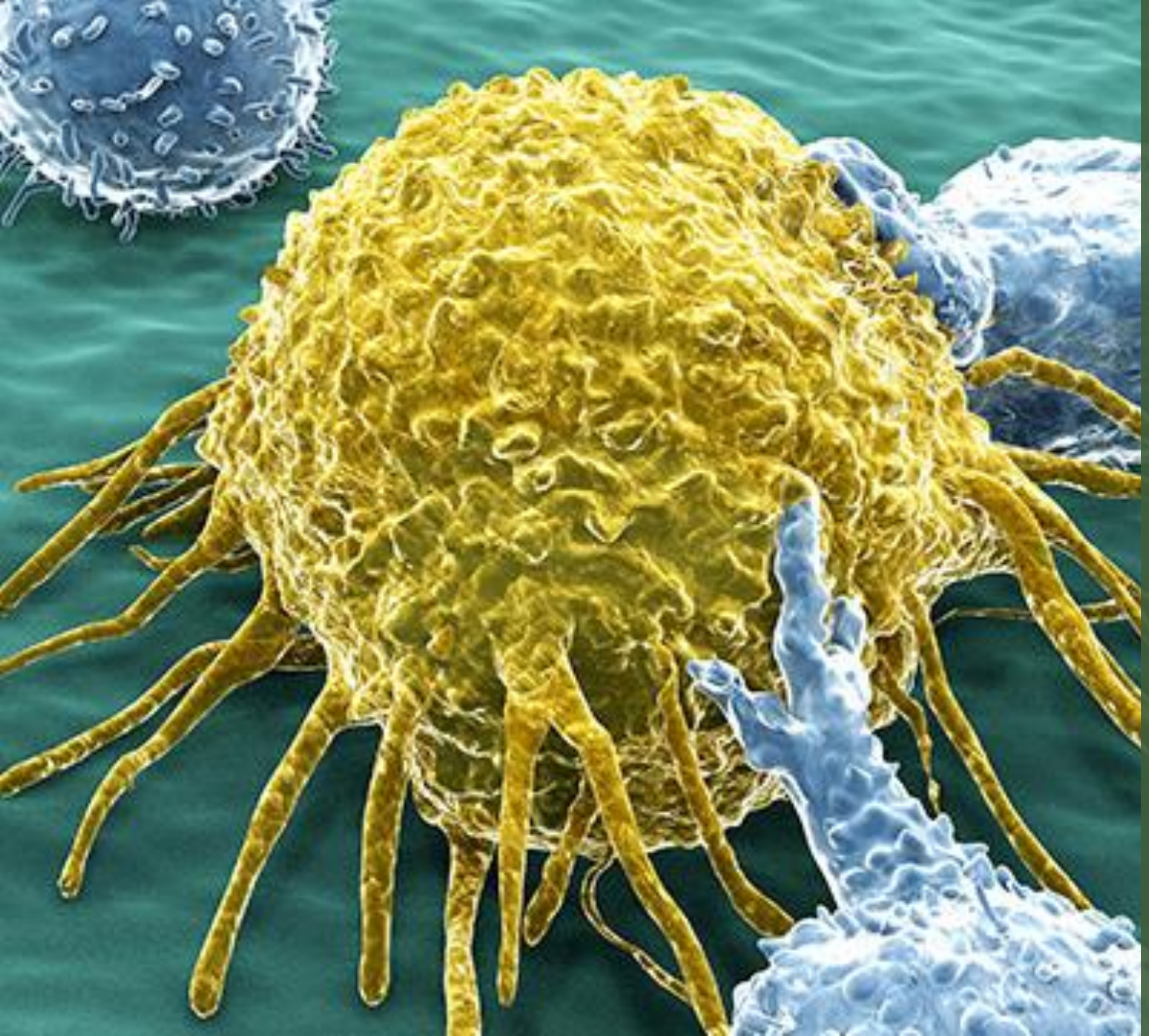


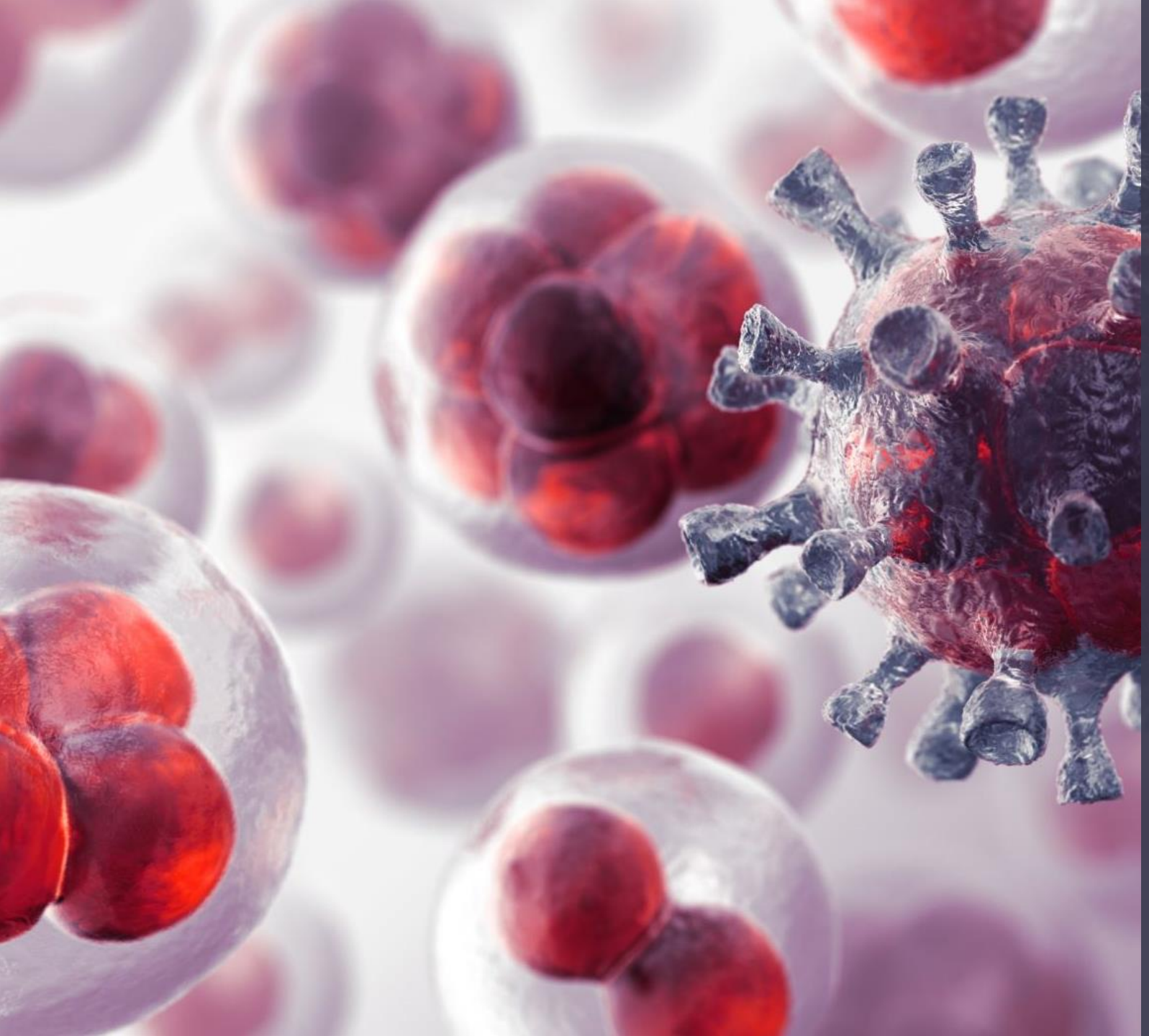
Immunotherapy 101

Caro Aberhart

September 2025

Learning Objectives

Explain	Explain the mechanism of action if immune checkpoint inhibitors in treating cancer
List	List the common immune-related adverse events (irAEs)
Suggest	Suggest appropriate monitoring and treatment of irAEs



Cancer and the Immune System

Immune System

Function

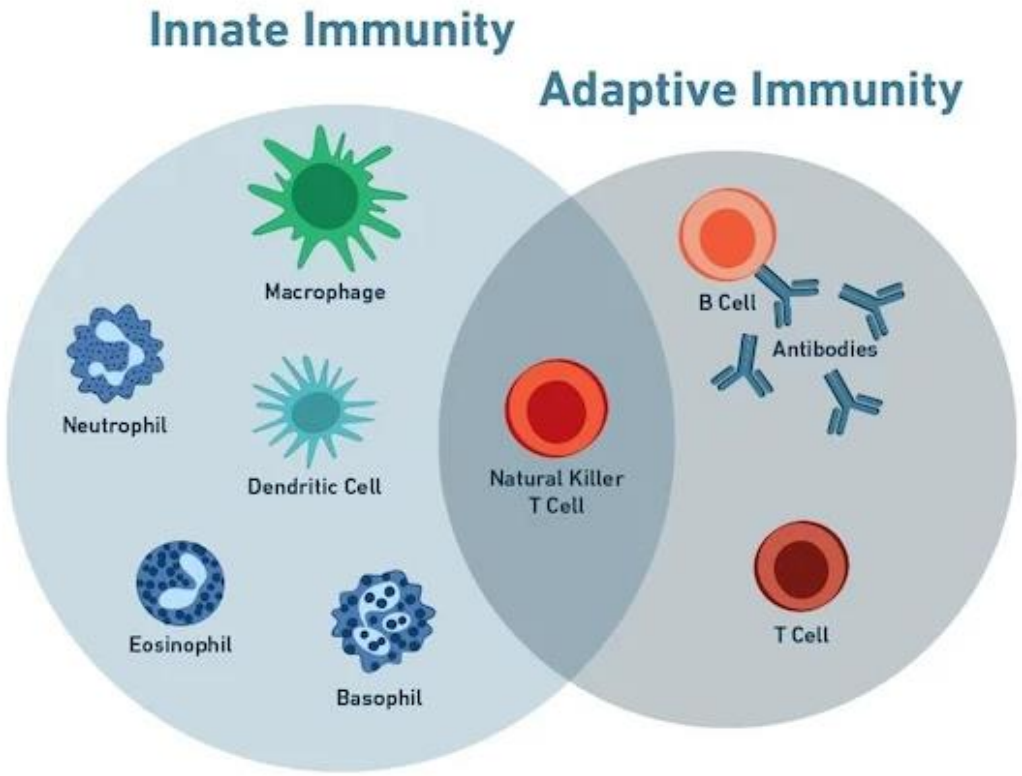
- Defence against pathogens
- Homeostasis
- Recognition and removal of damaged cells
- Surveillance

Two types of immune response

- Innate
- Adaptive

Important anti-cancer function is surveillance and identify foreign substances.

