WHAT THE PRIMARY CARE PHYSICIAN NEEDS TO KNOW ABOUT IMMUNOTHERAPY

Men's Health Summit 2020

Kala S. Sridhar MD, MSc, FRCPC
Medical Oncologist, Princess Margaret Hospital
Associate Professor, University of Toronto
Chair, GU Medical Oncologists of Canada

Disclosures

- Consultancy/Advisory: Pfizer, Merck, Roche, BMS, Bayer, AstraZeneca, Astellas, Janssen, Astellas

Introduction

- Until recently chemotherapy was the only option to treat most advanced cancers
- In the past two decades, cancer treatment has been transformed by targeted drugs and immunotherapy
- Targeted therapy inhibits specific genes or proteins that are altered or overexpressed on cancer cells
- Immunotherapy helps the body’s own immune system recognize and target cancer cells

Immune System

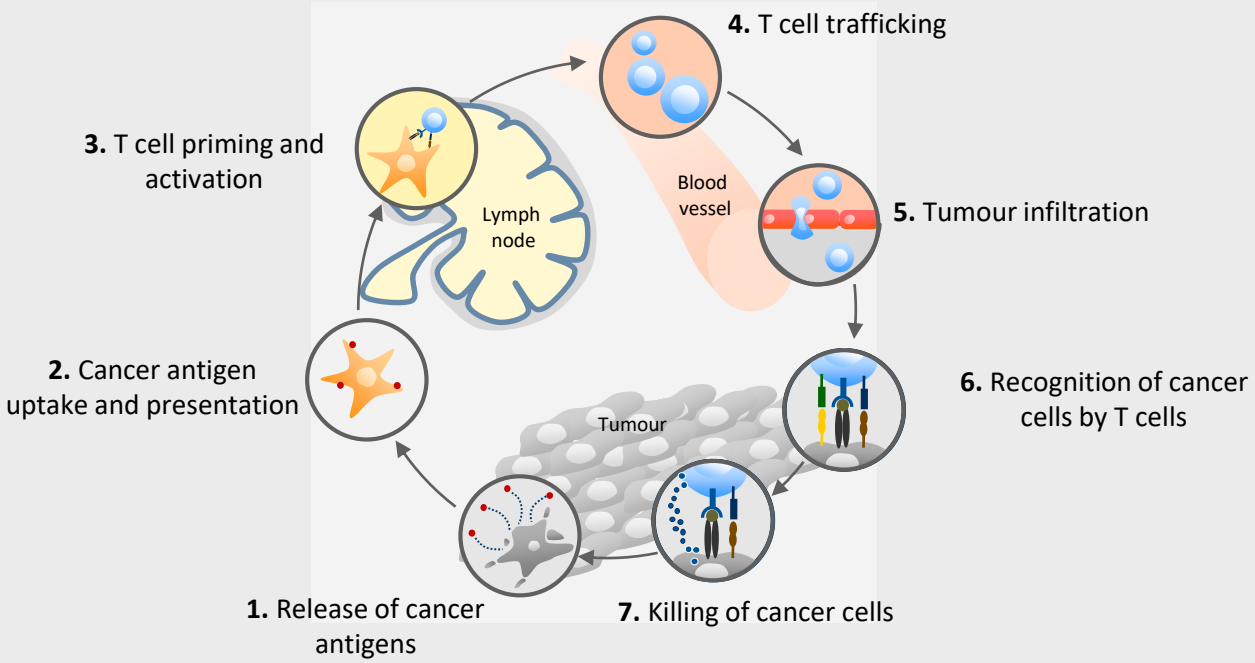
- Need an active immune response to a threat
- Once threat is over – immune system needs to shut off
- Negative regulators or checkpoints on the immune system

