# Immunotherapy as systemic anti-cancer therapy (SACT)

# Immunotherapy toxicities and their management

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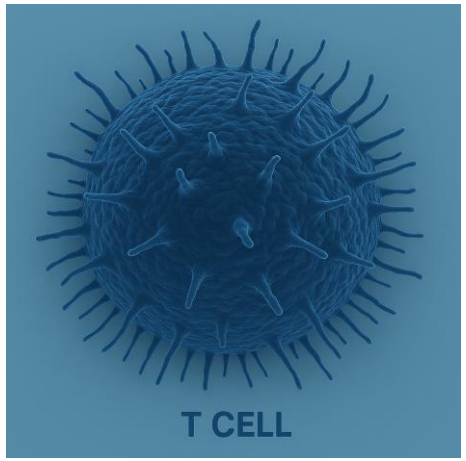
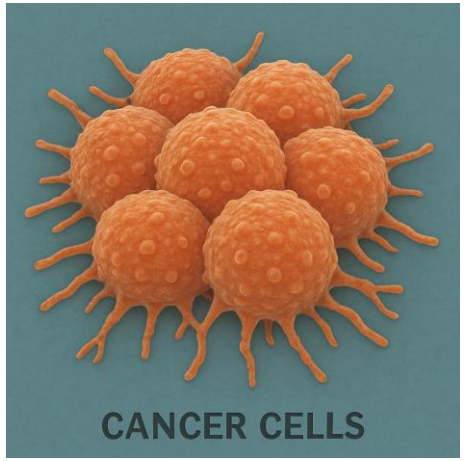
Disclosures

Speaker fees, Advisory Board Fees and Educational Meeting sponsorship from:
Bristol Myers Squibb, Merck Sharp & Dohme, Amgen, Roche, Pierre Fabre




# Immunotherapy:

Treatment resulting in activation of the immune system, enabling recognition and destruction of cancer cells



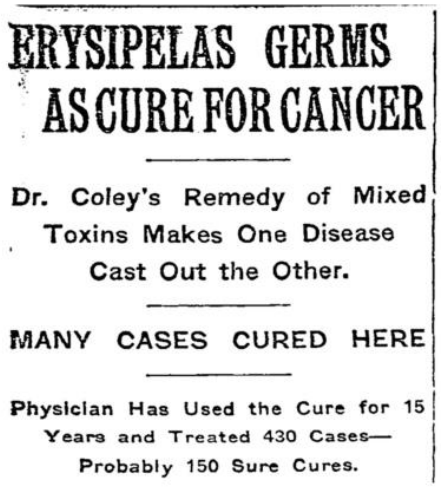
# Immunotherapy is not new

**Early 19th Century** Reports of tumours disappearing after infection with high fever

**1891**

William Coley

Fig. II.—Dr. Coley's Case of Sarcoma of Lower End of Femur. Portion Showing Granulating Surfaces Produced by the Erysipelas Culture.



ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

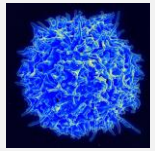
MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

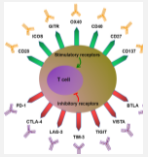
**1950's** Concept of immune surveillance – lymphocytes identify and eliminate abnormal cells

**1970's** Cytokines: interferons/interleukins – durable responses in some cancers

# Cancer & the Immune System



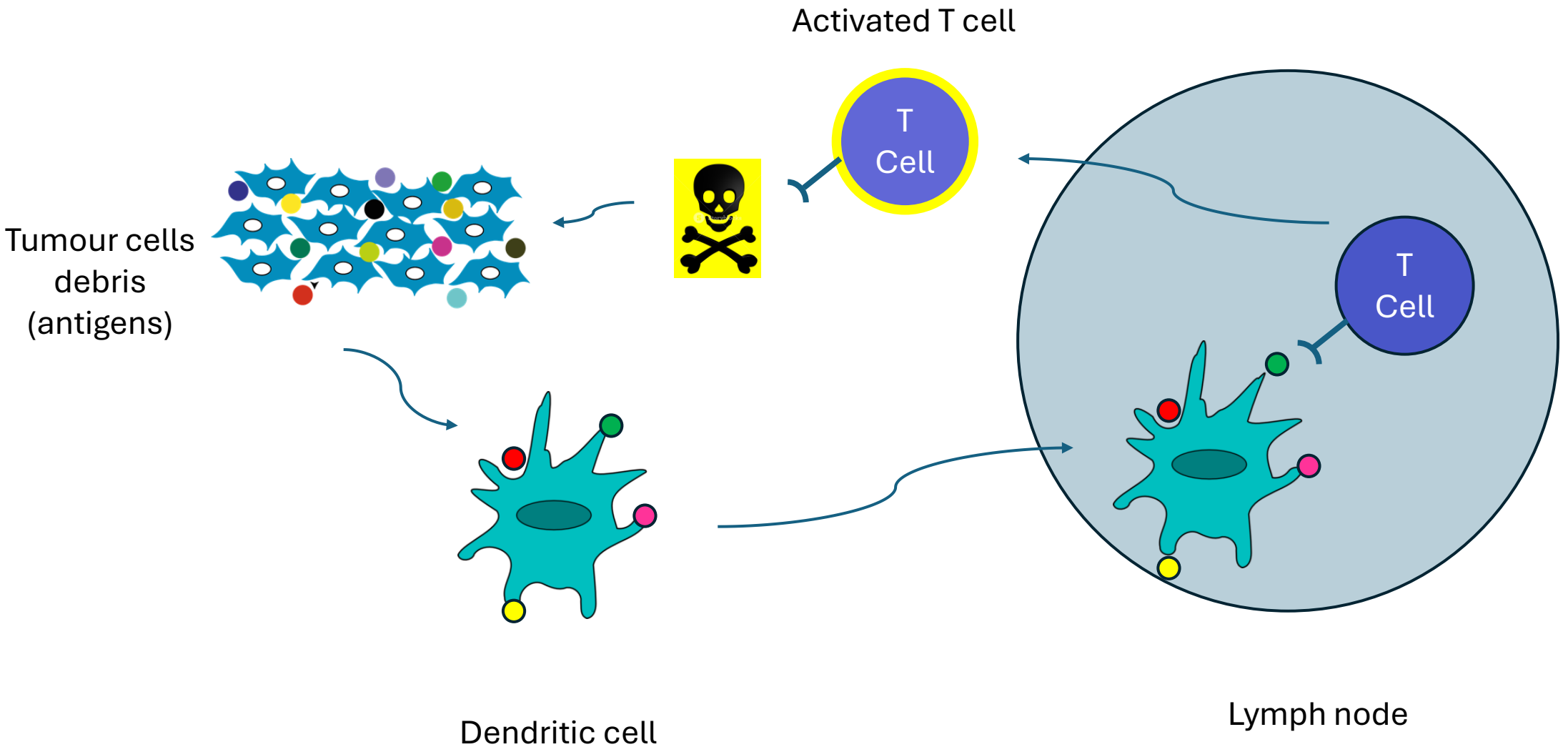
Immune system plays a significant role in protecting us against cancer– **Cytotoxic T cells.**



