Oncologic Emergencies

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April 28, 2017

Conflicts of Interest

- No disclosures.

Learning Objectives

- Review presentation and management of Malignant Epidural Spinal Cord Compression (MESCC)
- Introduce immune checkpoint inhibitors
- Provide a brief overview of the management immune related adverse events.

Three Key Messages

- MRI is the gold standard for diagnosis of malignant epidural spinal cord compression.
- If a patient is on an immune checkpoint inhibitor, drug induced autoimmunity should ALWAYS be included in the differential diagnosis.
- PO/IV corticosteroids the preferred method for managing moderate to severe immune related adverse events.

Outline

- Oncologic Emergencies
    - Malignant Epidural Spinal Cord Compression
- Introduction to Immune Checkpoint Inhibitors
    - Immune related adverse events

Oncologic Emergencies

Oncologic Emergencies

- Any complication related to cancer or anticancer therapy that requires immediate intervention.

Oncologic Emergencies

- **Classic List**
  - Febrile Neutropenia (High and Low Risk)
  - Malignancy Associated Hypercalcemia
  - **Malignant Epidural Spinal Cord Compression**
  - Superior Vena Cava Obstruction
  - Tumour Lysis Syndrome

Oncologic Emergencies

Classic List

- Febrile Neutropenia (High and Low Risk)
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- Superior Vena Cava Obstruction
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Extended List

- Hyperviscosity Syndrome
- Bleeding in the Cancer Patient
  - GI Bleeding, Hematuria, Hemoptysis
- Increased ICP, Seizures from Brain Mets
- DIC
- Malignant Airway Obstruction
- SIADH

Oncologic Emergencies

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New Oncologic Urgency/Emergency

- **Immune Related Adverse Events**

Malignant Epidural Spinal Cord Compression

Disclosures

- I am not a Radiation Oncologist, Neurosurgeon, Orthopaedic Surgeon, Neurologist or a Radiologist.

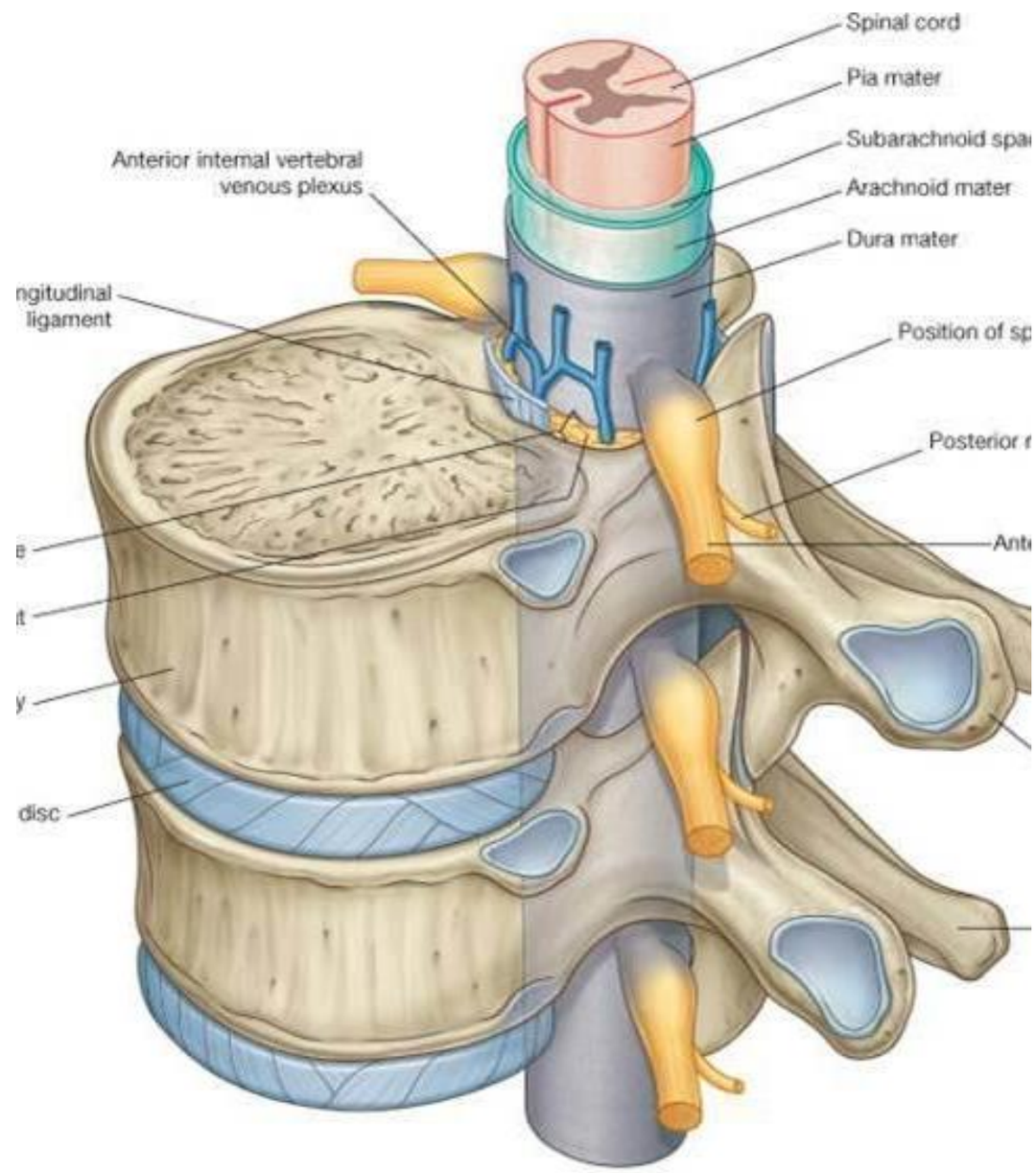
- Hmm … why did I choose this topic?