Nobel Prize for Immunotherapy in 2018

Allison discovered CTLA-4 which acts as a brake on T cells

Honjo discovered PD-1, which acts as a brake on T cells

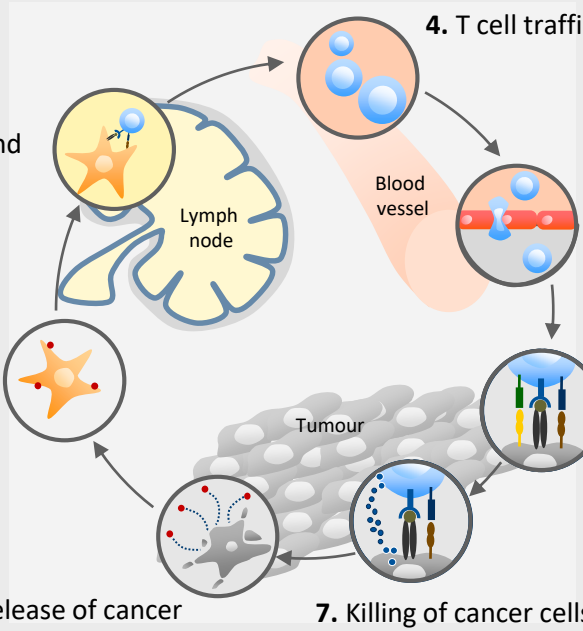
Cancer Immunity Cycle



A series of stepwise events leading to effective killing of cancer cells

Chen, Immunity 2013

Cancer Immunity Cycle



Anti-CTLA-4
Anti-CD137
Anti-OX40
Anti-CD27
IL-2
IL-12

Anti-VEGF

Vaccines
IFN-α
GM-CSF
Anti-CD40
TLR agonists

CARs

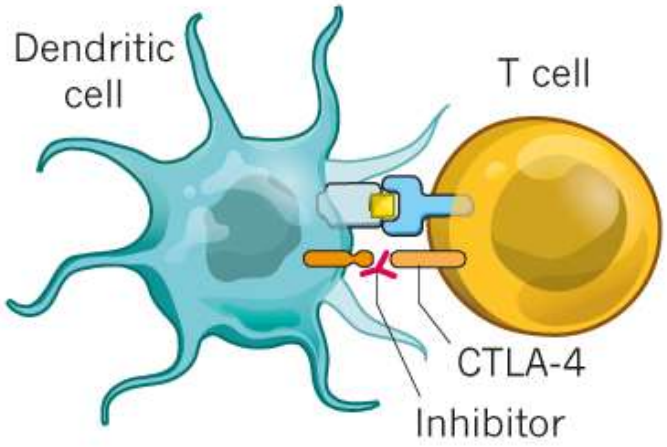
Chemotherapy
Radiation therapy
Targeted therapy

Anti-CTLA4
Anti PD1/PDL1

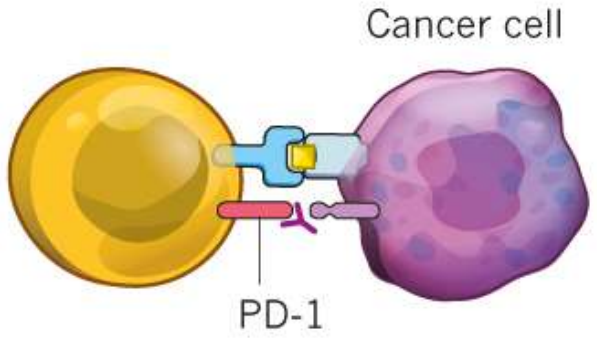
Can target at various points in this cycle

Chen, Immunity 2013

Checkpoint Inhibitors



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

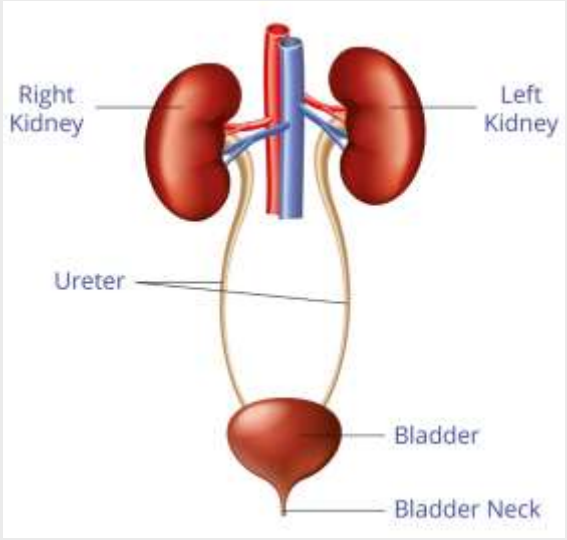
©nature

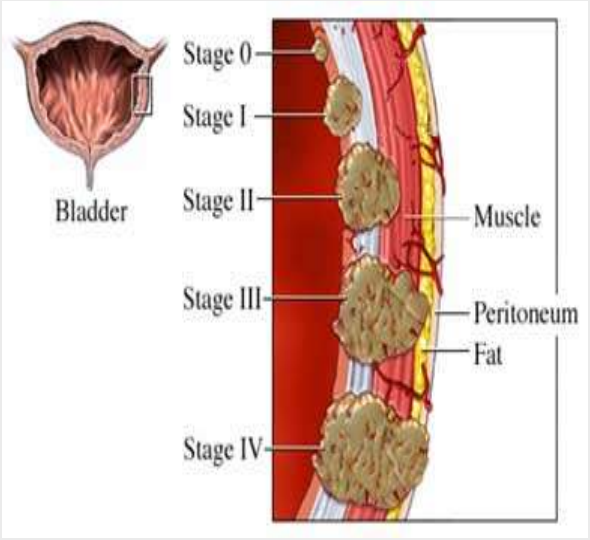
Does immunotherapy work in all patients?