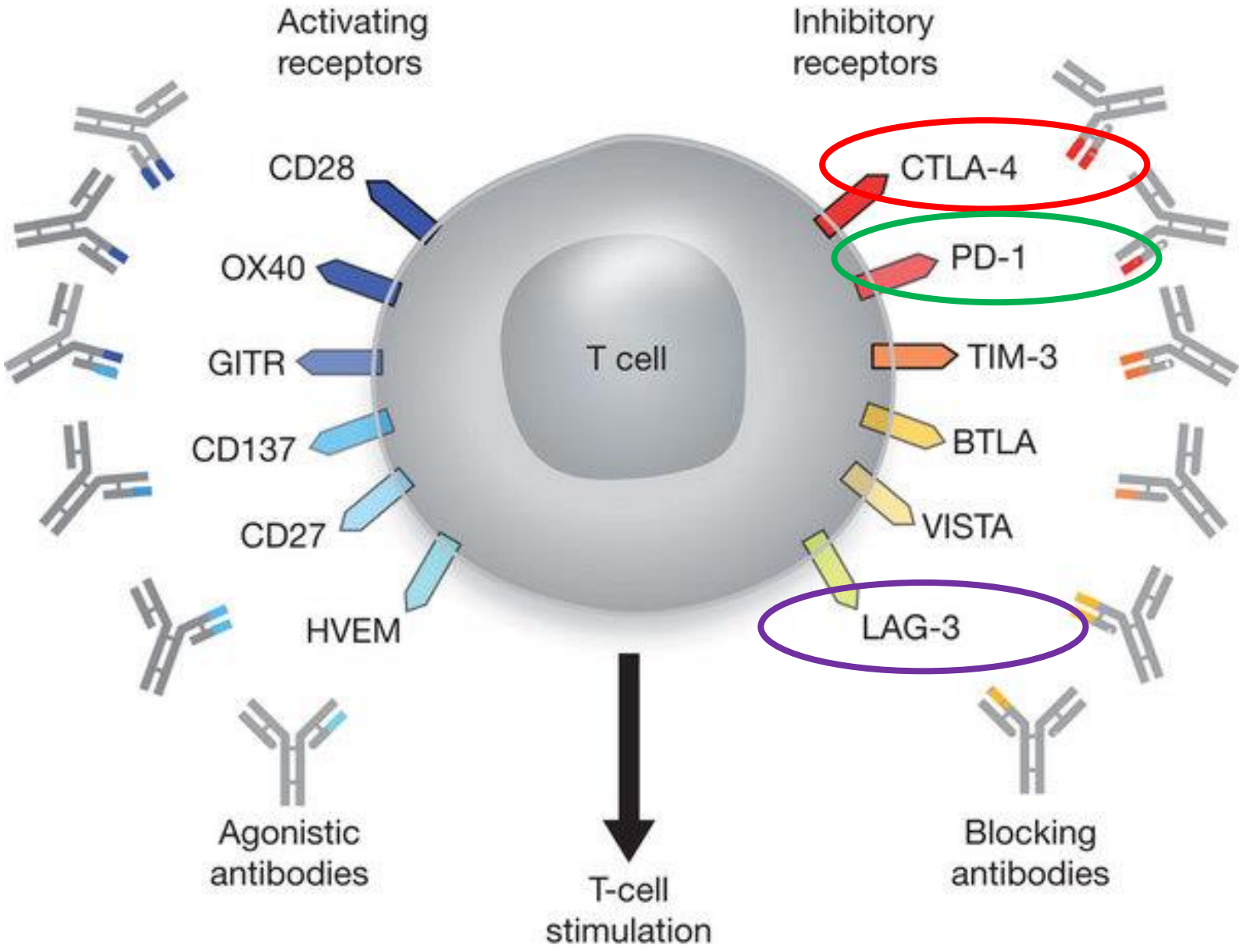
T cells have proteins on their surface that behave as “on/off” switches or **Checkpoints** when the immune system needs to fight infection or deal with a faulty/unknown cell

Cancer cells can “trick” the immune system and keep the inhibitory checkpoints switched on, therefore giving a permanent “stop” signal to T cells. Cell mutations impair control systems and cells may begin to grow unchecked

# Cancer cell killing by Cytotoxic T Cells



# Checkpoints



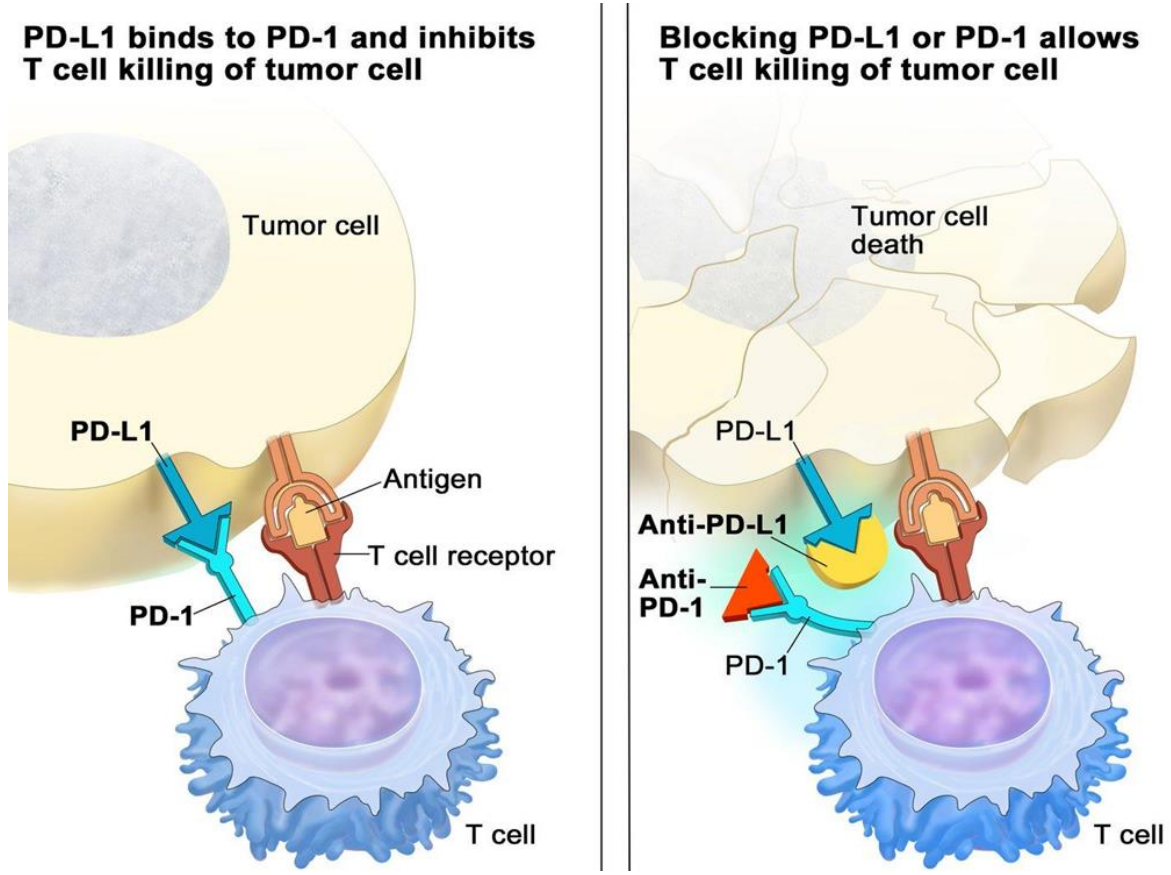

Ipilimumab

Pembrolizumab
Nivolumab
Cemiplimab
Atezolizumab
Avelumab
Durvalumab

Relatlimab
Fianlimab

# Mechanism of action

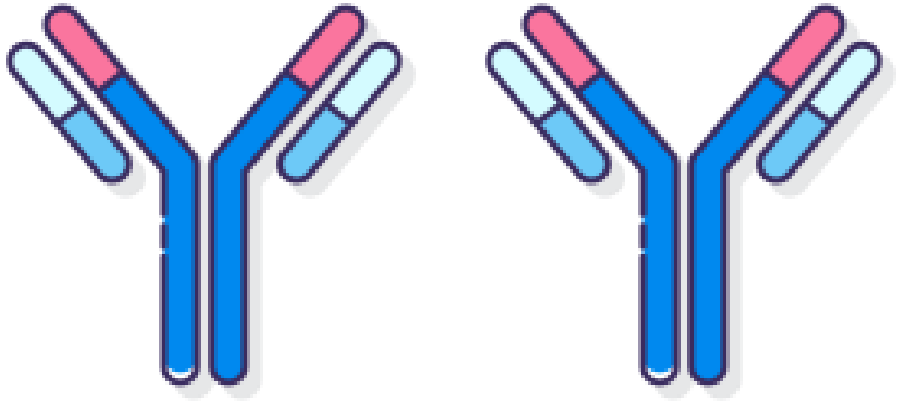
- Antigen on the surface of the tumour cell is recognized as foreign and triggers T cell activation
- Tumours upregulate inhibitory checkpoints preventing T cell activity
- Antibodies known as Immune Checkpoint Inhibitors (ICIs) block the actions of inhibitory T cell checkpoint receptors
- T cell can fulfill its role and destroy the cancer cell