Damaged DNA in cancer cells frequently directs the mutated cell to produce abnormal proteins known as tumour antigens

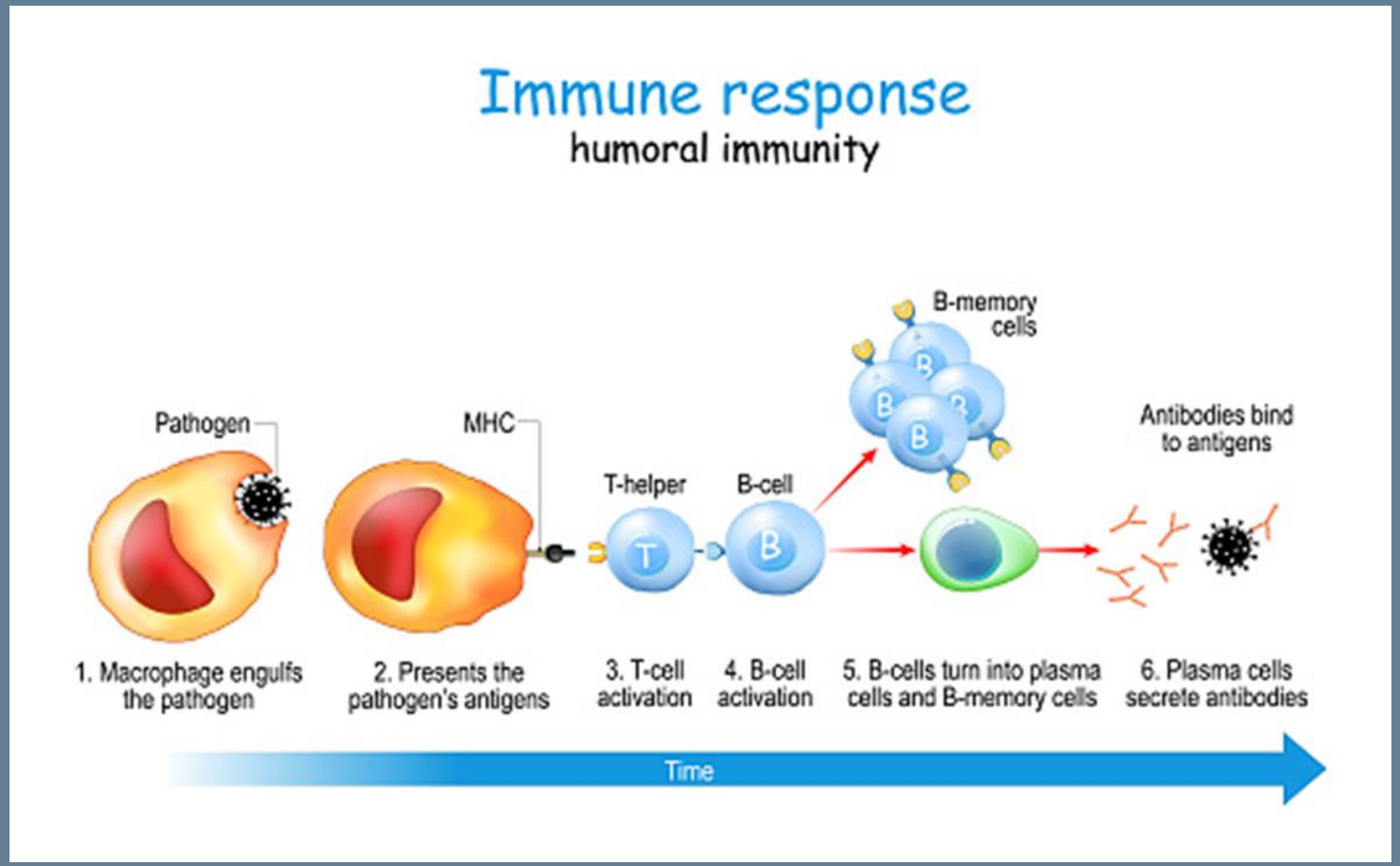


Immune System

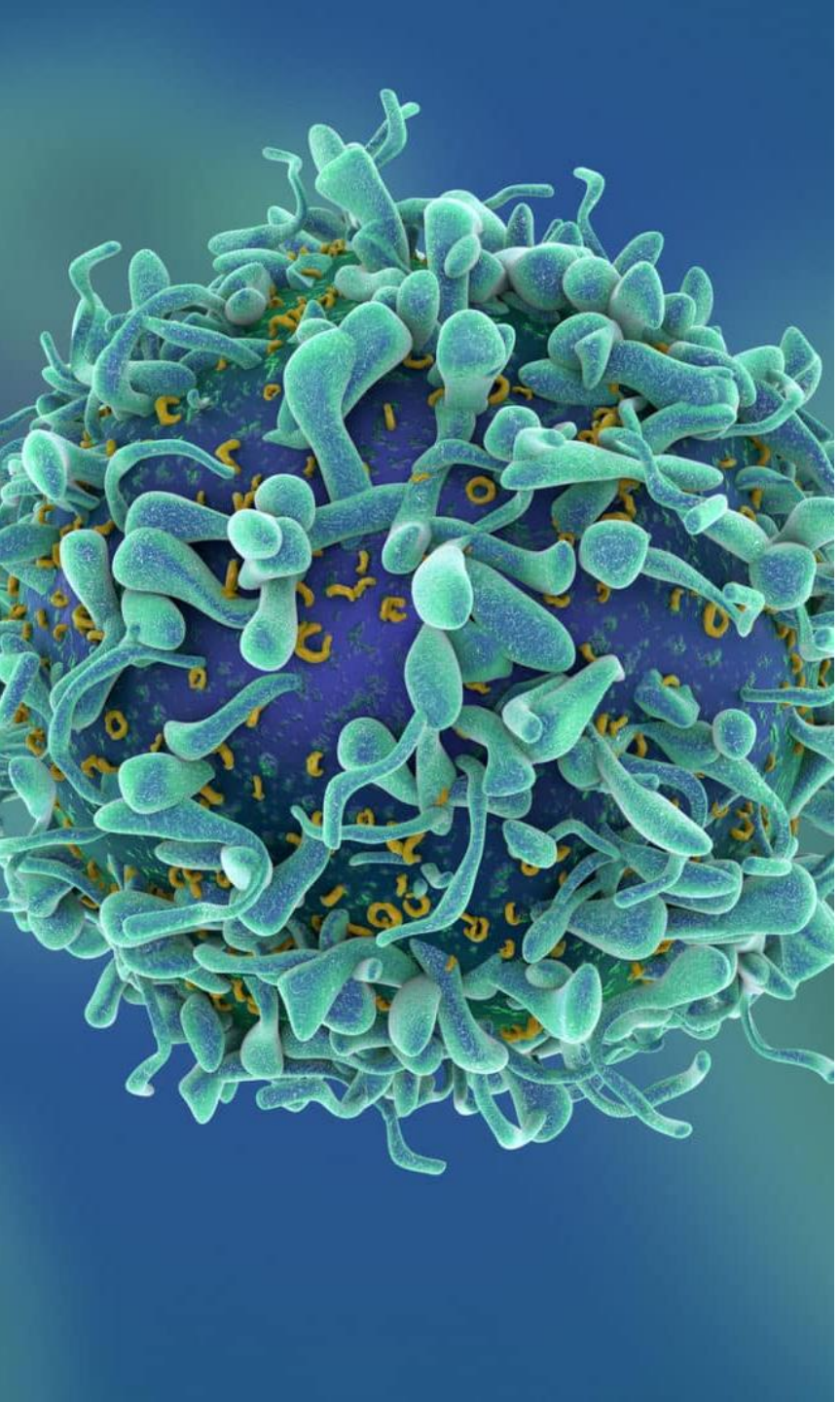
Both innate and adaptive immune system are involved in detection and elimination of tumour cells.

Innate – recognize stress-related ligands and tumour antigens on tumour cells which mark them as non-self.

Adaptive – cellular and humoral immunity to detect and eliminate cancer cells.