- It works better for certain cancers — Melanoma, Lung Cancer, Bladder Cancer*, Kidney Cancer*
- Cancers with higher levels of PD-L1 protein or many gene mutations due to DNA repair defects
- Not everyone responds, and we do not fully understand how best to select patients who will benefit
- Patients with pre-existing autoimmune conditions – colitis, arthritis etc. have not been well studied in trials so need to be very cautious

Bladder Cancer

- 8900 new cases, 2400 deaths/year
- Biggest risk factor is smoking!
- Urinary tract, most occur in the bladder





- Non-muscle invasive 70%, Muscle invasive 25%, Metastatic 5%

Canadian Cancer Society, 2019

Immunotherapy

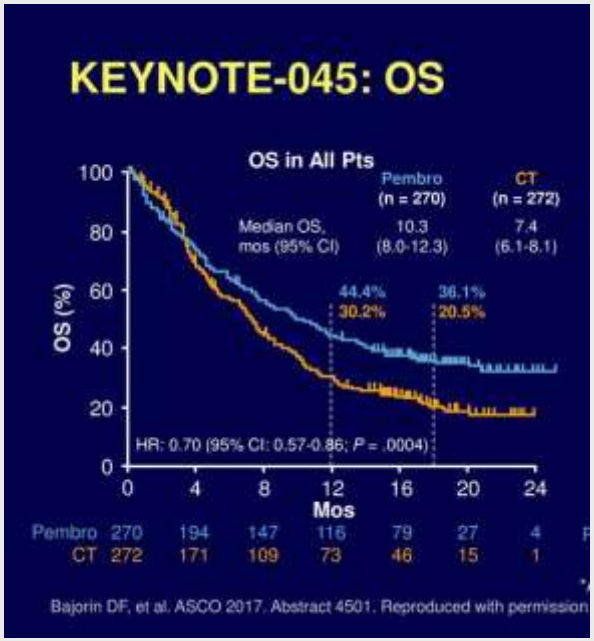
- Immunotherapy is not a new concept in this disease
- For high risk NMIBC, BCG has commonly been used
- Live attenuated strain of mycobacterium bovis
- Developed as a vaccine against TB in 1921
- Role in cancer explored after autopsy studies showed lower cancer rates in TB patients
- BCG was first used in 1976 for melanoma of the bladder and then for urothelial cancer

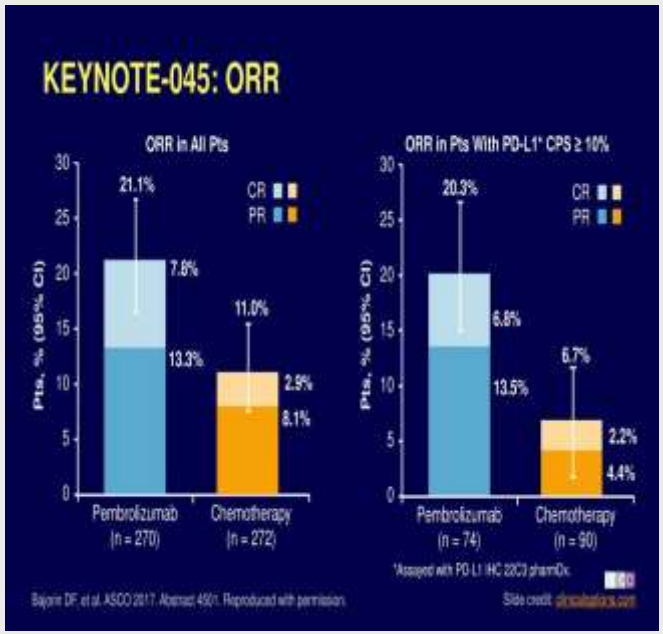
Brandau, Biomed Pharm 2007

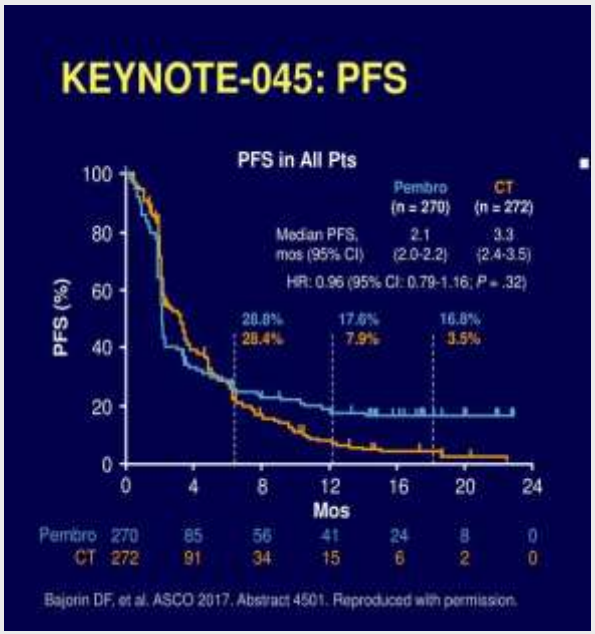
Bladder Cancer

- Metastatic disease is incurable with a life expectancy of ~15 months
- First line chemotherapy is gemcitabine and cisplatin
- High response rates 45-60%, not durable
- Some patients can’t tolerate first line
- Significant unmet need
- Checkpoint inhibitors are well tolerated and have been evaluated across the spectrum of bladder cancer