NCI dictionary

# Immunotherapy - Checkpoint Inhibitors

Single agent

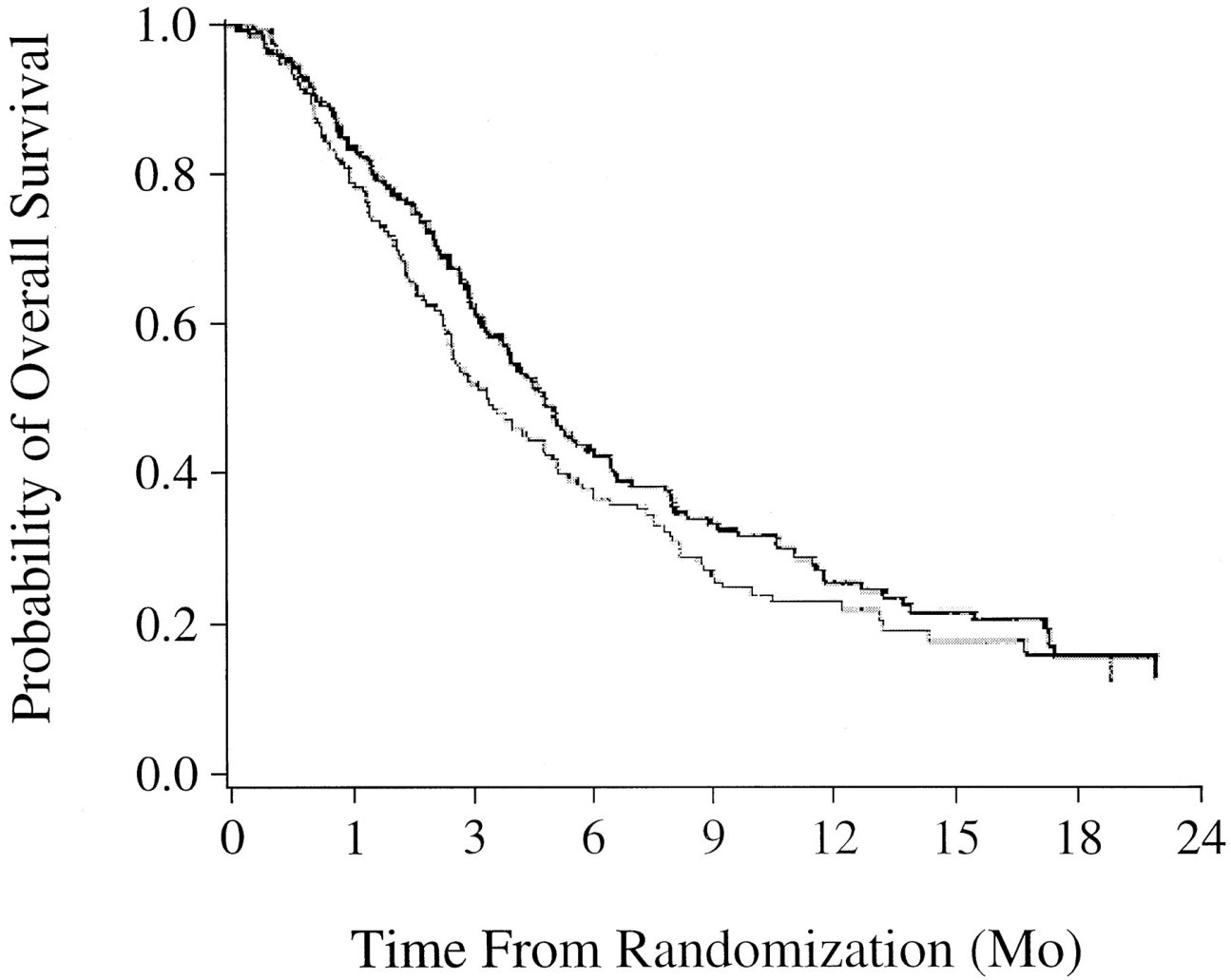


Combination

Why is this important?

# Metastatic melanoma before immunotherapy


**Median overall survival 6-9 m**




Middleton et al 2000

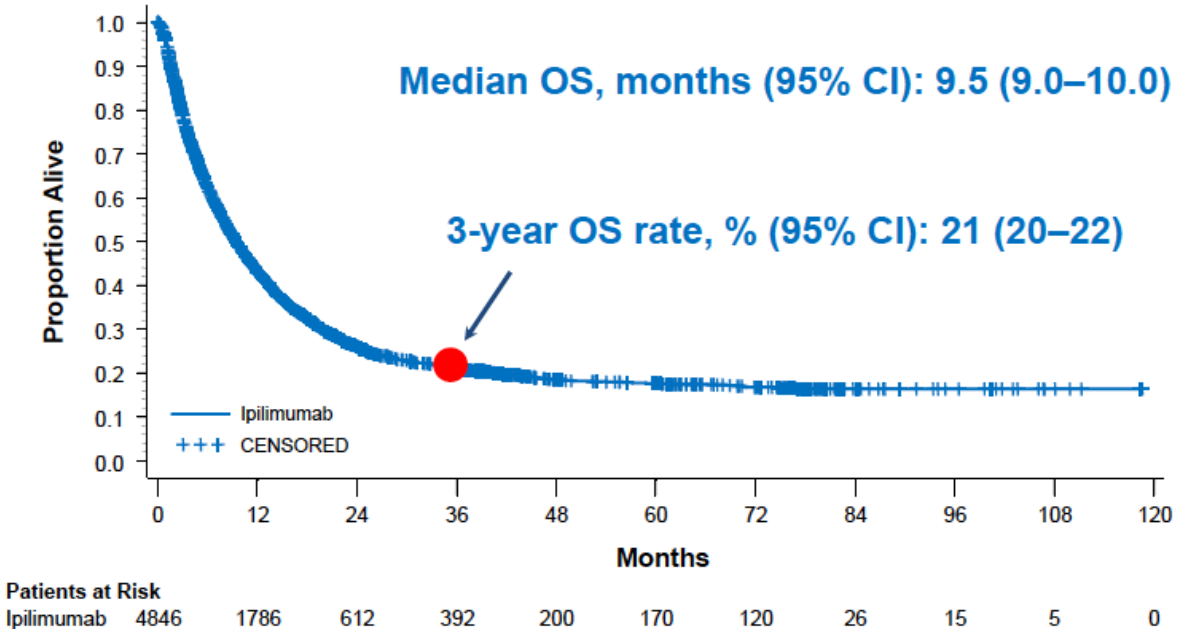
# The Tail on The Curve.....

