
FSH: 4.7
LH: 2.5
Prolactin <1
ACTH: 1.2
IGF-1: 75 (54-258 ng/mL)
hGH: 0.10

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estradiol (high sensitivity): <3
FSH: 4.7
LH: 2.5
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ACTH: 1.2
IGF-1: 75 (54-258 ng/mL)
hGH: 0.10

-HC changed to 15mg QAM & 5mg QPM

-LT4 increased to 137 mcg

-Advised to start OCPs

-Referral to Reproductive Endo given desire for pregnancy

Further Course

- Received 4 cycles of Ipilimumab 3mg/kg (Aug-Oct 2016)
- 1/6/17 CT Chest showed interval development of pulmonary nodules & metastatic disease in sternum
- Added Nevilomab on 1/26/17 (in conjunction with 2nd round of Ipilimumab infusions), got 1st cycle of both drugs
- Admitted on 2/14/17 with Hg 2.9 and hypotension 80/40s when she presented for 2nd ipi/Nevilomab infusions
- Anemia thought to be due to MAHA vs HLH, discharged after several transfusions and treatment with high dose steroids
- Unclear if she will be continued on chemotherapy at this time

Conclusions

- Hypophysitis has emerged as distinctive side effect of CTLA-4 blocking antibodies
- Endocrine disease experienced by patients treated with ipilimumab includes mostly hypophysitis, and more rarely thyroid disease, occasional AI
- Hypothyroidism following initiation of immune therapy, has been seen with use of anti-PD-1 Abs & has immunologic and non immunologic mediated mechanisms and is likely to be persistent

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Objectives

- To learn about the anti-CTLA4 monoclonal Abs in the treatment of metastatic melanoma
- To discuss the most common endocrinopathies associated with immune checkpoint inhibitors