Cisplatin-Refractory (Second Line)
Keynote 045 Pembrolizumab vs. Chemotherapy







Pembrolizumab is FDA and Health Canada approved in second line…
But, only **20%** respond, not considered a cure

Bajorin D, ASCO 2017

Cisplatin-Unfit (First line)
Single arm studies

	Pembrolizumab[2]	Atezolizumab[1]
Phase	Phase II (Keynote-052)	Phase II (IMvigor Cohort 1)
Patients	370	119
Dosing	200mg every 3 weeks	1200mg every 3 weeks
ORR	29% (7% CR)	23% (9% CR)
Duration of Response	82% responses ongoing at ≥ 6 months	70% responses ongoing at 17.2 months
Median OS	Not reached	15.9 months
Median PFS	2 months	2.7 months

Immunotherapy may also have a role in first line
But, cisplatin based chemotherapy still has higher response rates

Balar A et al, 2018

ICI are moving earlier..

- Recent data suggests these drugs may also work in the NMIBC setting
- FDA approved
- May represent a large number of patients who are on these treatments
- Questions around who will manage these patients
- Need support of family physicians!

Kidney Cancer

- 7200 new cases annually
- Immunotherapy is not new to this disease
- Interferon and Interleukin, had shown benefit in a small minority, but significant toxicity
- First-line advanced disease drugs targeting blood vessels – Sunitinib and Pazopanib – became the standard of care
- Second line is nivolumab (ICI) showed superiority to other agents and has moved into second line
- These drugs are given IV every 4 weeks – resource implications

First line treatment is changing

- Combination strategy of immunotherapy and angiogenesis inhibitors is superior to Sunitinib alone

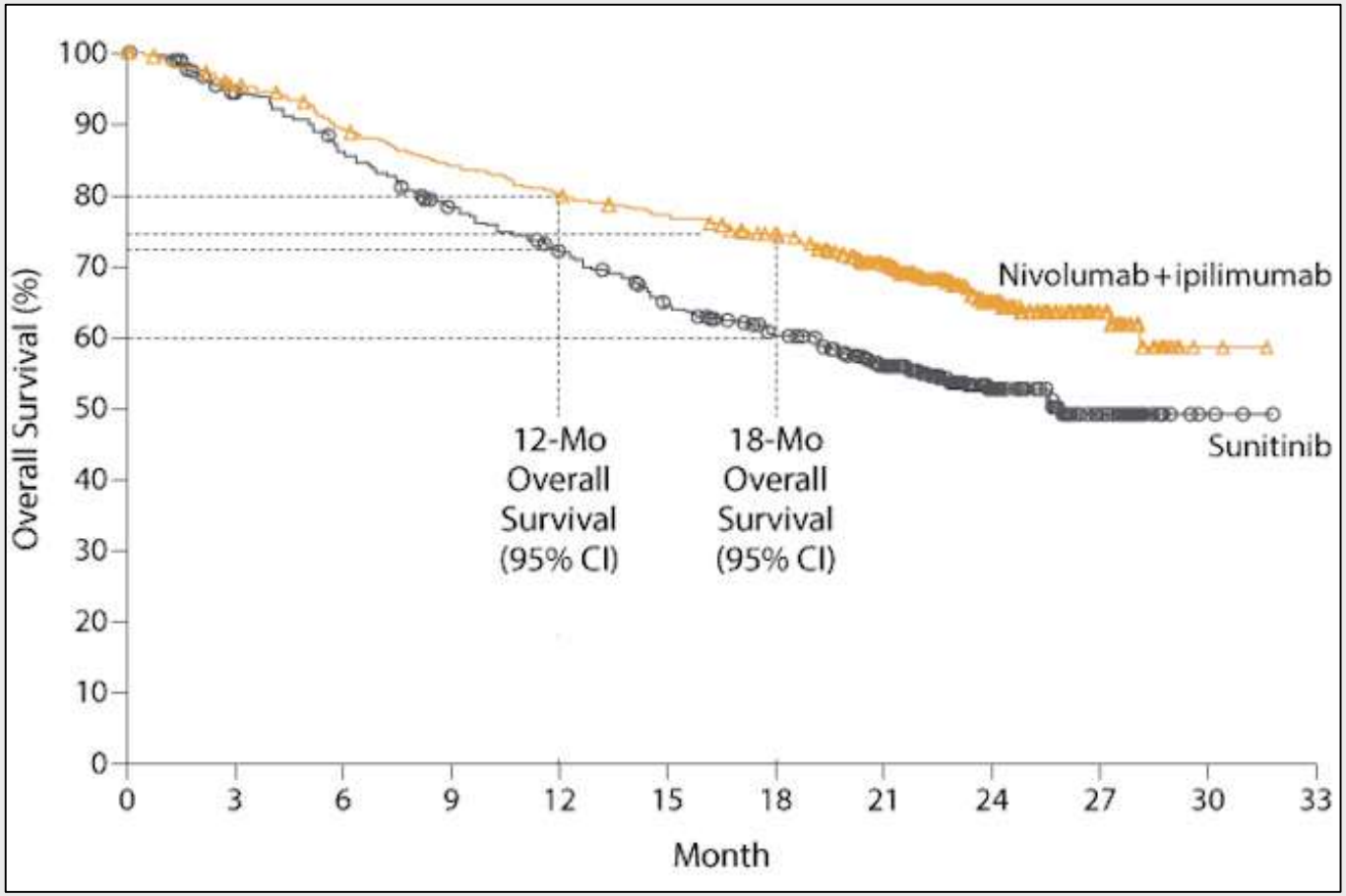
- Combination immunotherapy (Anti-Ctla4+anti-PD1)