## Anti-CTLA 4


RR 20%

ecco

## Pooled OS Analysis Including EAP Data: 4846 Patients

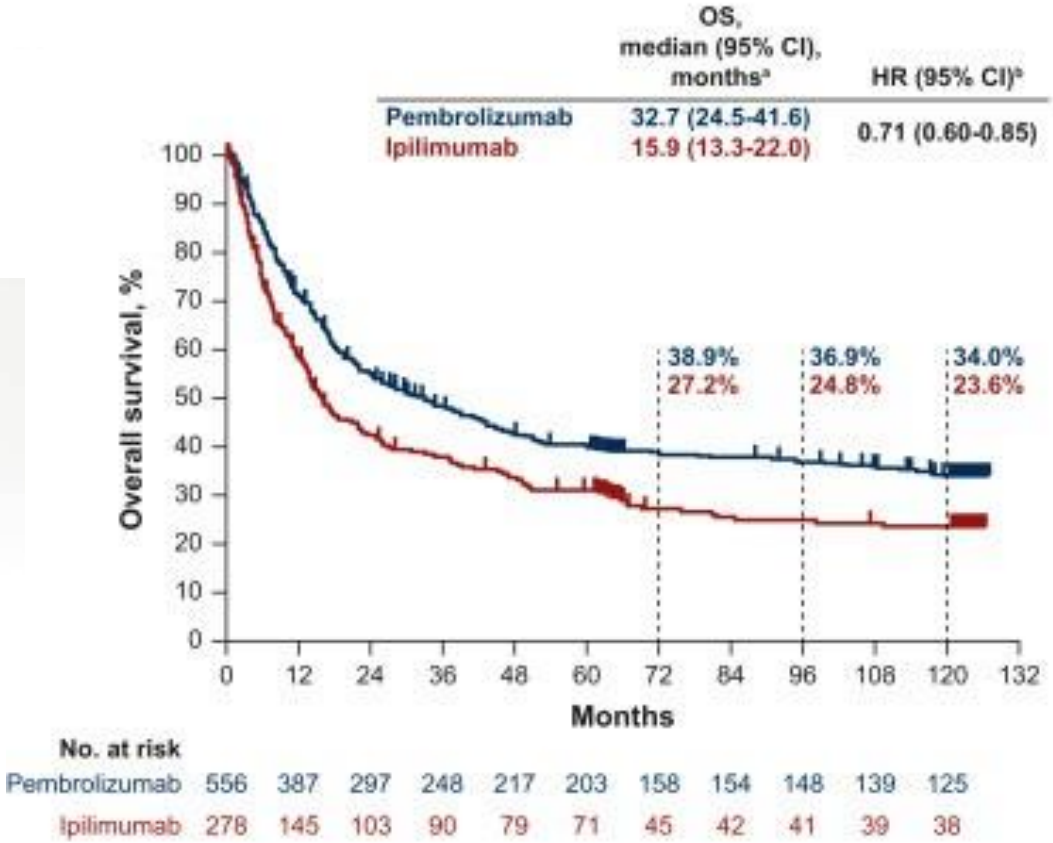



**2013**

BARCELONA 2024 ESMO congress

# Anti-PD1


RR 40%

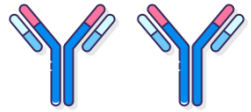


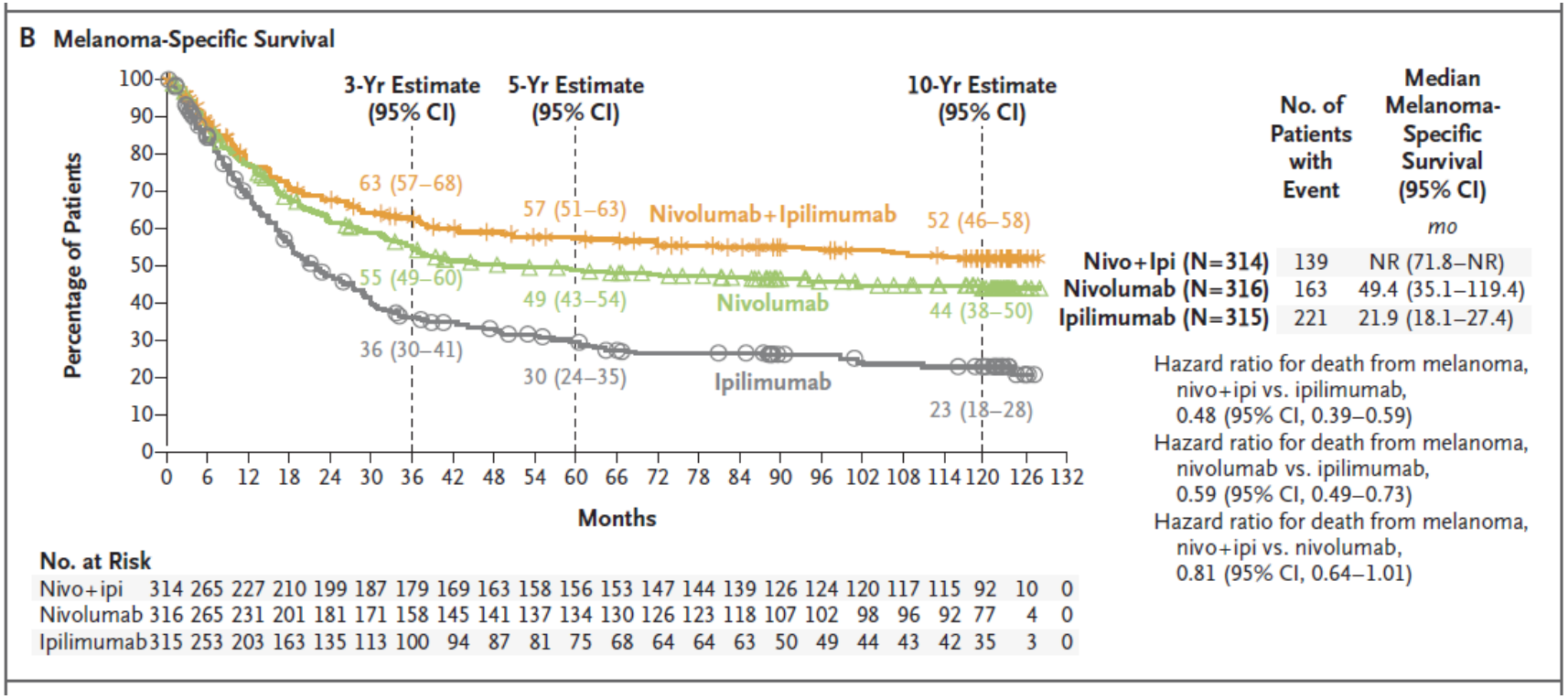

**10 yr overall survival**
**Keynote 006**

| | |
|---|---|
| Pembrolizumab (anti-PD1) | 34% |
| Ipilimumab (anti-CTLA4) | 23.6% |