Malignant Epidural Spinal Cord Compression

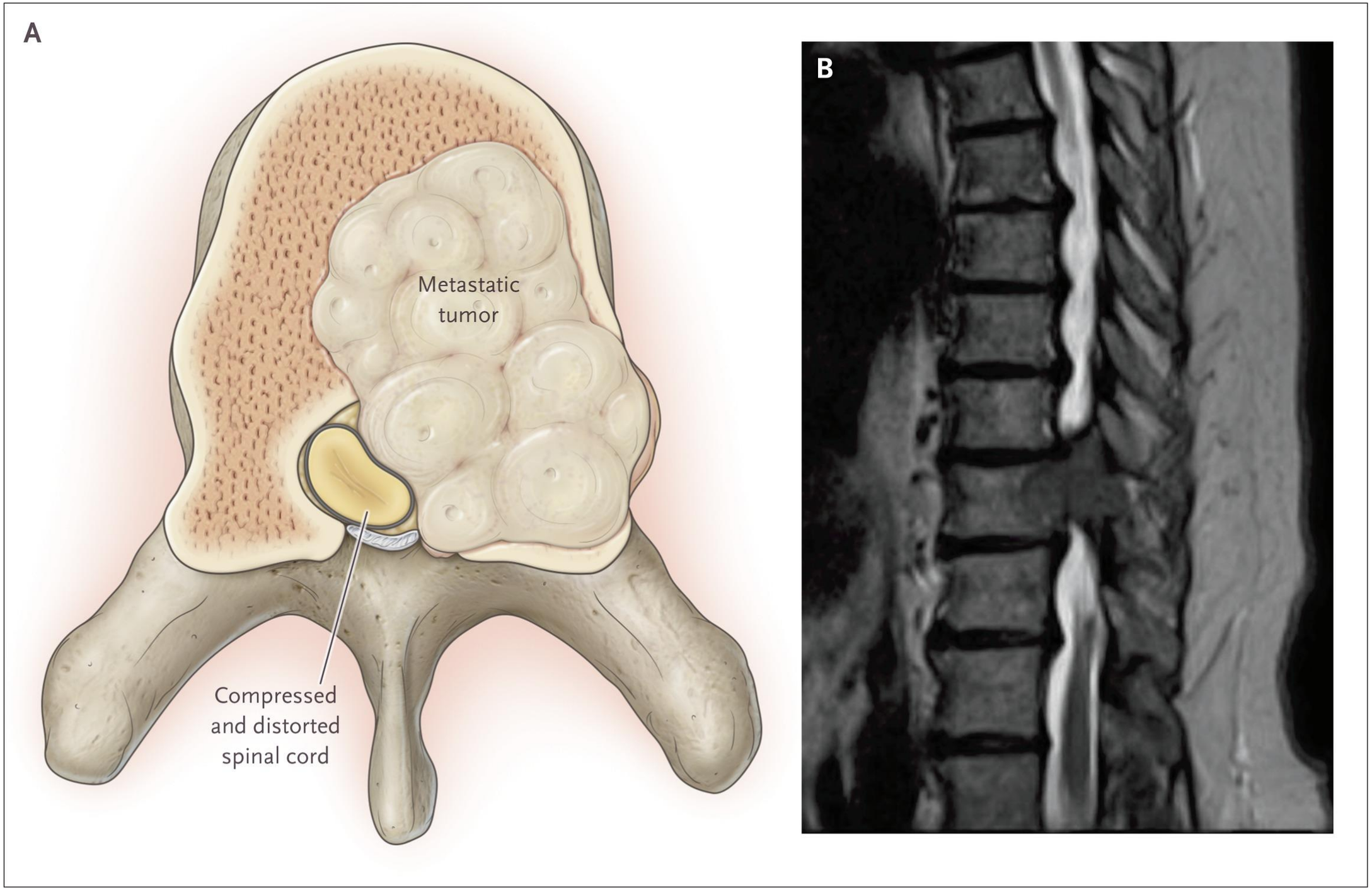
- T9 Lesion, CT on left, MRI 7 days later on right.
- It can be missed!!

Malignant Epidural Spinal Cord Compression

- **Definition:** Any radiologic evidence of indentation of the thecal sac
- Affects 5% of all adult cancer patients (2.5% may be more accurate).
- 20% of cases occur as the initial presentation of malignancy.



Malignant Epidural Spinal Cord Compression



Ropper AE, Ropper AH. N Engl J Med 2017;376:1358-1369

Malignant Epidural Spinal Cord Compression

Distribution among cancers

- Breast 15-20%
- Prostate 15-20%
- Lung 15-20%
- Non Hodgkin Lymphoma 5-10%
- Multiple Myeloma 5-10%
- Renal Cell Ca 5-10%
- Others: Colorectal Ca, Cancer of Unknown Primary and Sarcoma

Malignant Epidural Spinal Cord Compression

Anatomic Distribution

- 60% Thoracic
- 30% Lumbosacral
- 10% Cervical

Malignant Epidural Spinal Cord Compression

Signs/Symptoms

- Back Pain 83-95% (Local, referred or radicular)
- On average, pain precedes other neurologic symptoms of ESCC by seven weeks.
- Pain is often worse with recumbency and at night
- Weakness is present in 60 to 85 percent of patients with ESCC at the time of diagnosis
- ESCC generally produces fairly symmetric lower extremity weakness.
- Sensory findings are less common than motor findings but are still present in a majority of patients at diagnosis

Malignant Epidural Spinal Cord Compression

Delay in Diagnosis

- Median time from onset of to diagnosis = 2 months
- 10-day delay between the onset of neurologic symptoms and the start of therapy. The majority of patients had deterioration of motor or bladder function during the delay.