Pembrolizumab and Axitinib vs. Sunitinib

KEYNOTE-426: OS in the ITT Population

From Rini BI et al. *N Engl J Med* 2019;380:1116–27. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Nivolumab + Ipilumumab vs Sunitinib



Choice in first line will come down to patient characteristics, toxicity

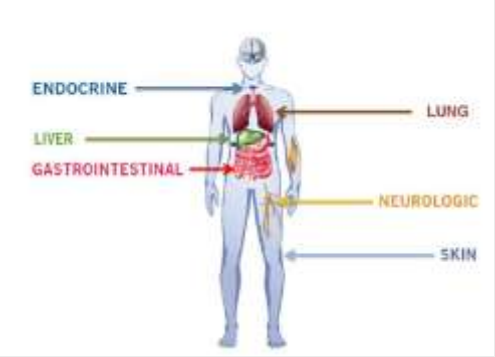
Motzer R, Lancet, 2019

Prostate Cancer

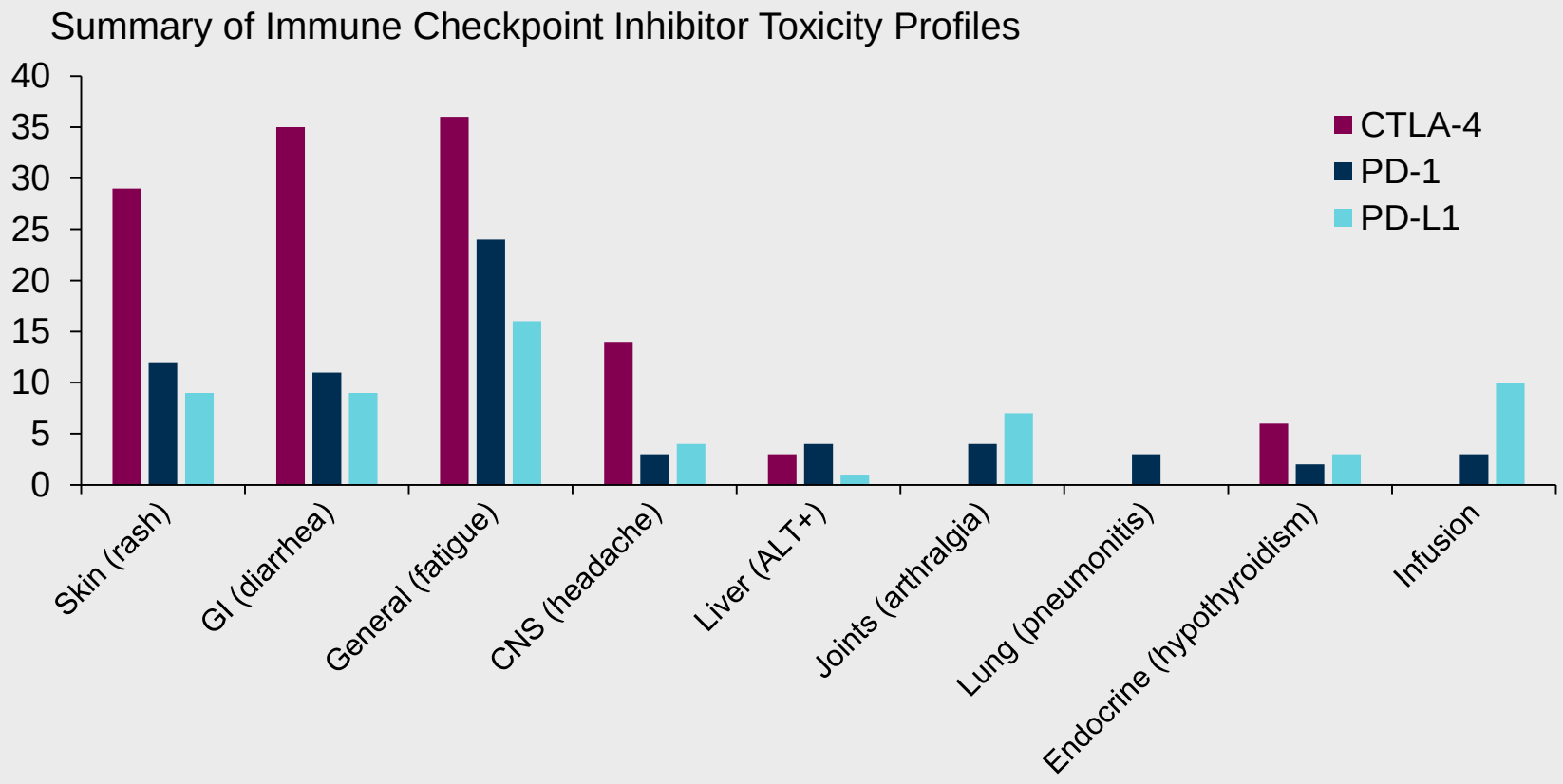
- Although many studies, currently there is no role for immunotherapy in this setting..