BARCELONA 2024 ESMO congress

# Combination Anti-CTLA4 and anti-PD1



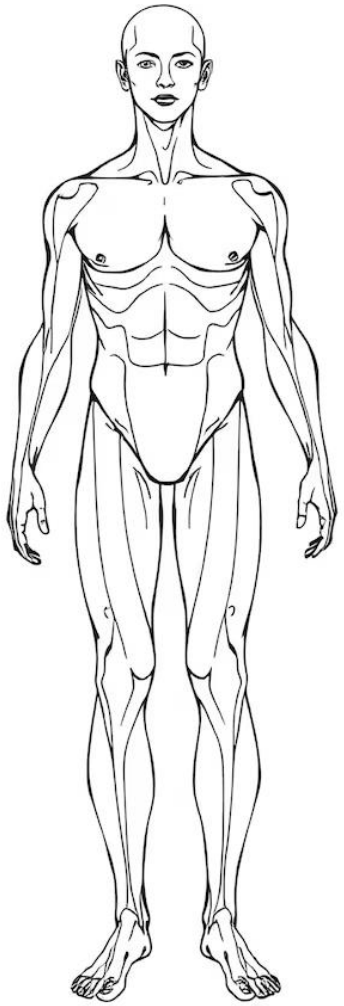



## 10 Yr Melanoma Specific Survival Checkmate 067

| | |
|---|---|
| Ipi/nivo | **52%** |
| Nivo | 44% |
| Ipi | 23% |

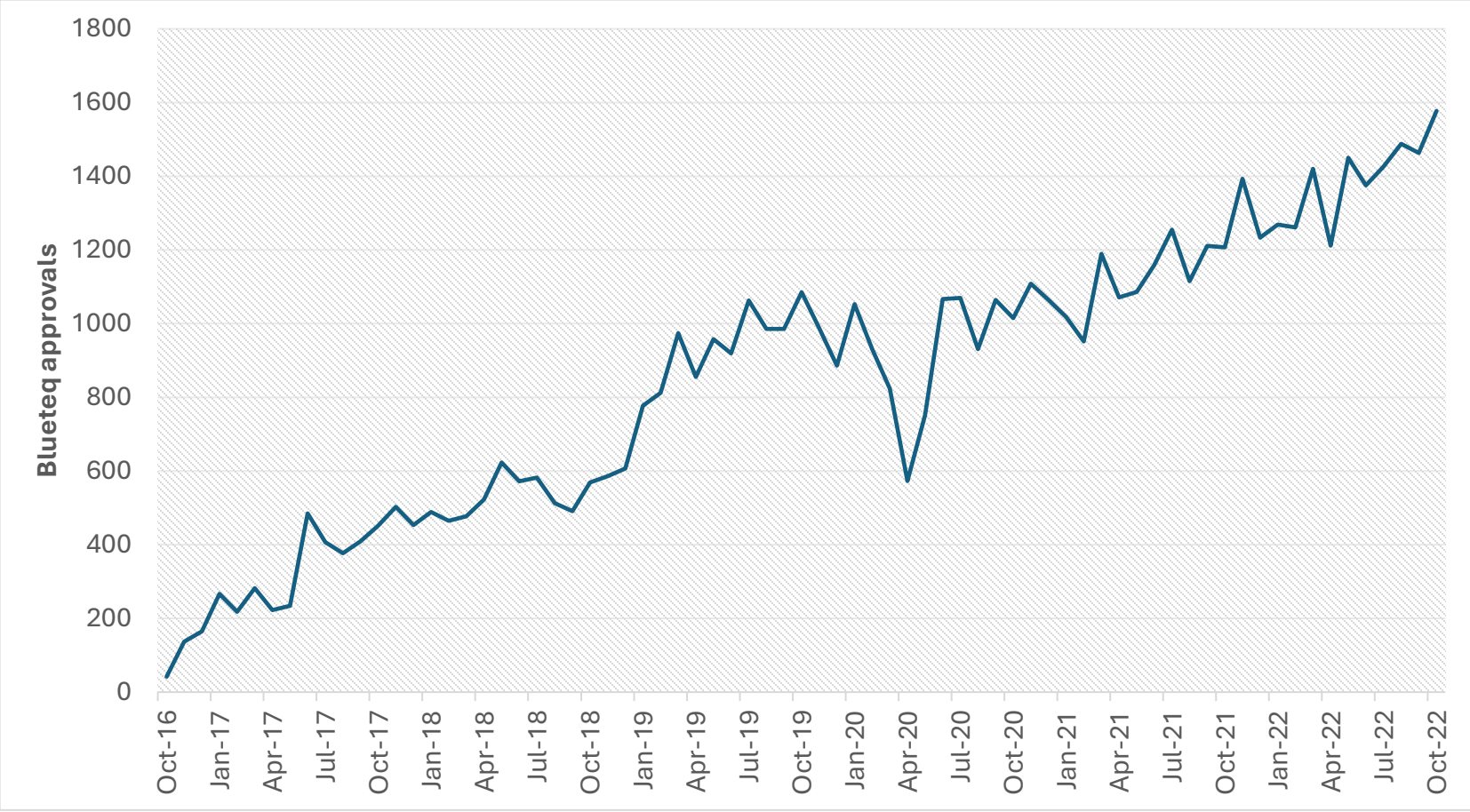
# Immunotherapy indications by cancer type

- Melanoma
- Renal Cell Carcinoma
- Bladder Cancer
- Oesophageal Cancer
- Colorectal Cancer
- Gastric Cancer
- Liver Cancer
- Bile Duct Cancer



- Lung Cancer
- Mesothelioma
- Lymphoma
- Head & Neck Cancers
- Squamous Cell Skin Cancer
- Merkel Cell Carcinoma
- Cervical Cancer
- Endometrial Cancer
- Triple-Negative Breast Cancer