Malignant Epidural Spinal Cord Compression

Outcomes

- The ability to ambulate must be assessed – this is a highly predictive finding of the chance of recovery:
  - >80% of SCC patients who were ambulatory prior to SCC treatment will be ambulatory post-treatment
  - <50% of SCC patients who experienced weakness prior to SCC treatment will be ambulatory post-treatment
  - <10% of SCC patients who experienced paraplegia prior to SCC treatment will be ambulatory post-treatment

Malignant Epidural Spinal Cord Compression

JAMA: Back Pain

- Malignancy accounts for less than 1% of episodes of low back pain
- Previous history of cancer in the patient: (Sensitivity 31%: Specificity 98%)
- Most patients with back pain due to cancer report unrelieved by bed rest. (Sensitivity >0.9)
- In a study of nearly 2000 patients; No cancer was found in any patient under 50 years old without
  - a history of cancer,
  - unexplained weight loss or
  - a failure of conservative therapy (Sensitivity 100%)

Deyo The Rational Clinical Exam 1994

Malignant Epidural Spinal Cord Compression

Investigations

- MRI is gold standard (Sen 93%, Spec 97%)
  - CT Scan is often used but beware of false positives
- If no signs/symptoms to suggest C-Spine involvement then MRI **Thoracic and Lumbosacral spine**
- In patients with symptomatic thoracic or lumbar epidural lesions 21% had a second lesion that would have been missed if T and L spine not imaged together.

Schiff et al Cancer 1998

Malignant Epidural Spinal Cord Compression

Management

1) Steroids

- A bolus of 8 to 10 mg dexamethasone (or equivalent) can be given, followed by 16 mg/day (usually in BID or QID for tolerance).
- Patients with dense paraparesis should be considered for higher bolus (100 mg) and maintenance doses (up to 96 mg per day) (Done in consultation with Radiation Oncology or Neurosurgery)

2) Pain Management

- Opioids (Bowel Regimen) +/- Neuropathic pain adjuvants +/- bisphosphonates

ASTRO Guidelines

Malignant Epidural Spinal Cord Compression

Management

3) Consult Radiation Oncology

- Did you know that there is 24/7 Radiation Oncology coverage?

4) Consult Spine Service/Neurosurgery

- Ask the opinion about all patients but especially when there is:
  - No tissue diagnosis
  - Vertebral Column instability
  - Radio-resistant tumours (lung, colon, renal cell)
  - Intractable pain unrelieved by radiotherapy

Decompressive surgery followed by postoperative radiotherapy has been shown to be superior to radiotherapy alone for select patients with malignant epidural SCC.

ASTRO Guidelines

Malignant Epidural Spinal Cord Compression

Take Home points:

- **All new-onset back or neck pain in a patient with a history of cancer** should increase suspicion of malignant epidural SCC.
- **A True Emergency! As soon as SCC is suspected corticosteroids should be administered.**
  - IV bolus of dexamethasone at 10 to 20 mg, followed by 4-6 mg every 4 hours. Dexamethasone rapidly reduces spinal cord edema and back pain, and may also improve neurologic functioning.
- MRI is the preferred imaging study.
- **Urgent radiation oncology consult +/- Spine Surgeon Assessment**

References : CCNS Oncologic Emergencies/AHS CPG

Malignant Epidural Spinal Cord Compression

- Start Steroids and call Radiation Oncology!

Introduction to Immune Checkpoint Inhibitors

Disclosures

- Immunology was one of my least favourite courses in medical school.