Immune Response



T-Cells

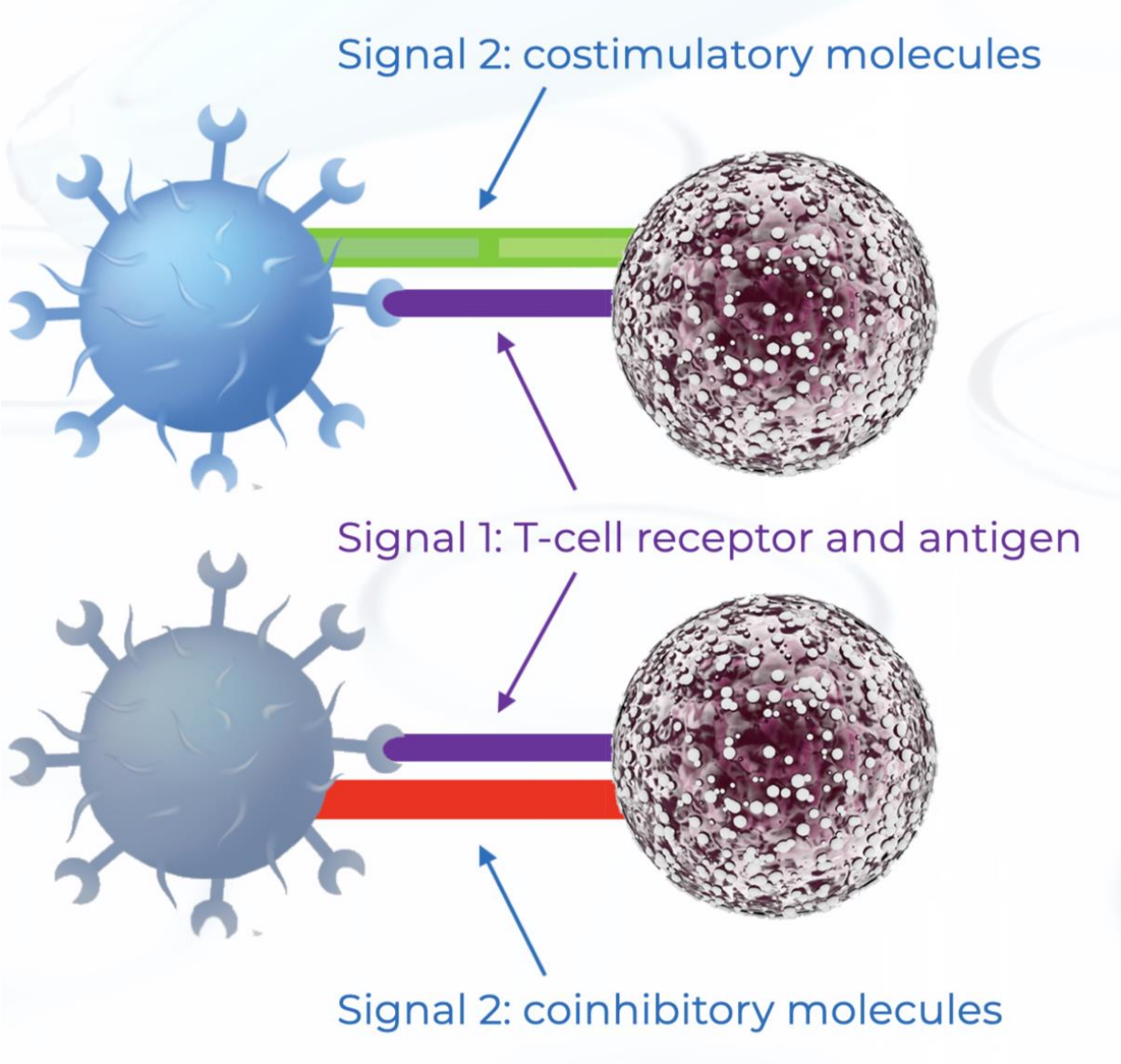
Helper T-cells upon activation release IL-2 to stimulate growth and proliferation

Release cytokines to stimulate an inflammatory response and recruit phagocytic monocytes and neutrophils to area

Some helper T-cells differentiate into regulatory T-cells

- Assist in preventing overactive immune response

Regulatory T-cells reduce clonal expansion of effector T-cells

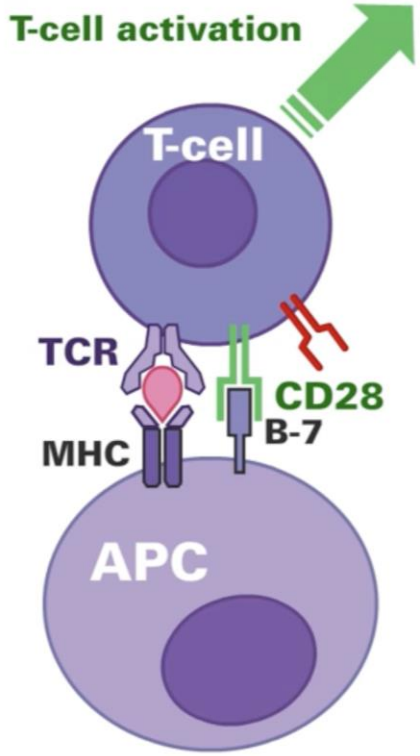


T-cells

Two signals required to activate T-cells in priming phase and stimulate action against antigens in effector phase

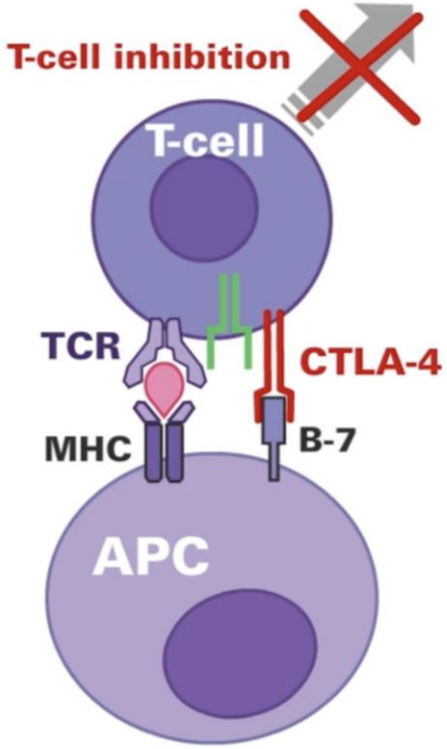
Signal 1: binding of antigen to T-cell receptor

Signal 2: binding of costimulatory or coinhibitory molecules



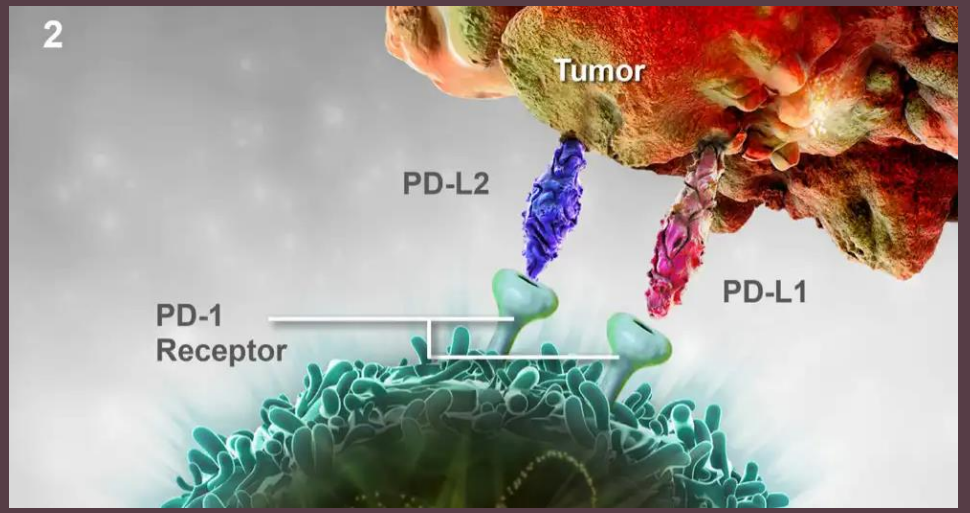
On switch:
T-cell activated by costimulatory CD28

Off switch:
T-cell attack prevented by coinhibitory molecule CTLA-4



T-cells

Programmed Death Molecule 1 (PD-1)



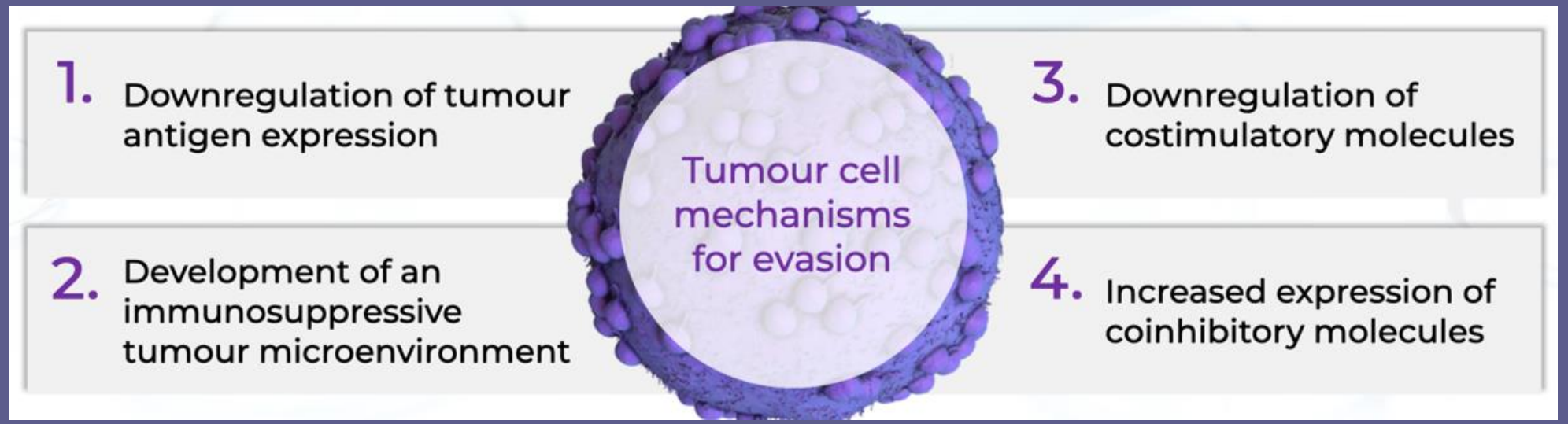
During effector phase T-cells express more PD-1

When PD-1 binds to coinhibitory signal 2 molecules on surface of cells (e.g. PD-L1 or PD-L2) effector function of T-cell deactivated