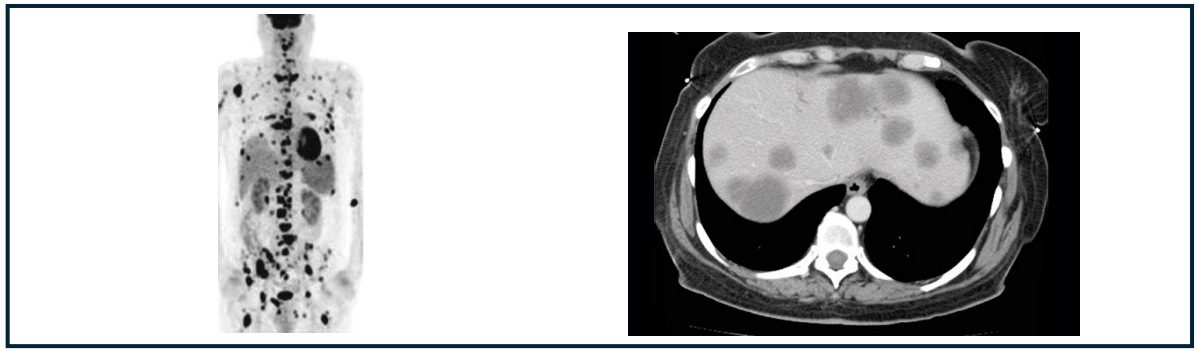
# Immunotherapy: all indications



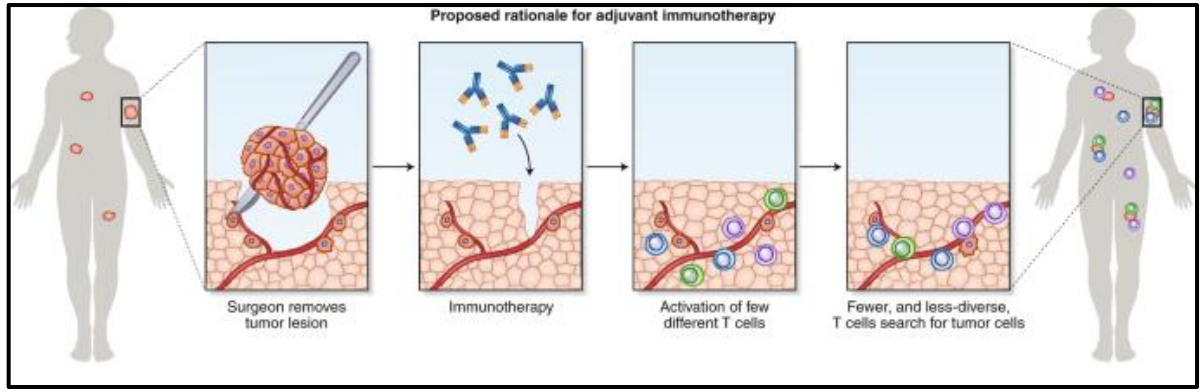

NHS England, 2023

# Immunotherapy indications – disease status

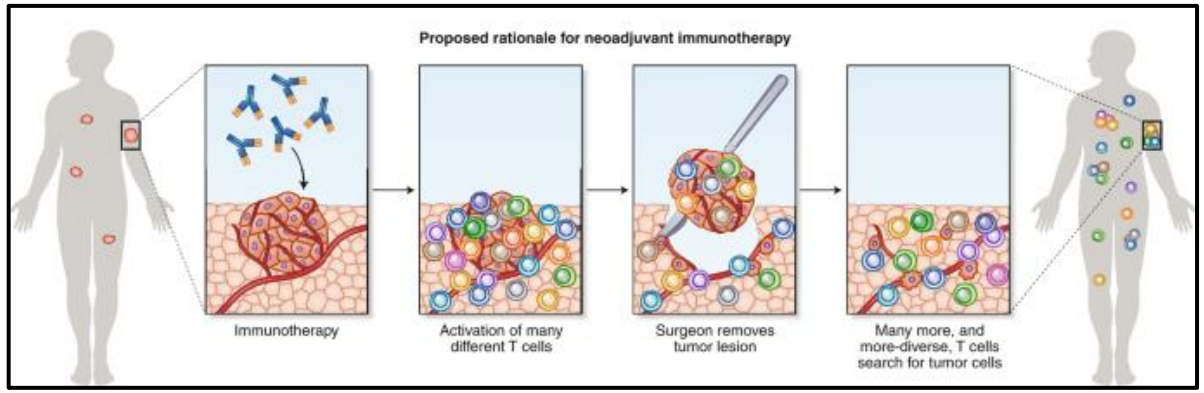
Metastatic disease



Adjuvant therapy




Neo-adjuvant therapy



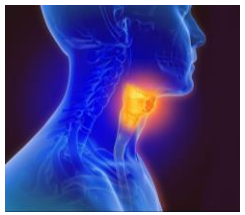

*Nature Medicine 2020*

# Immunotherapy in combination with SACT/RT

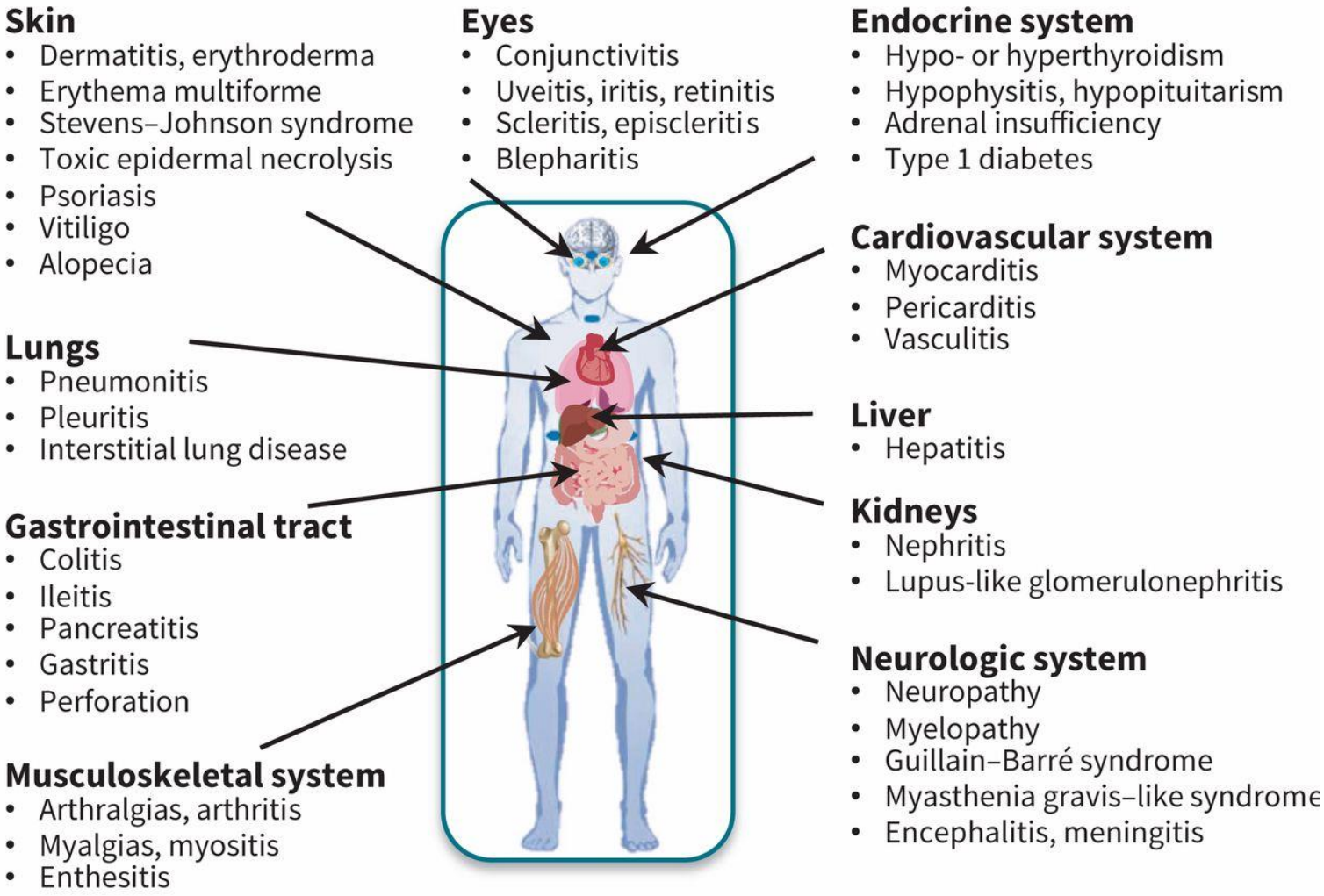
Chemotherapy


Targeted therapy

Radiotherapy



# Immune related adverse events (irAEs)




*Canadian Medical Association Journal*

# Immune-related adverse events ( irAEs)

- Inflammation in any organ/system
- Side effects can occur at any time – during, years after treatment finished
- Present with subtle symptoms – easily overlooked
- Mimic organ-specific autoimmune diseases, but not the same
- Approx 70% patients will experience toxicity
- Often low grade but G3/4 in 10-15% (single agent) and 50% (combination)
- Most are manageable with steroids
- May require additional immunosuppression DMARDS, Biologics
- Endocrine side effects are permanent
- Can be organ or life threatening

# Patient pathway irAE

New symptom

↓

Call 24h triage line

↓

Triage according to UKONS/Clatterbridge Immune-related adverse event Guidelines

↓

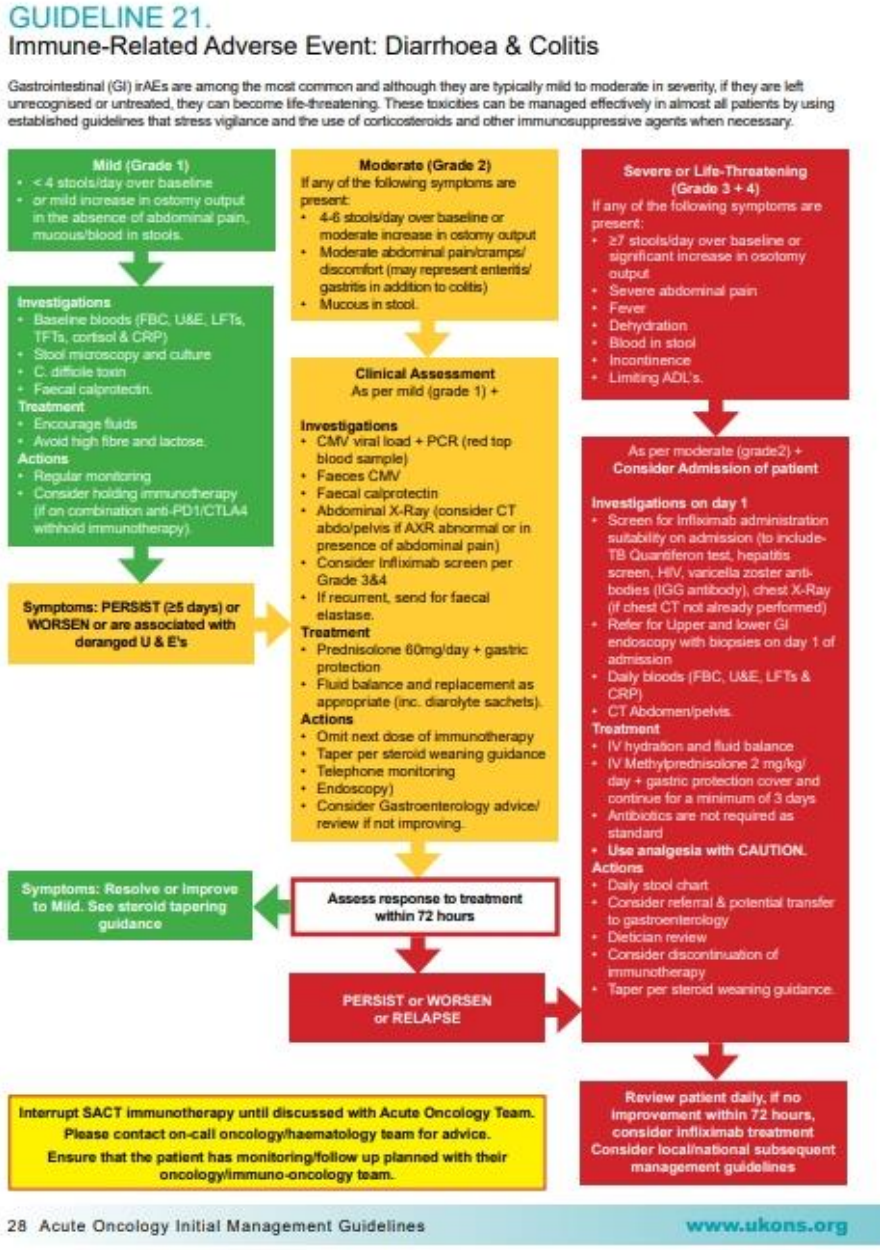
Low grade toxicity managed as OP

↓

High grade toxicity may require admission

**AOS team**

**Immunotherapy service**



GUIDELINE 21.

Immune-Related Adverse Event: Diarrhoea & Colitis

Gastrointestinal (GI) irAEs are among the most common and although they are typically mild to moderate in severity, if they are left unrecognised or untreated, they can become life-threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary.