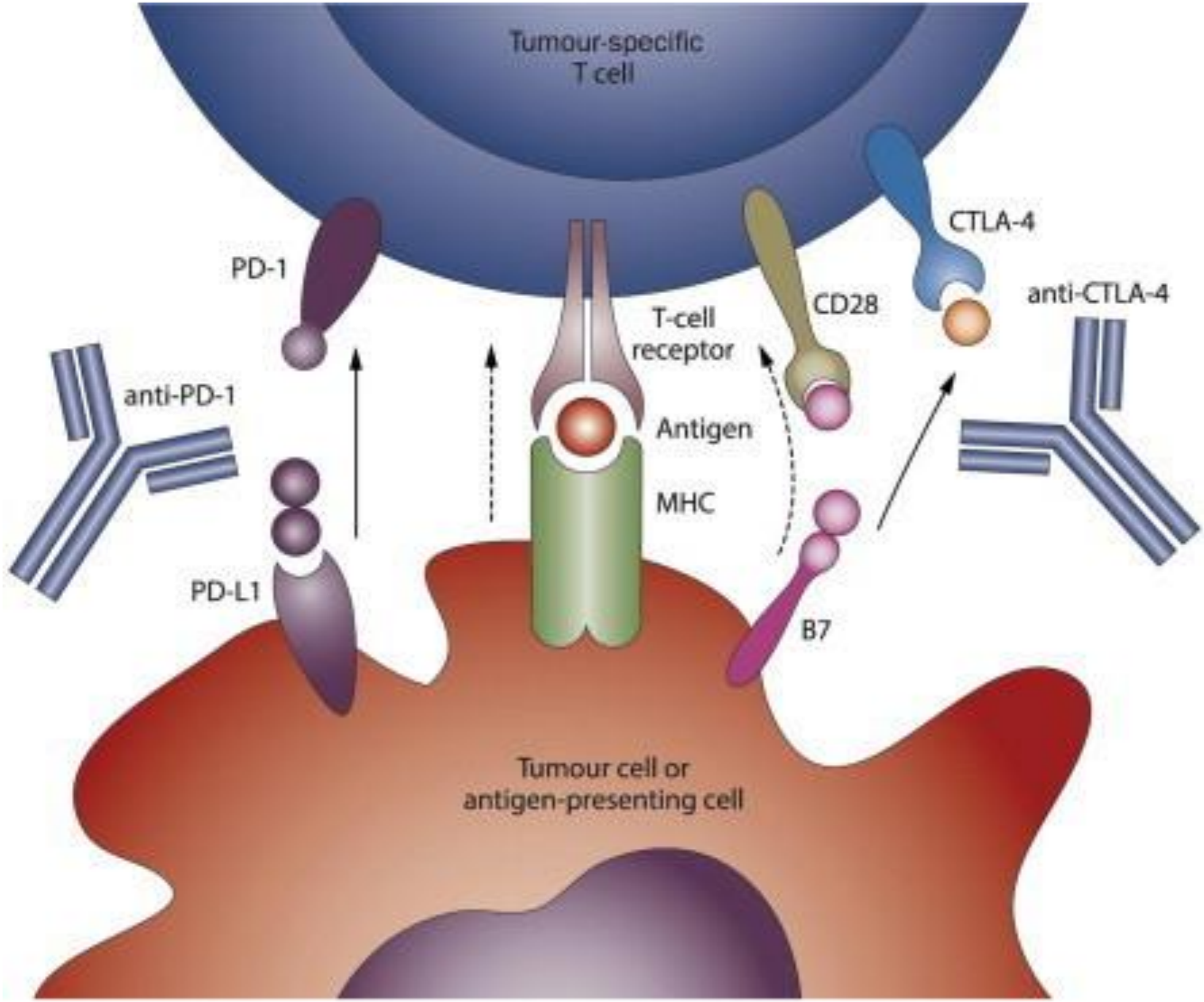
Immune Checkpoint Inhibitors

- Immune system relies on multiple checkpoints to avoid over activation.
- Tumour cells hijack these checkpoints to escape detection.
- CTLA-4 (cytotoxic T-lymphocyte-associated protein) and PD-1 (Programmed Cell Death) receptors serve as two of these checkpoints.