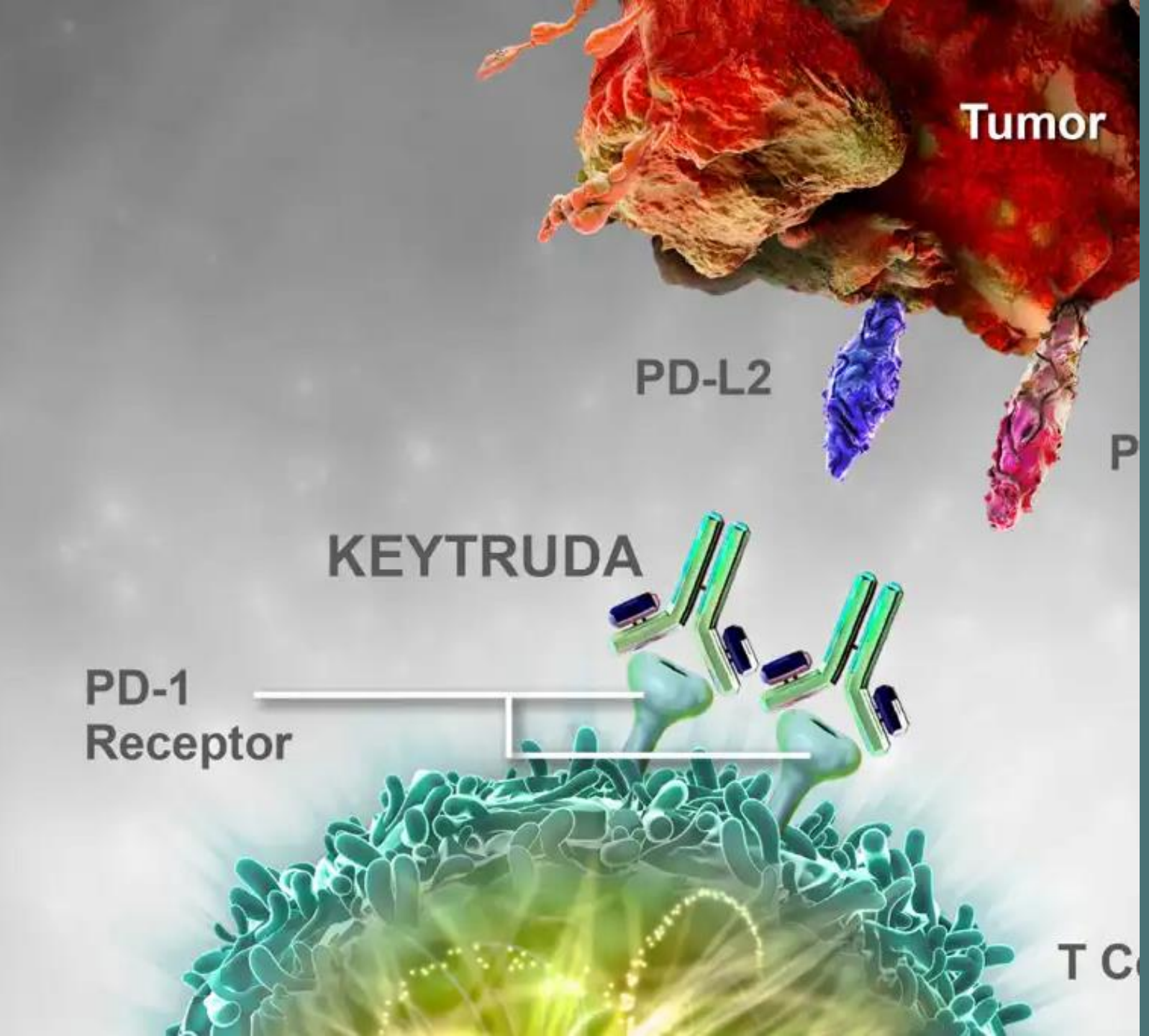
- Immune checkpoint
- Prevent overactive immune response and protect against autoimmunity

Tumour cells can overexpress PD-L1 or PD-L2 on their surface

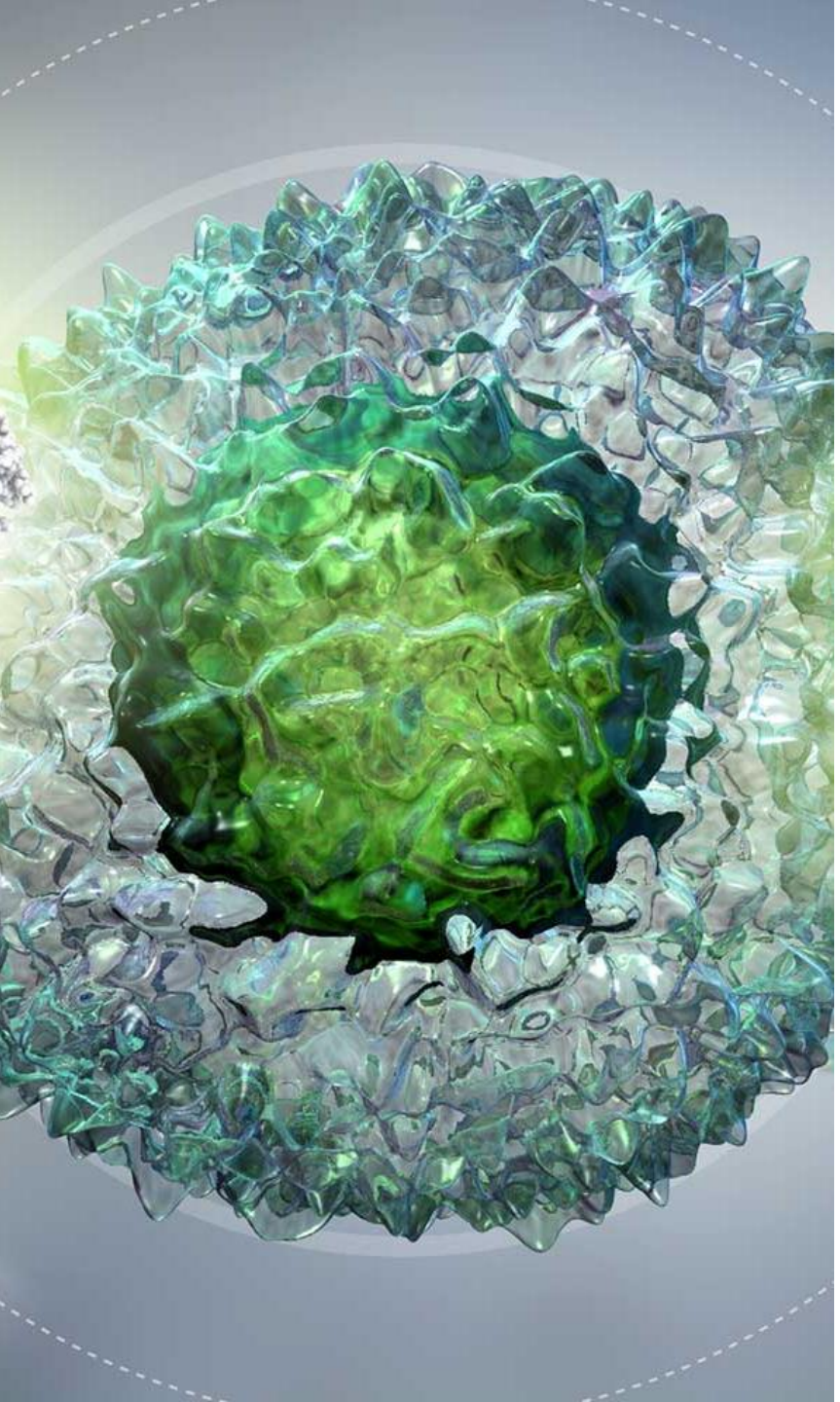
- Increased capacity to deactivate T-cell



Cancer and the Immune System



Checkpoint Inhibitors



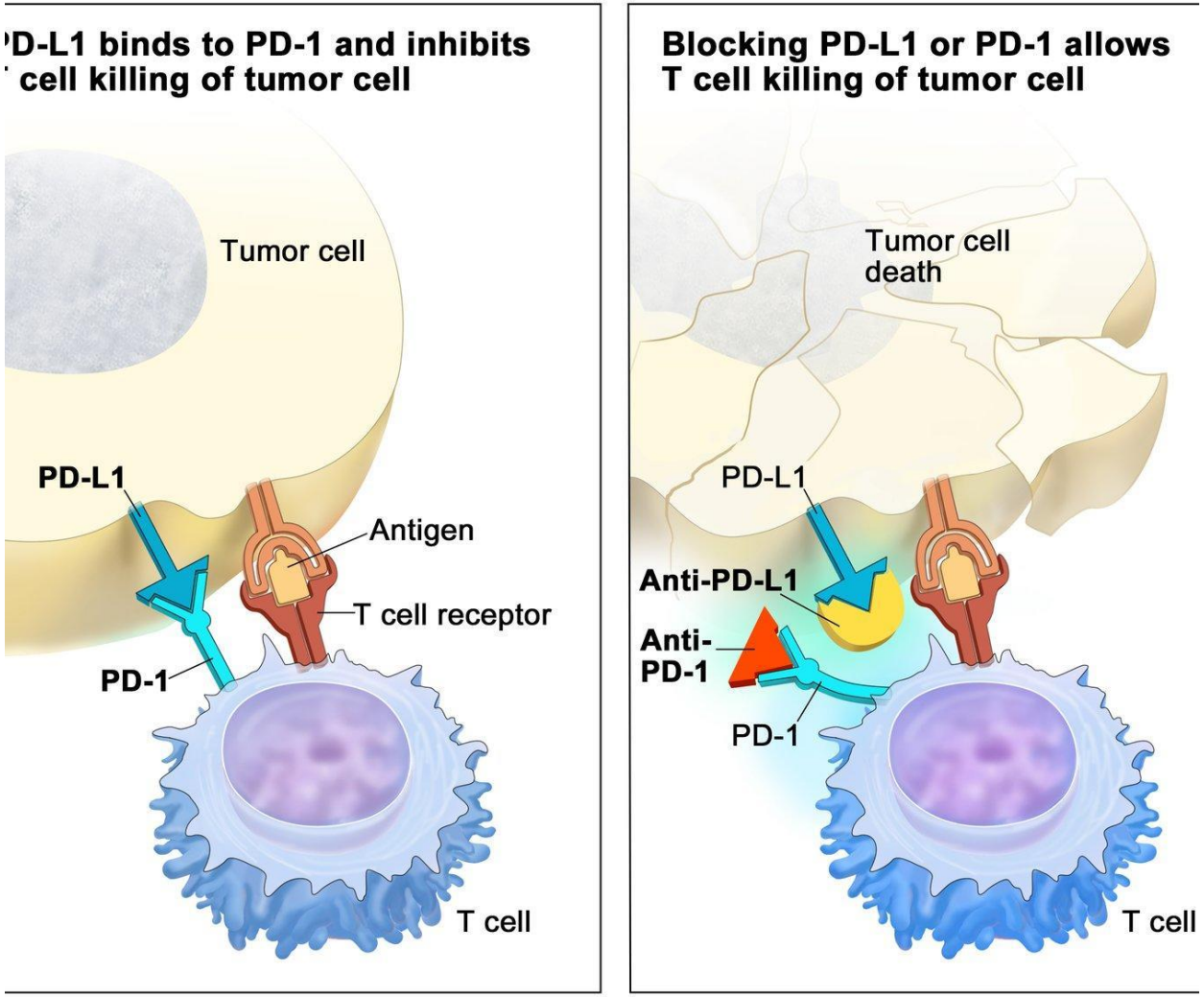
Immune Checkpoint Inhibitors

The interaction between PD-1 on T-cells and PD-L1 on tumour cells inactivates the T-cell