What about toxicity?

- Toxicity appear s~ 2-3 months
- Symptoms can be non-specific
- Symptoms can affect any body organ
- Need to be aware and treat promptly
- Stop immunotherapy
- Steroids remain the mainstay of treatment
- Need to consider referral to specialists



Immune Checkpoint Inhibitors Have a Unique Side Effect Profile



1. Hodi F S, et al. *N Engl J Med*. 2010; 2. Topalian S, et al. *N Engl J Med*. 2012; 3. Robert C, et al. *Lancet.* 2014;

Immune Related AEs

System	Select AE
Gastrointestinal	Diarrhea, nausea, colitis, perforation, pancreatitis
Endocrine	Thyroiditis, hypophysitis, hypopituitarism, adrenal insufficiency, Fatigue
Pulmonary	Pneumonitis
Liver	Hepatitis, transaminitis
Kidney	Nephritis
Neurologic	Central and peripheral; meningitis, Guillain-Barré syndrome, myasthenia gravis
Skin	Dermatitis, rash, vitiligo
Ocular	Uveitis, iritis, conjunctivitis
Cardiac	Pericarditis

Endocrinopathy imAE Case

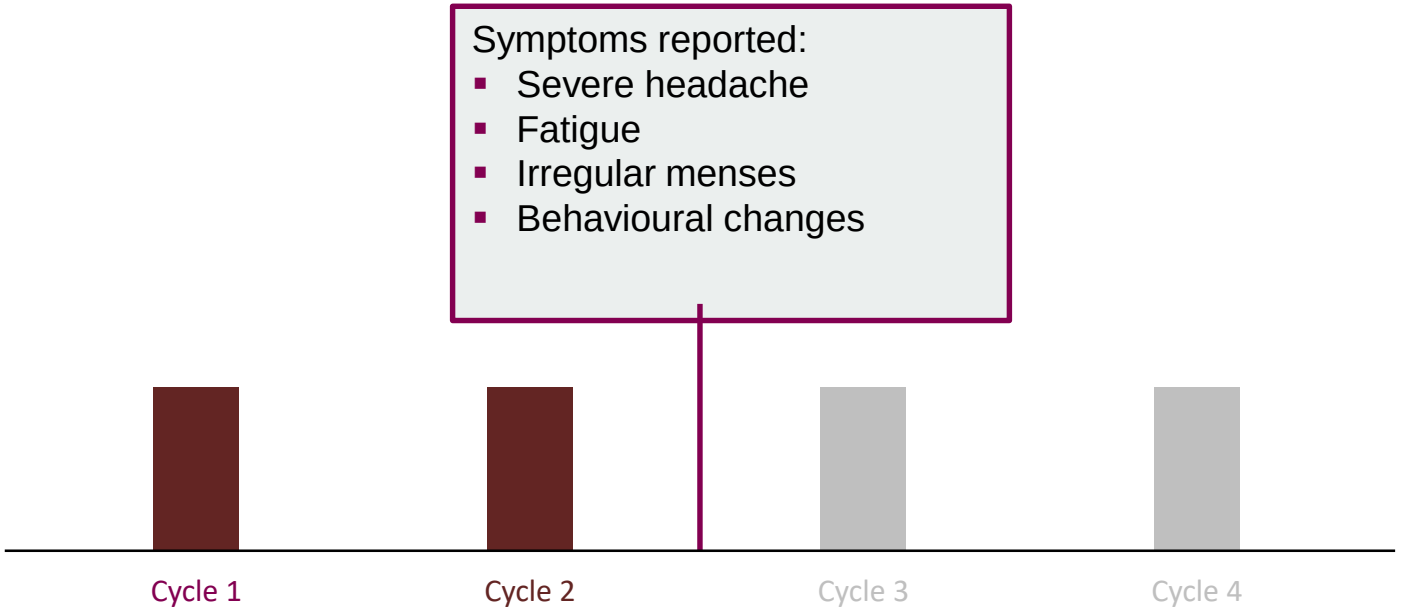
THE PATIENT

- 30-year-old female
- Metastatic renal cell cancer to the lungs
- No significant comorbidities or medical history
- Currently treated with a combination of anti-CTLA-4 and anti-PD-L1 therapy

CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-L1, programmed death ligand 1

SYMPTOMS

- Cycle 1 was completed without incident
- Two weeks after Cycle 2, the patient reported symptoms



FIRST REACTION

What would be your first reaction?

1. This is a gynaecological problem
2. This might be an imAE

imAE, immune-mediated adverse event

FIRST REACTION

What would be your first reaction?

1. This is a gynaecological problem
2. **This might be an imAE**

When a patient being treated with immunotherapy presents with headache and behavioural changes, one should be alert for imAEs

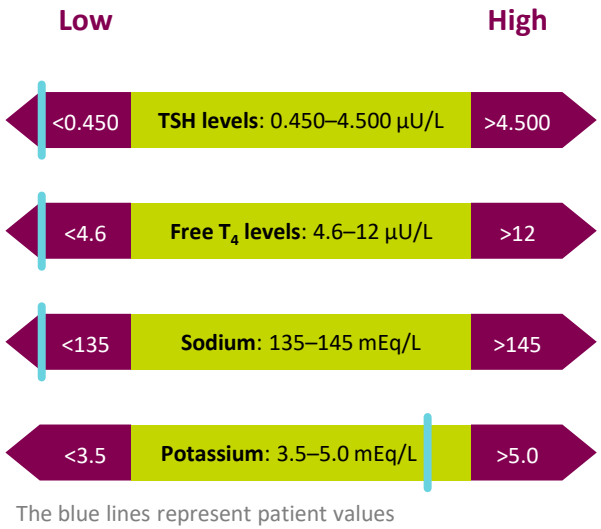
imAE, immune-mediated adverse event

- The same evening the patient reported the symptoms, she attended the emergency department
- Initial examination: profuse sweating, hypotension and increased heart rate

INITIAL DIAGNOSTIC TEST RESULTS

	Regular	Recorded
Blood pressure (SBP/DBP)	115/70	95/60
Heart rate (bpm)	64	96

- A comprehensive blood panel, including thyroid function, was performed
  - The results indicated hypothyroidism (TSH 0.02 µU/L; free T_4 levels 1 µU/L) and hyponatraemia
- All other values within the normal range



The blue lines represent patient values

bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; T_4, thyroxine; TSH, thyroid-stimulating hormone

INITIAL DIAGNOSIS

What would be your initial diagnosis?

1. Nothing is wrong here; the patient can receive her next immunotherapy dose
2. Brain metastasis
3. Aseptic meningitis
4. Primary thyroiditis
5. Hypophysitis (with secondary hypothyroidism)
6. Addison's disease

INITIAL DIAGNOSIS

What would be your initial diagnosis?

1. Nothing is wrong here; the patient can receive her next immunotherapy dose
2. Brain metastasis
3. Aseptic meningitis
4. Primary thyroiditis
5. **Hypophysitis (with secondary hypothyroidism)**
6. Addison's disease

Low T_4 and low TSH are suspect for central hypothyroidism. Low blood pressure and hyponatraemia could indicate adrenal problems, such as hypoaldosteronism or Addison's disease. The combined information in a patient taking immunotherapy points in the direction of a central cause, potentially hypophysitis

INITIAL DIAGNOSIS

- Hypophysitis is rare in the general population but known to be an imAE in patients receiving immune checkpoint inhibitor therapy

imAE, immune-mediated adverse event

FURTHER DIAGNOSTIC TESTS

What additional lab tests would you order to confirm hypophysitis?

1. ACTH
2. Cortisol
3. LH
4. FSH
5. Prolactin
6. GH
7. All of the above

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone

FURTHER DIAGNOSTIC TESTS

What additional lab tests would you order to confirm hypophysitis?

1. ACTH
2. Cortisol
3. LH
4. FSH
5. Prolactin
6. GH
7. **All of the above**

Performing all relevant hormone tests associated with the hypothalamic–pituitary axis will identify isolated changes in one or more hormones. A thorough endocrine work-up is required in the setting of possible hypophysitis

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone

FURTHER DIAGNOSTIC TESTS

What additional imaging tests would you order to confirm hypophysitis?

1. MRI
2. CT
3. X-ray sella turcica
4. All of the above

CT, computed tomography; MRI, magnetic resonance imaging

FURTHER DIAGNOSTIC TESTS

What additional imaging tests would you order to confirm hypophysitis?