**Mild (Grade 1)**
- < 4 stools/day over baseline
- or mild increase in ostomy output in the absence of abdominal pain, mucous/blood in stools.

**Investigations**
- Baseline bloods (FBC, U&E, LFTs, TFTs, cortisol & CRP)
- Stool microscopy and culture
- C. difficile toxin
- Faecal calprotectin.

**Treatment**
- Encourage fluids
- Avoid high fibre and lactose.

**Actions**
- Regular monitoring
- Consider holding immunotherapy (if on combination anti-PD1/CTLA4 withhold immunotherapy)

**Symptoms: PERSIST (≥5 days) or WORSEN or are associated with deranged U & E's**

**Moderate (Grade 2)**
If any of the following symptoms are present:
- 4-6 stools/day over baseline or moderate increase in ostomy output
- Moderate abdominal pain/cramps/ discomfort (may represent enteritis/ gastritis in addition to colitis)
- Mucous in stool.

**Clinical Assessment**
As per mild (grade 1) +

**Investigations**
- CMV viral load + PCR (red top blood sample)
- Faeces CMV
- Faecal calprotectin
- Abdominal X-Ray (consider CT abdo/pelvis if AXR abnormal or in presence of abdominal pain)
- Consider Infliximab screen per Grade 3&4
- If recurrent, send for faecal elastase.

**Treatment**
- Prednisolone 60mg/day + gastric protection
- Fluid balance and replacement as appropriate (inc. diarolyte sachets).

**Actions**
- Omit next dose of immunotherapy
- Taper per steroid weaning guidance
- Telephone monitoring
- Endoscopy)
- Consider Gastroenterology advice/ review if not improving.

**Symptoms: Resolve or improve to Mild. See steroid tapering guidance**

**Assess response to treatment within 72 hours**

**PERSIST or WORSEN or RELAPSE**

**Severe or Life-Threatening (Grade 3 + 4)**
If any of the following symptoms are present:
- ≥7 stools/day over baseline or significant increase in osotomy output
- Severe abdominal pain
- Fever
- Dehydration
- Blood in stool
- Incontinence
- Limiting ADL's.

As per moderate (grade2) +
**Consider Admission of patient**

**Investigations on day 1**
- Screen for Infliximab administration suitability on admission (to include- TB Quantiferon test, hepatitis screen, HIV, varicella zoster anti-bodies (IGG antibody), chest X-Ray (if chest CT not already performed)
- Refer for Upper and lower GI endoscopy with biopsies on day 1 of admission
- Daily bloods (FBC, U&E, LFTs & CRP)
- CT Abdomen/pelvis.

**Treatment**
- IV hydration and fluid balance
- IV Methylprednisolone 2 mg/kg/ day + gastric protection cover and continue for a minimum of 3 days
- Antibiotics are not required as standard
- **Use analgesia with CAUTION.**

**Actions**
- Daily stool chart
- Consider referral & potential transfer to gastroenterology
- Dietician review
- Consider discontinuation of immunotherapy
- Taper per steroid weaning guidance.

**Interrupt SACT immunotherapy until discussed with Acute Oncology Team.**
**Please contact on-call oncology/haematology team for advice.**
**Ensure that the patient has monitoring/follow up planned with their oncology/immuno-oncology team.**

**Review patient daily, if no improvement within 72 hours, consider infliximab treatment**
**Consider local/national subsequent management guidelines**

# Management of irAEs

## Initial management corticosteroids

Oral prednisolone 0.5-1mg/kg
IV methylprednisolone 1-2mg/kg

## Recurrent/refractory toxicities – additional immunosuppressants

Mycophenolate Mofetil (MMF)
Tacrolimus
Infliximab/vedolizumab/other biologics

Involvement of medical specialists locally and nationally

## Additional considerations

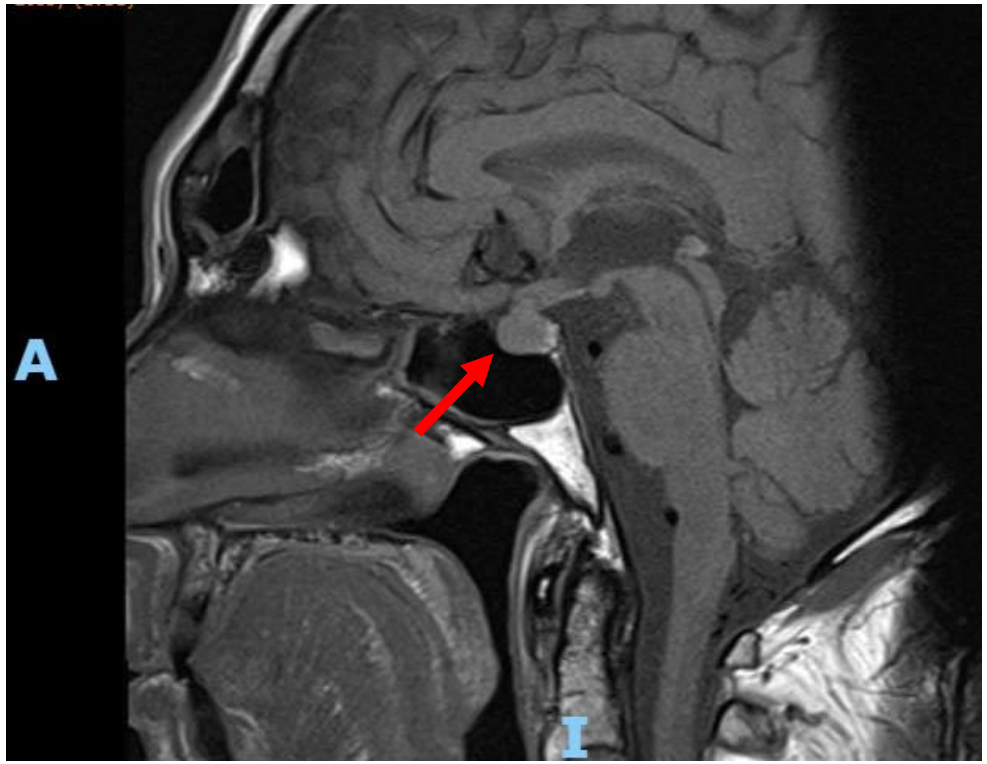
Prophylaxis
Bone health

# Case History 1

56 year old man

| | |
|---|---|
| 2015 | Melanoma R upper chest<br>WLE and axillary LN dissection |
| Feb 2019 | Lump R clavicle, FNA +ve<br>CT mediastinal and hilar LN<br>Commenced immunotherapy with ipilimumab and nivolumab |
| April 2019 | #3 transient hyperthyrpoidism |
| May 2019 | #4 tired, headache, no visual disturbance<br>Free T4 4.9<br>Cortisol 17<br><br>Commenced hydrocortisone and levothyroxine<br>OP MRI pituitary |