- Helps cancer evade the immune system

PD-1 inhibitors block the binding of PD-L1 to PD-1

- Stop T-cells becoming deactivated
- Enhance the immune system's ability to kill cancer cells



Immune Checkpoint Inhibitors

CTLA-4 inhibitors

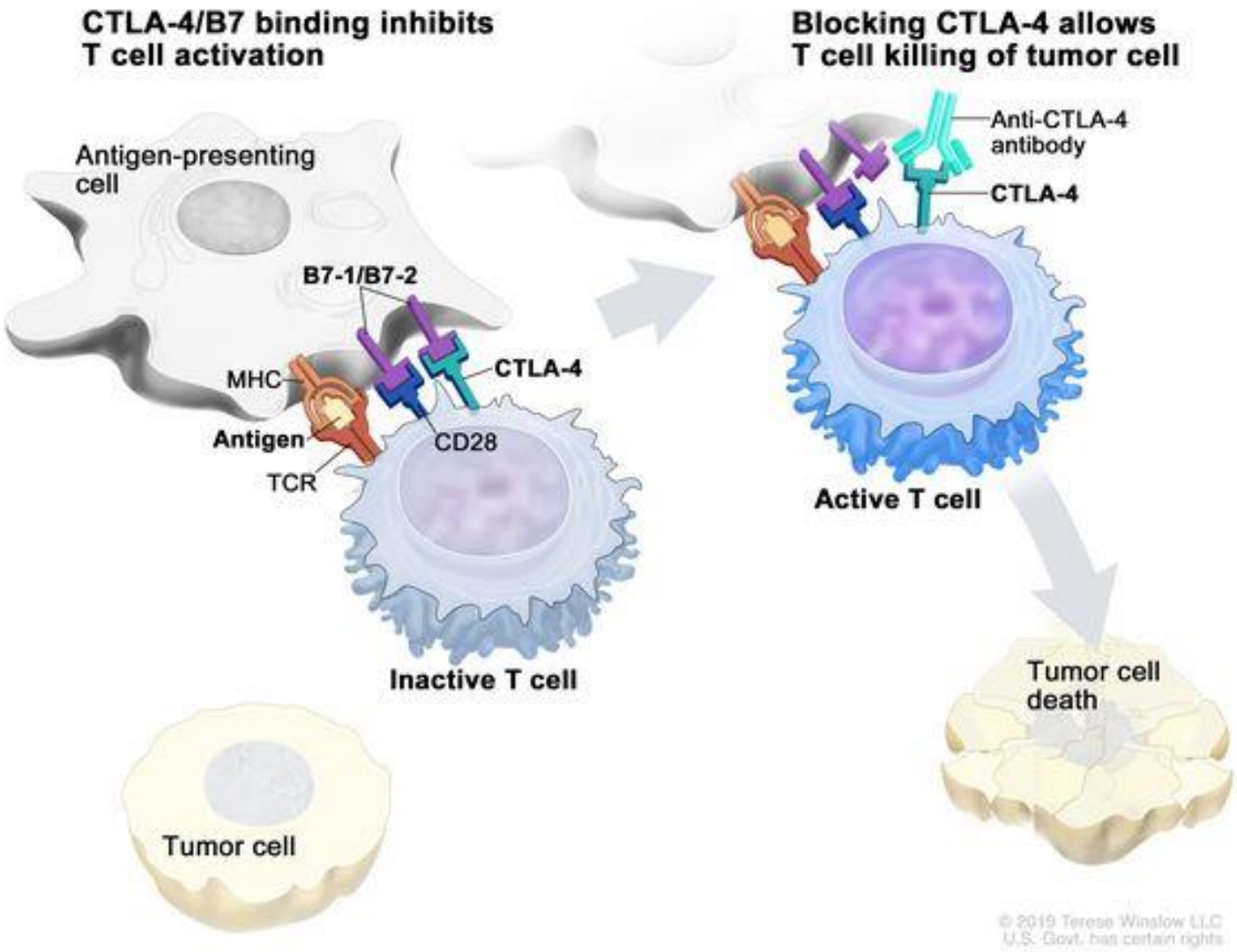
- Ipilimumab

PD-1 inhibitors

- Pembrolizumab
- Nivolumab

PD-L1 inhibitors

- Atezolizumab
- Durvalumab


CTLA-4/B7 binding inhibits
T cell activation
Antigen-presenting
cell
B7-1/B7-2
MHC
CTLA-4
Antigen
CD28
TCR
Inactive T cell
Tumor cell
Blocking CTLA-4 allows
T cell killing of tumor cell
Anti-CTLA-4
antibody
CTLA-4
Active T cell
Tumor cell
death
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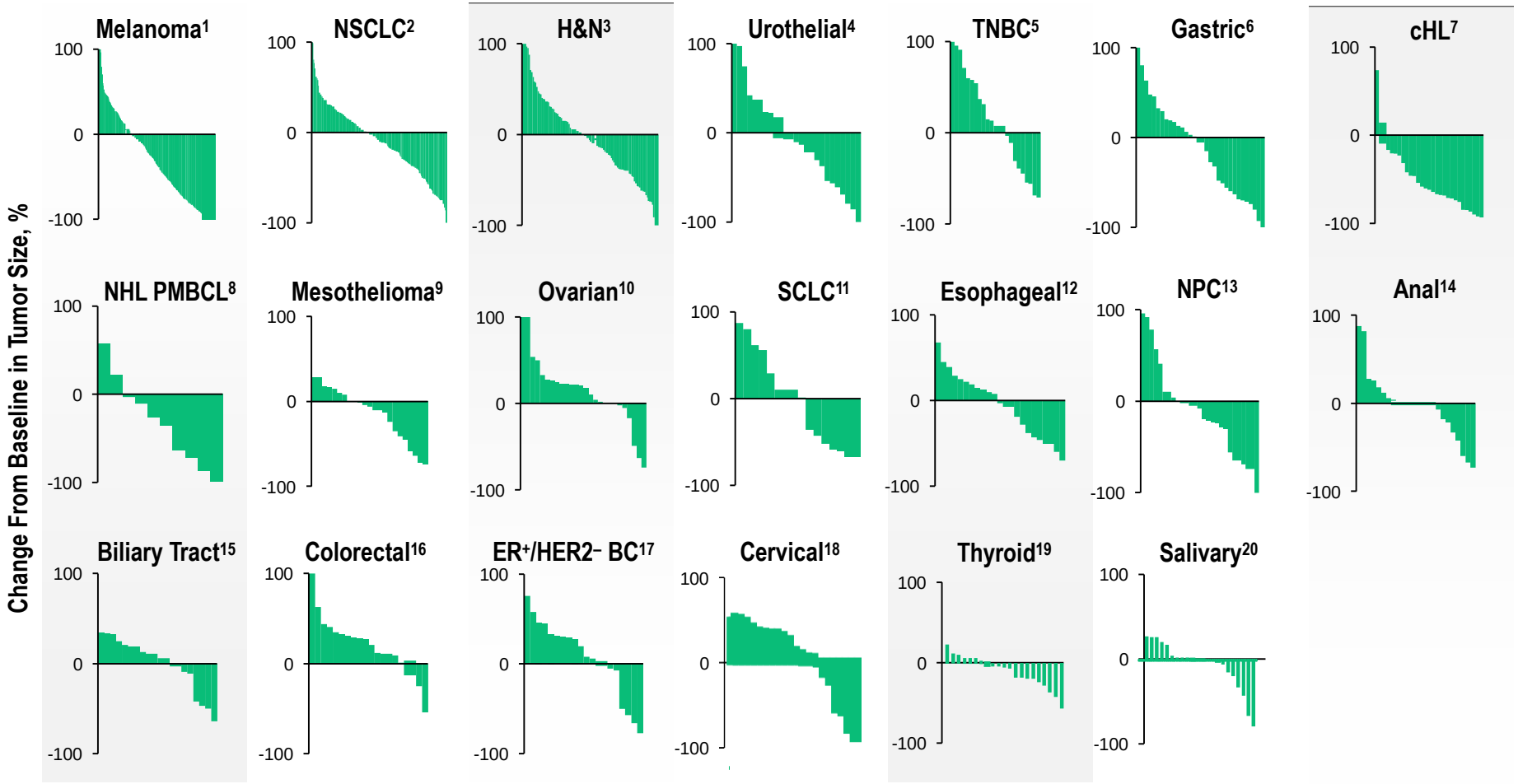
Pembrolizumab monotherapy has shown activity in >20 tumours



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015; 18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016.

ICIs in Aotearoa

Non-small cell lung cancer	Renal cell carcinoma	Melanoma
Hodgkin lymphoma	Head and neck squamous cell carcinoma	Urothelial cancer
Breast cancer	Unresectable hepatocellular carcinoma	Atezolizumab and bevacizumab