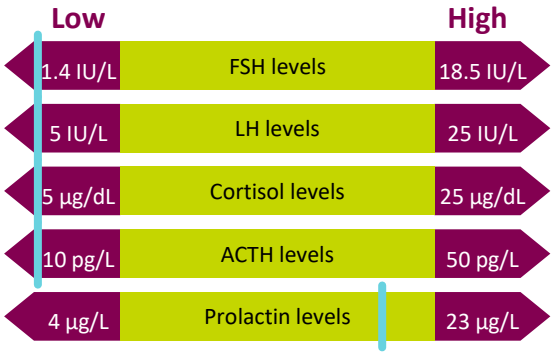
1. **MRI**
2. CT
3. X-ray sella turcica
4. All of the above

MRI, more specifically the 'pituitary protocol', is the most specific imaging test when hypophysitis is suspected

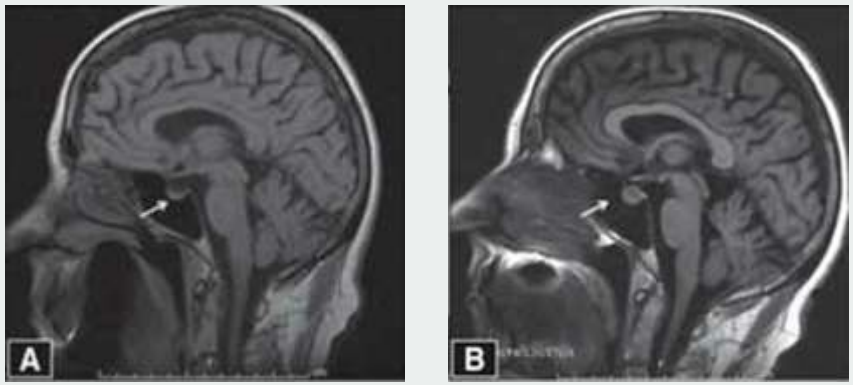
CT, computed tomography; MRI, magnetic resonance imaging

FURTHER DIAGNOSTIC TEST RESULTS

- Further lab diagnostic tests showed:
  - FSH, LH, cortisol and ACTH were abnormally low
  - Prolactin levels were high normal



The blue lines represent patient values



MRI findings show the pituitary gland before therapy (A) and during therapy (B)

- MRI showed a diffuse enlargement of the pituitary gland which was not present 6 months earlier

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging

PATIENT DIAGNOSIS

The patient was diagnosed with **Grade 2 immune-mediated hypophysitis**

- Symptoms were moderate
- The patient required medical intervention
- She could be managed without hospitalisation

CT, computed tomography; MRI, magnetic resonance imaging

TREATMENT

How would you treat this patient?

1. Thyroid replacement therapy
2. Prednisone starting at 1–2 mg/kg/day
3. Both thyroid replacement and oral prednisone
4. Other

TREATMENT

How would you treat this patient?

1. Thyroid replacement therapy
2. Prednisone starting at 1–2 mg/kg/day
3. **Both thyroid replacement and oral prednisone**
4. Other

TREATMENT

- Treated as an outpatient
- Hypophysitis was effectively managed with the prescribed therapy, which included:
  - Prednisone at 2 mg/kg/day
  - Levothyroxine sodium to treat the secondary hypothyroidism
- Combined CTLA-4 and PD-L1 immunotherapy was suspended

CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-L1, programmed death ligand 1

- Symptoms improved within 48 hours
- Laboratory values normalised in the following weeks
- Repeat MRI showed complete normalisation of the pituitary gland

FOLLOW-UP

- After the symptoms were resolved, prednisone was discontinued in a slow taper over 28 days
- Levothyroxine sodium treatment was continued
- If there was no recurrence of symptoms, the patient could be restarted on her immunotherapy

MRI, magnetic resonance imaging

KEY POINTS

- Immune-mediated endocrinopathy is the inflammation of any organ in the hypothalamic–pituitary–adrenal axis
- Immune-related endocrinopathies may present with non-specific constitutional symptoms. They can become highly symptomatic if left undiagnosed
- Most are typically reported to affect the pituitary, thyroid and / or adrenal glands leading to hypophysitis, thyroid dysfunction and / or adrenal insufficiency
- Communication and patient education to report symptoms as early as possible will enable prompt and effective intervention
- Imaging and / or regular blood screening for hormonal abnormalities,
  even in asymptomatic patients, is a key tool to ensure early detection
- Even severe symptoms generally resolve quickly with prompt initiation of hormone replacement therapy and / or corticosteroid therapy

Conclusions

- Immunotherapy has changed how we treat many cancers, with several studies ongoing
- Need to remember that it doesn’t work in everyone and response rates are only about 20%
- Toxicity is different, and physicians need to be aware of the variety of side effects.
- As these drugs move earlier in the treatment paradigm patients may be on them for longer