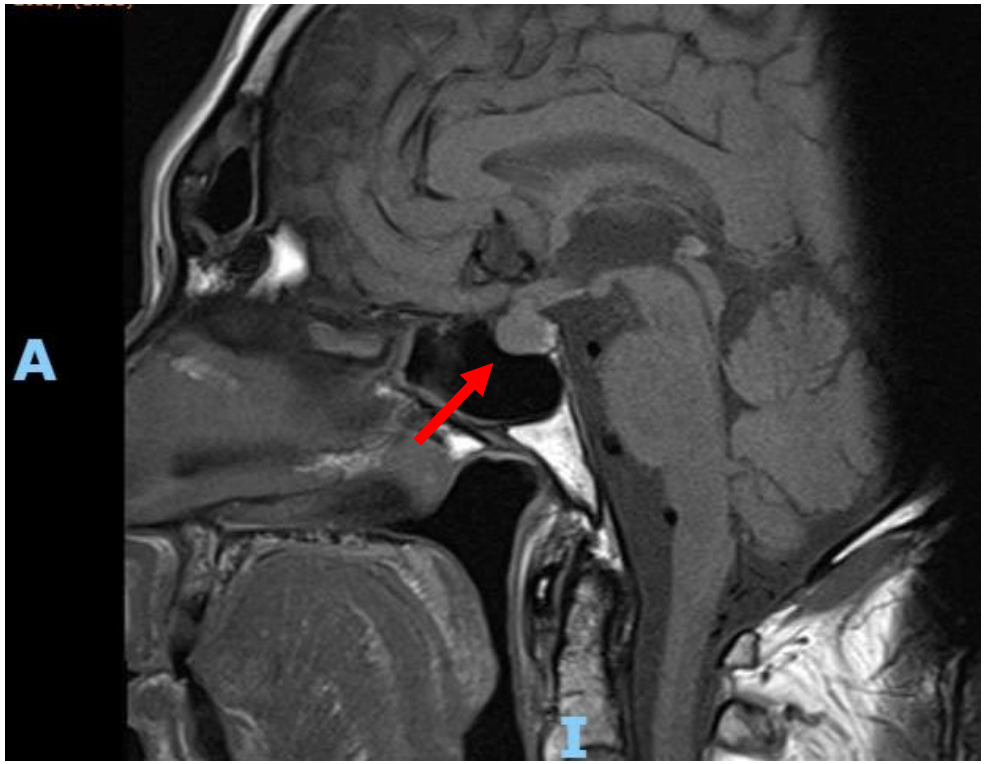
May 2019



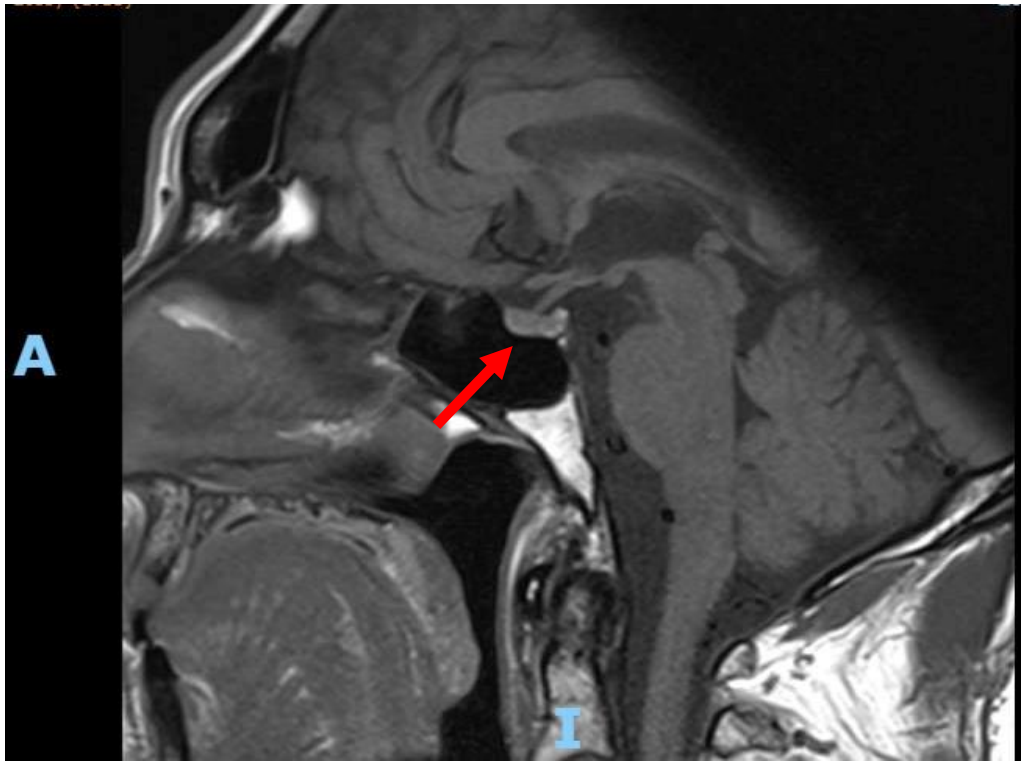

Enlarged pituitary
Encroachment on optic chiasm

IV methylprednisolone
Oral prednisolone weaned
Oral hydrocortisone

May 2019




June 2019



| | |
|---|---|
| June 2019 | CT Partial response |
| Aug 2019 | CT Complete response |
| Feb 2012 | Completed 2 years treatment |
| April 2025 | Disease free – long term steroid dependence |

# Case History 2

63 year old man

| | |
|---|---|
| July 2021 | Stage IIIC melanoma upper back<br>WLE and axillary LN dissection<br>1 year adjuvant targeted therapy (BRAF mutation) |
| March 2023 | Recurrent disease R arm, neck, axilla, lung, spleen<br><br>1st line immunotherapy in metastatic setting ipilimumab and nivolumab<br>4 cycles |
| June 2023 | **Grade 4 colitis** (Faecal calprotectin 603, flexi-sig active colitis)<br>**G2 hepatitis**<br><br>Commenced IV Methylprednisolone 2mg/kg<br><br>Hepatitis resolved<br>Colitis no response to steroids |

| | | |
|---|---|---|
| July 2023 | 1st line biologic | Infliximab X 2 |
| Aug 2023 | 2nd line biologic | Vedolizumab<br>Completed 3 doses, symptoms resolved after #1 |
| | **G2 arthralgia** | Steroids weaned but remained on low dose for > 6 months |
| | CT scan | Complete response |
| | Immunotherapy discontinued due to G4 colitis | |
| Feb 2025 | Well, ongoing complete response, off all immunosuppression | |

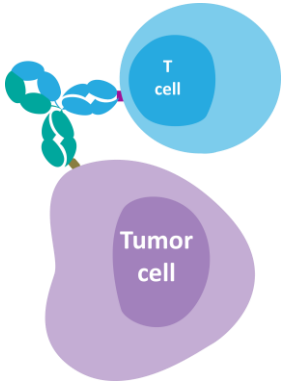
# What's coming down the track?

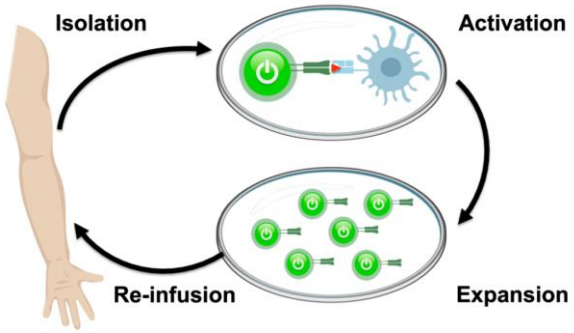
Bispecific molecules

Adoptive cell therapy

Microbiome

Vaccines




# Resources

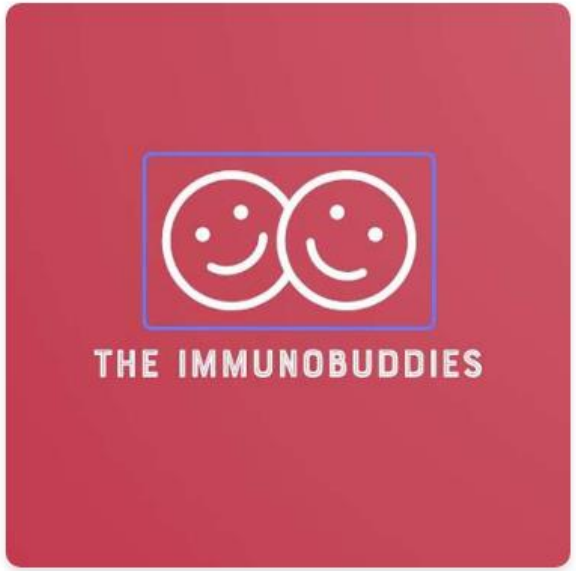
Immunobuddies podcast

South West Immunotherapy Group

IO Clinical Network (IOCN)

www.ioclinicalnetwork.co.uk

# The Immunobuddies




Buddies with an interest in the area of immunotherapy and its development. We simply discuss the dilemmas, challenges and progress made in the...
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Tue 6 May 2025, 6:30PM
Online


### IOCN Webinar: Ask a Question - A Focus on Musculoskeletal Toxicity

Tue 10 Jun 2025, 6:30PM
Online


### IOCN Webinar - New & Novel: Combination Therapies - Considerations and Horizons

Mon 23 Jun 2025, 6:30PM
Online

- Thank you

- Any Questions?