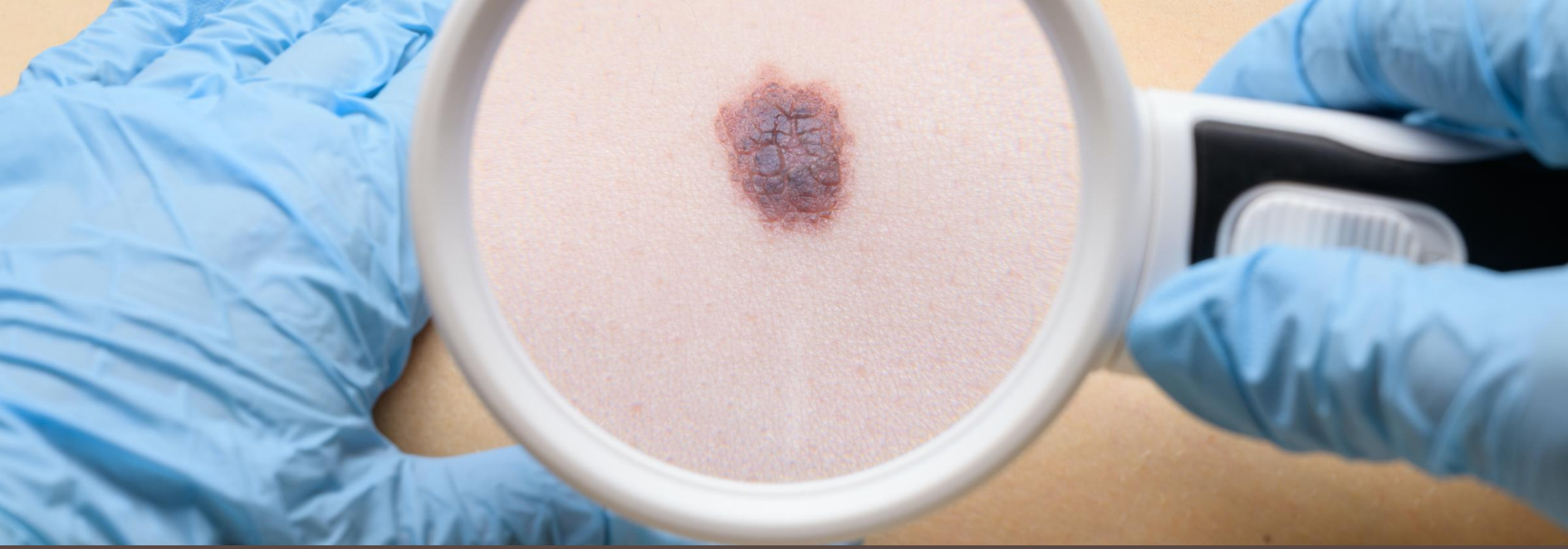
Pembrolizumab

Nivolumab

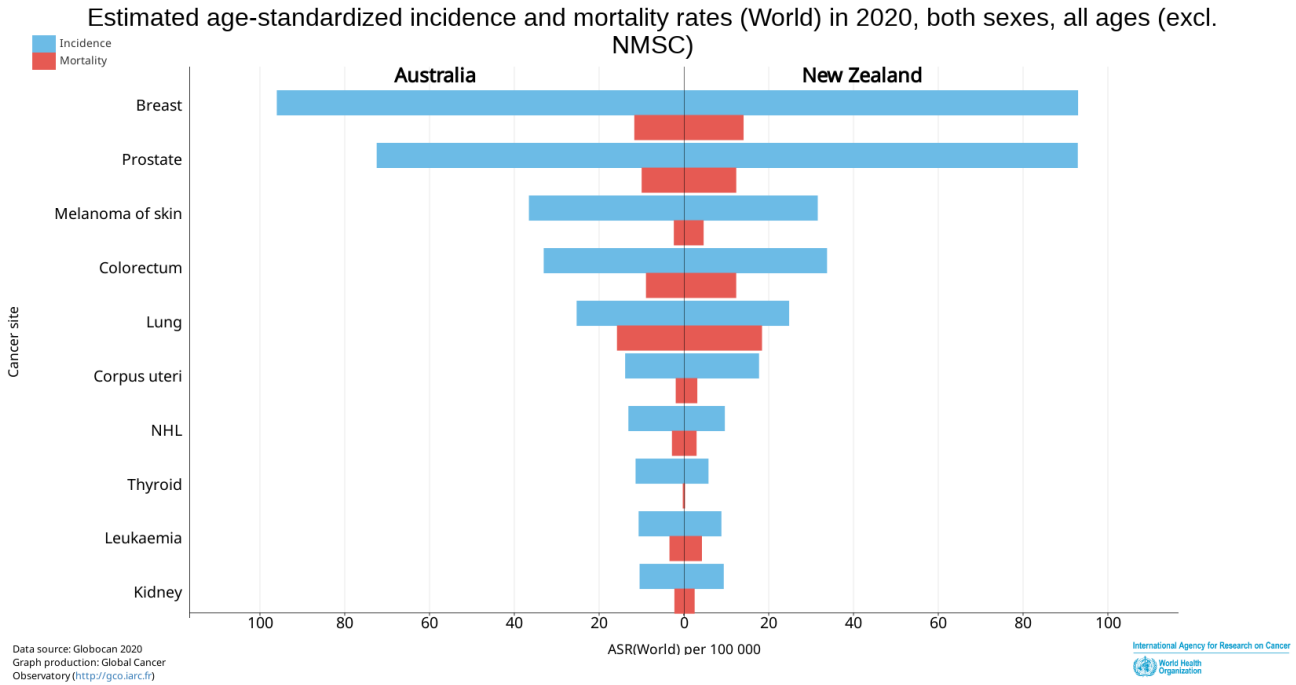
Atezolizumab

Durvalumab

Ipilimumab



Checkpoint Inhibitors and Melanoma



Metastatic Melanoma without Checkpoint Inhibitors

3rd most common cancer in NZ

Median survival 6 to 12 months

10 year survival = 5%

Dacarbazine chemotherapy

- < 20% response rate, no survival improvement

Targeted therapy with BRAF/MEK inhibitors

- Good response rate but most eventually relapse

PD-1 Inhibitors in Practice

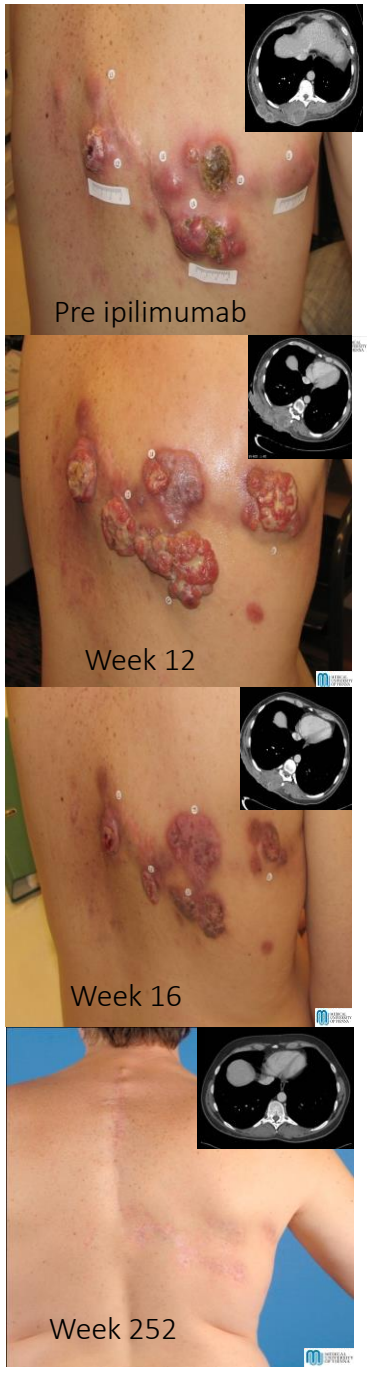
Average time to respond 8 weeks

Sometimes see unusual response patterns

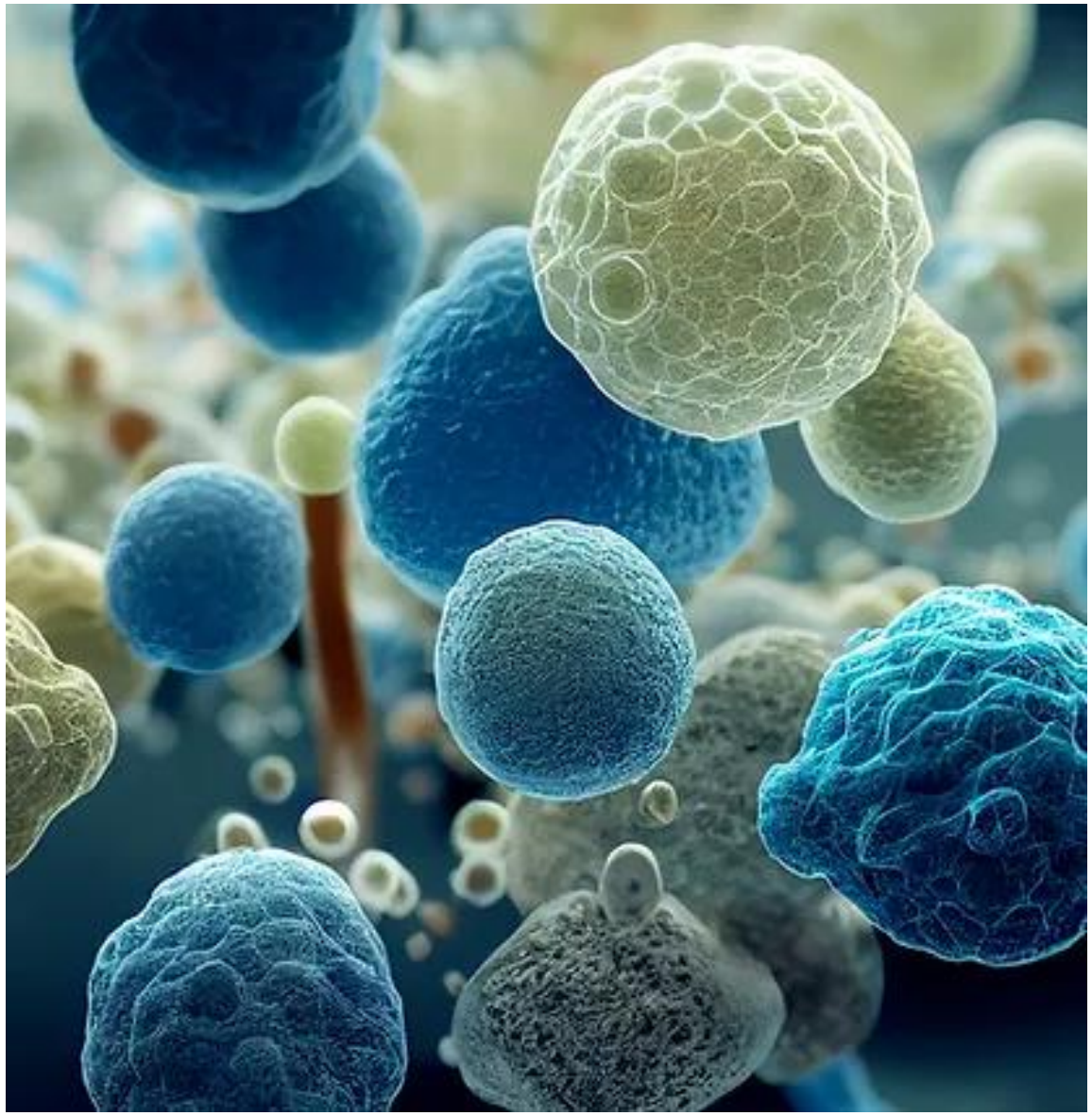
- Pseudoprogression (caution in stopping treatment early)

Virtually no drug interactions

No concern about immunosuppression (like chemotherapy)



Adverse Effects of Checkpoint Inhibitors



Immune related adverse effects

Generally well tolerated

Unique spectrum of side effects – immune related adverse events believed to arise from general immunologic enhancement

Can occur at any time during treatment

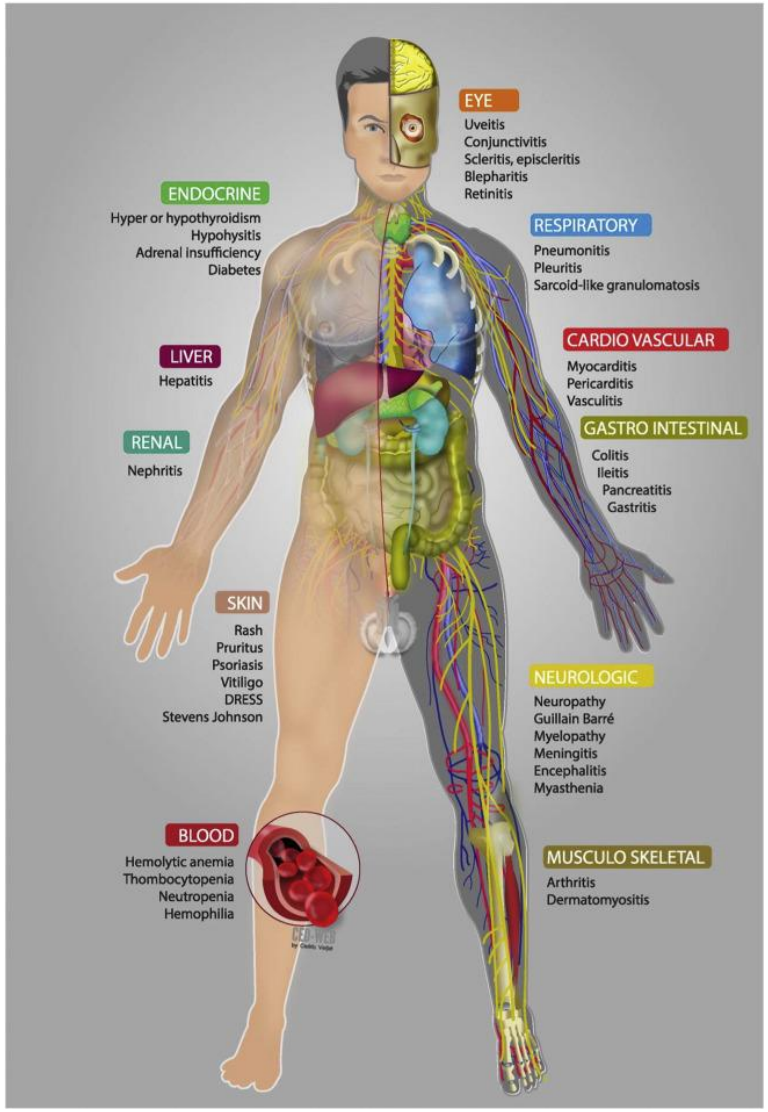
Grade 3/4 toxicity: 11 – 16%

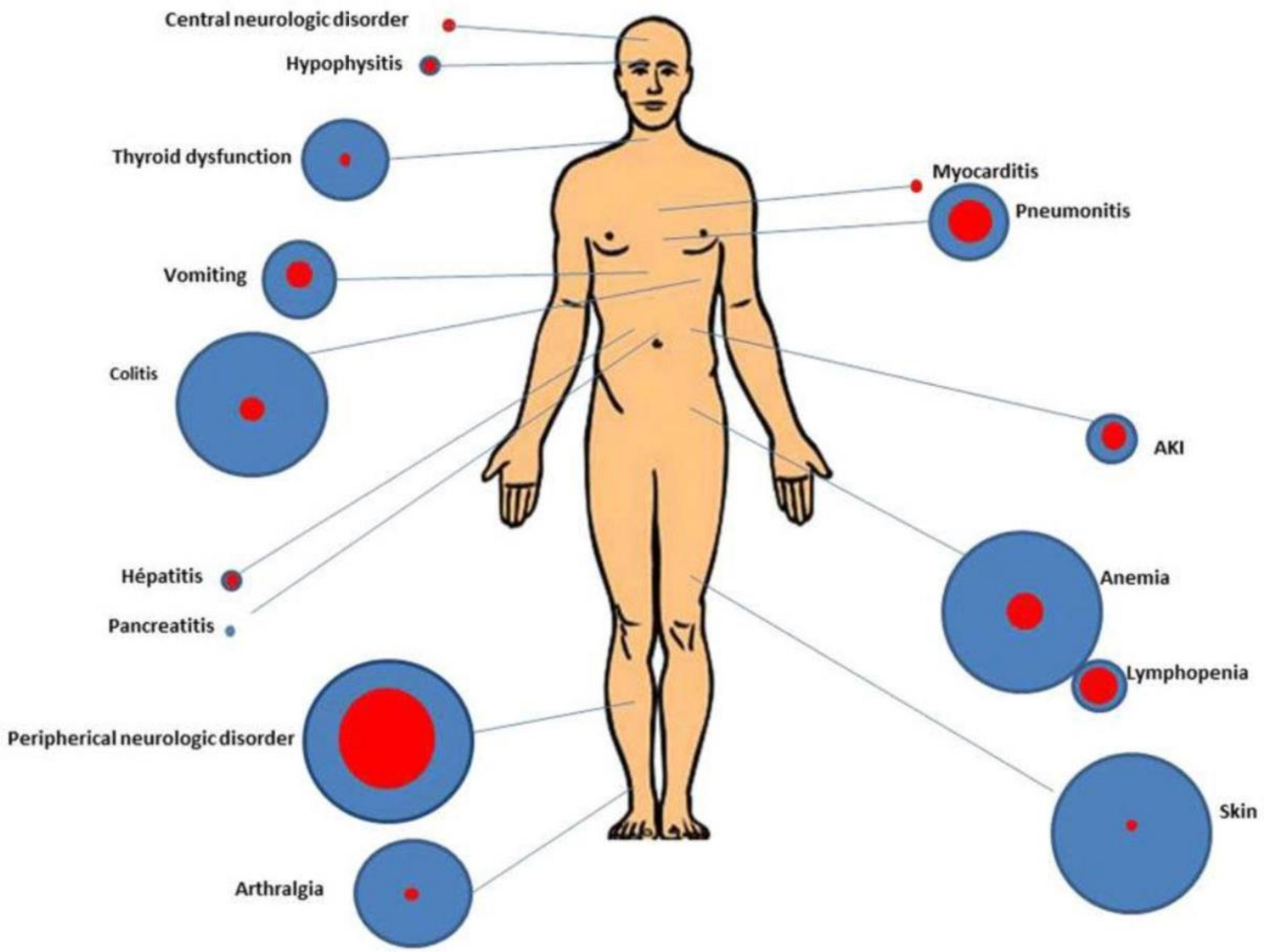
Most common irAEs:

- Fatigue (30%)
- Pruritis (22.8%)
- Rash (19.8%)
- Arthralgia (14.8%)
- Diarrhoea (14.8%)

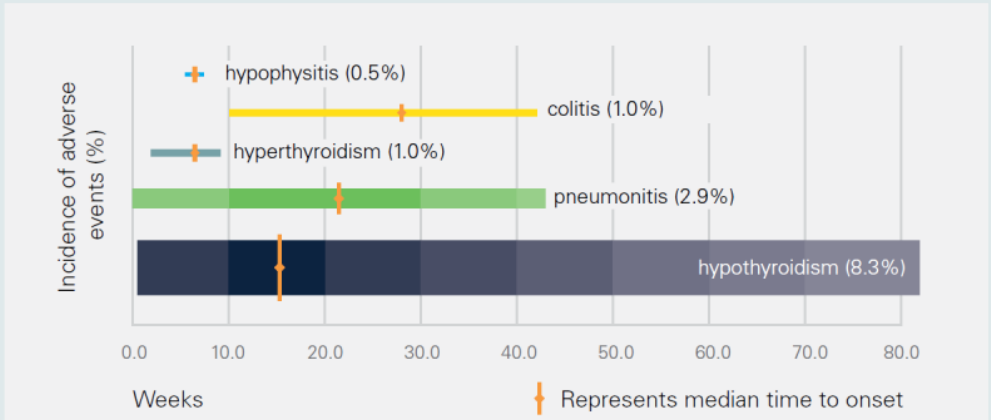
Fatal toxicities may occur

irAEs associated with improved efficacy?


EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis
ENDOCRINE
Hyper or hypothyroidism
Hypohysitis
Adrenal insufficiency
Diabetes
RESPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis
CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis
LIVER
Hepatitis
GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis
RENAL
Nephritis
SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson
NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia
BLOOD
Hemolytic anemia
Thombocytopenia
Neutropenia
Hemophilia
MUSCULO SKELETAL
Arthritis
Dermatomyositis


Central neurologic disorder
Hypophysitis
Thyroid dysfunction
Vomiting
Colitis
Hépatitis
Pancreatitis
Peripherical neurologic disorder
Arthralgia
Myocarditis
Pneumonitis
AKI
Anemia
Lymphopenia
Skin

Time after initiation of therapy to onset of various immune-mediated adverse events (n = 411)*



Adapted from Tepley 2014.[6]

* Pooled safety data from 411 patients studied across three doses (2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks) during KEYNOTE-001.

irAE Timing

Monitoring irAEs

Every cycle

- LFTs
- Creatinine
- CBC
- Cortisol
- Thyroid function
- Glucose

Monitored clinically for signs of colitis, pneumonitis, hepatitis etc

EviQ assessment tool

Has anything changed for you?

Managing irAE: General Principles

Early recognition is key

- High level of suspicion for seemingly benign symptoms e.g. cough, diarrhoea

Grade 1 toxicity:

- Treat symptomatically - continue ICI

Grade 2 toxicity:

- Withhold ICI until toxicity is grade 1
- Start prednisone 0.5 mg/kg/day

Grade 3 or 4 toxicity:

- Permanently discontinue ICI
- Prednisone PO 1-2 mg/kg/day or methylprednisolone IV 0.5-2 mg/kg/day. Taper over 4 weeks when symptoms resolve.
- Refractory? Consider other immunomodulating drugs e.g. infliximab, mycophenolate

Managing irAEs: Pneumonitis

Uncommon (5%) potentially fatal

Present with dyspnoea and cough (53 v 35%).

30% asymptomatic

>50% will present with another irAE e.g. colitis, thyroiditis

Median time to development 2.8 months (9 days to 19 months)

Suspect in pts on active treatment with ICI with new or worsening cough, SOB, dyspnoea on exertion

Managing irAEs: Endocrinopathies

Inflammation of pituitary, thyroid or adrenal glands

Nonspecific symptoms nausea, headache, fatigue, vision changes

Hypothyroidism, hyperthyroidism, hypophysitis

Clinically significant in approx 10%

Long term supplementation of the affected hormones

Levothyroxine or hydrocortisone 20mg mane 10mg nocte

Diabetes: 0.2 – 0.9%

Insulin

Managing irAEs: Less common

Cardiovascular

May develop in absence of history of cardiac risk factors

Myocarditis, pericarditis, heart failure, arrhythmias, vasculitis

High dose steroids, may need infliximab

Ocular: <1%

Episcleritis, conjunctivitis, uveitis, orbital inflammation

Photophobia, pain, dryness, blurred vision

Ophthalmology consultation and topical steroid

Gastrointestinal: <1%

New onset celiac disease, esophagitis, acute cholecystitis, gastroparesis

Hepatitis

Incr ALT/AST x 1.5 – 5%

Typically occurs 8 – 12 weeks after initiation of treatment

AKI: 1.5 – 5%

steroids indicated

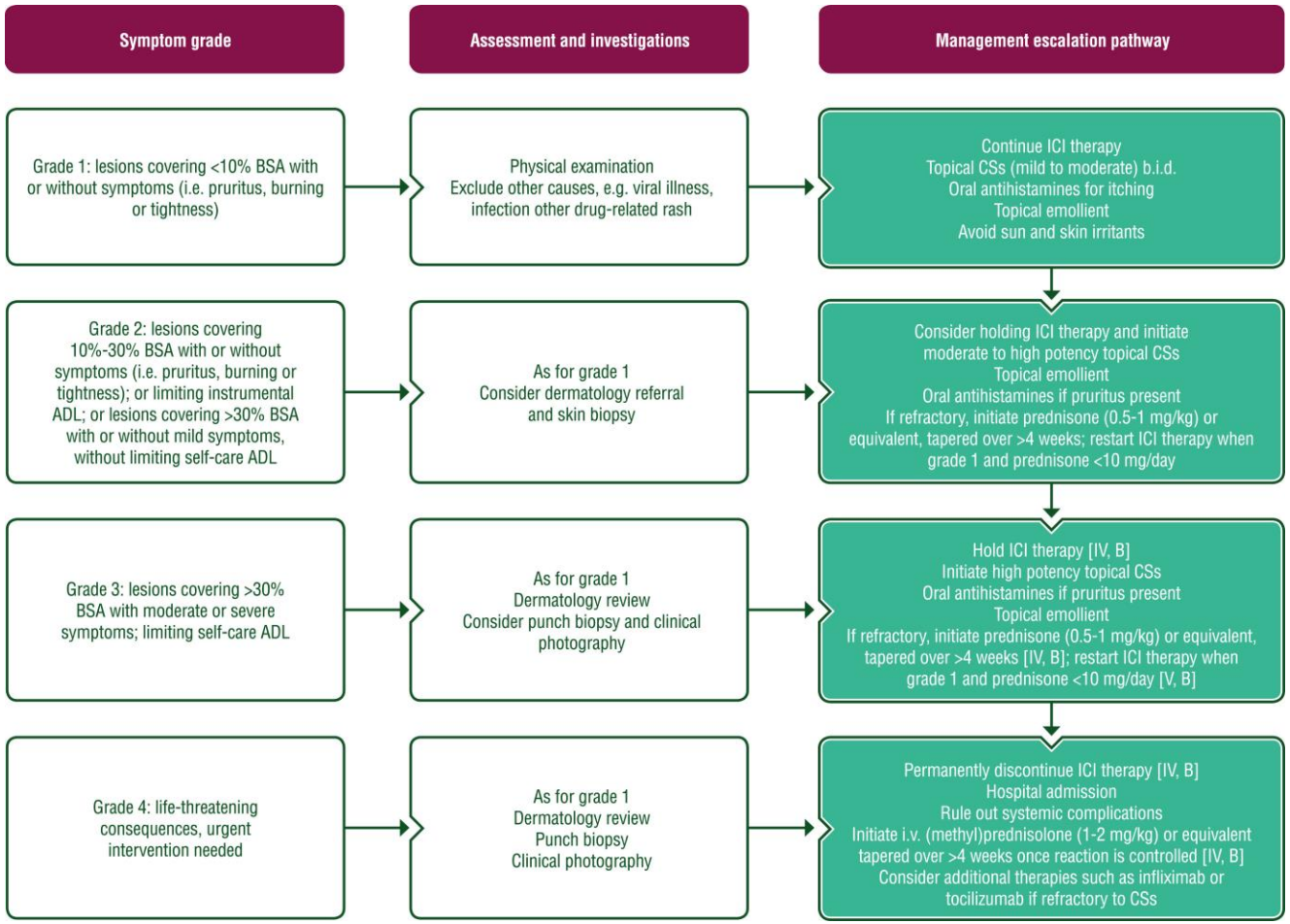
Neurologic

1 – 14% highest rates with combined immunotherapy

Headache, peripheral sensory neuropathy most common

Meningitis, autoimmune encephalitis

irAEs: Rash Guideline



Case

- 77 Māori male
- Stage IV squamous cell lung cancer

  T2bN1M1a PDL1<1%

- Comorbidities

  - COPD, HTN. Weight 109kg

- Increasing SOB. Exercise tolerance 50m.

Case – clinic 1

- Post cycle 1
  - well tolerated
  - pruritic rash ??? irAE
  - nausea

- Plan
  - watch rash – may need steroids
  - no addition to antiemetic regimen

Case – clinic 2

- Post cycle 2
  - well tolerated
  - no rash
  - nausea increasingly problematic
  - increased fatigue
  - mild anaemia
  - constipation – hates laxsol

- Plan
  - add aprepitant
  - add lax-sachet

Case – clinic 3

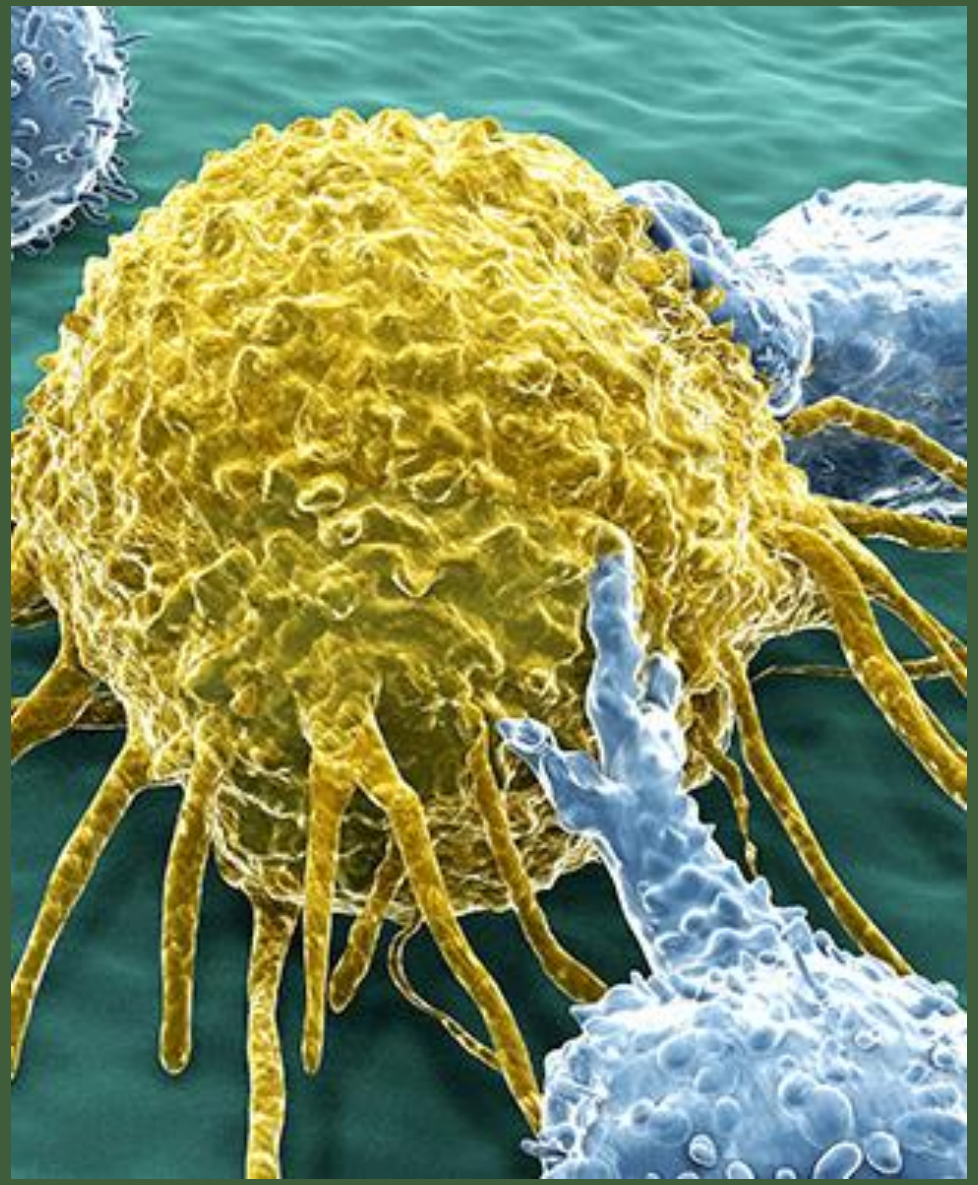
- Post cycle 3
  - increasing fatigue
  - improved nausea control
  - inadequate analgesia (pain not increasing)
  - weight 96.5kg
  - Hb 88 – SOB, dizziness, decreased exercise tolerance
  - BP 154/74, HR 96 bpm
  - episodes of burning sensation in chest radiating to back and right arm. Pain-free during appointment.

Case – the ick factor

- Trop 844

- **CVD?**
- **irAE?**

- **Referral to ED. Transfer to Nelson**
- **Triple vessel CVD – medical management**



Any Questions?