Immune Checkpoint Inhibitors

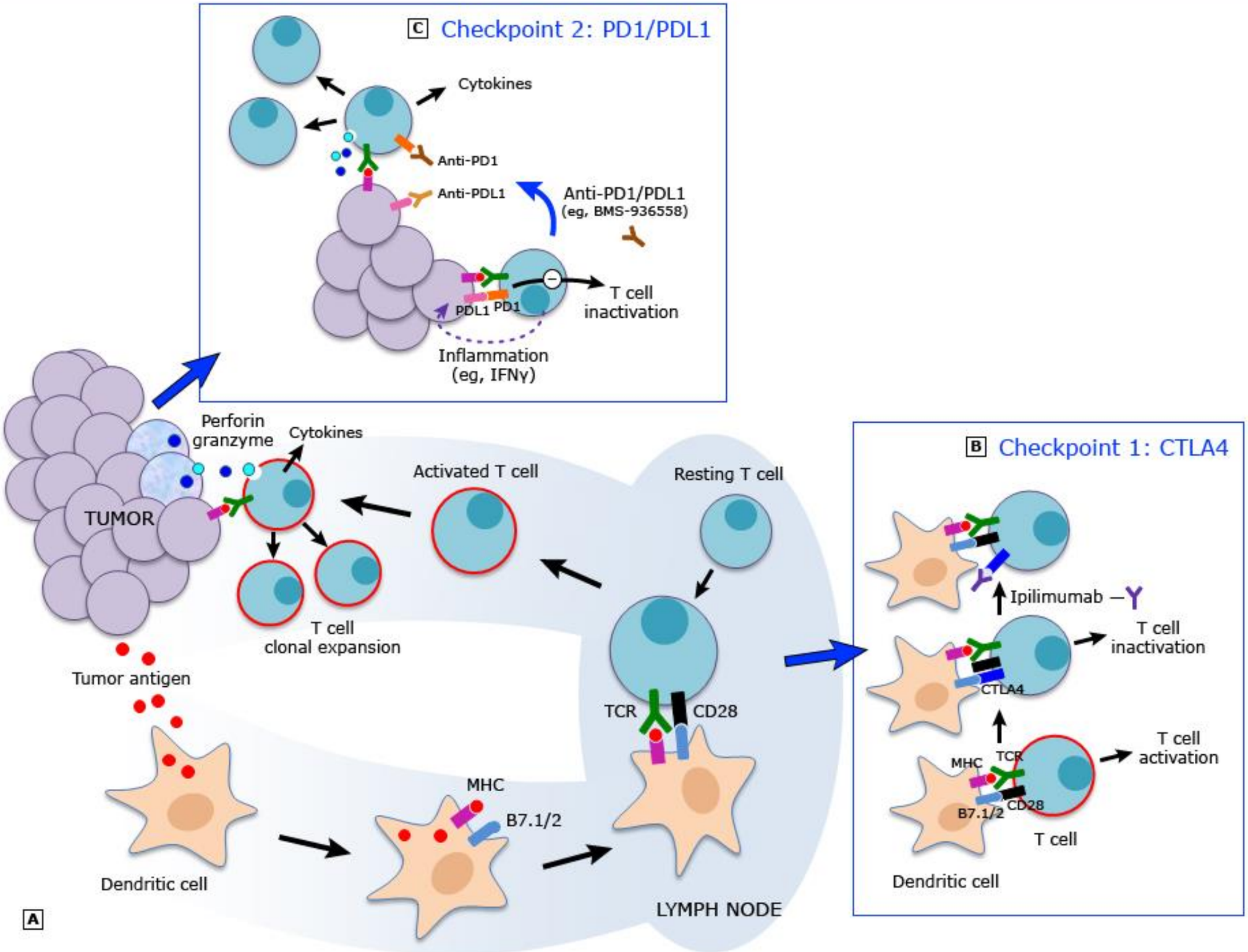
- Inhibition of CTLA-4 and PD-1 receptors on activated T-lymphocytes allows for increased T-lymphocyte activation leading to improved anti-tumour immune responses.
- Simplistically, CTLA-4 inhibition occurs in the lymph node while PD-1 inhibition occurs in the tumour microenvironment.

In Pictures



Drake CG et al. Nat Rev Clin Onc. 2014;11:24-37.

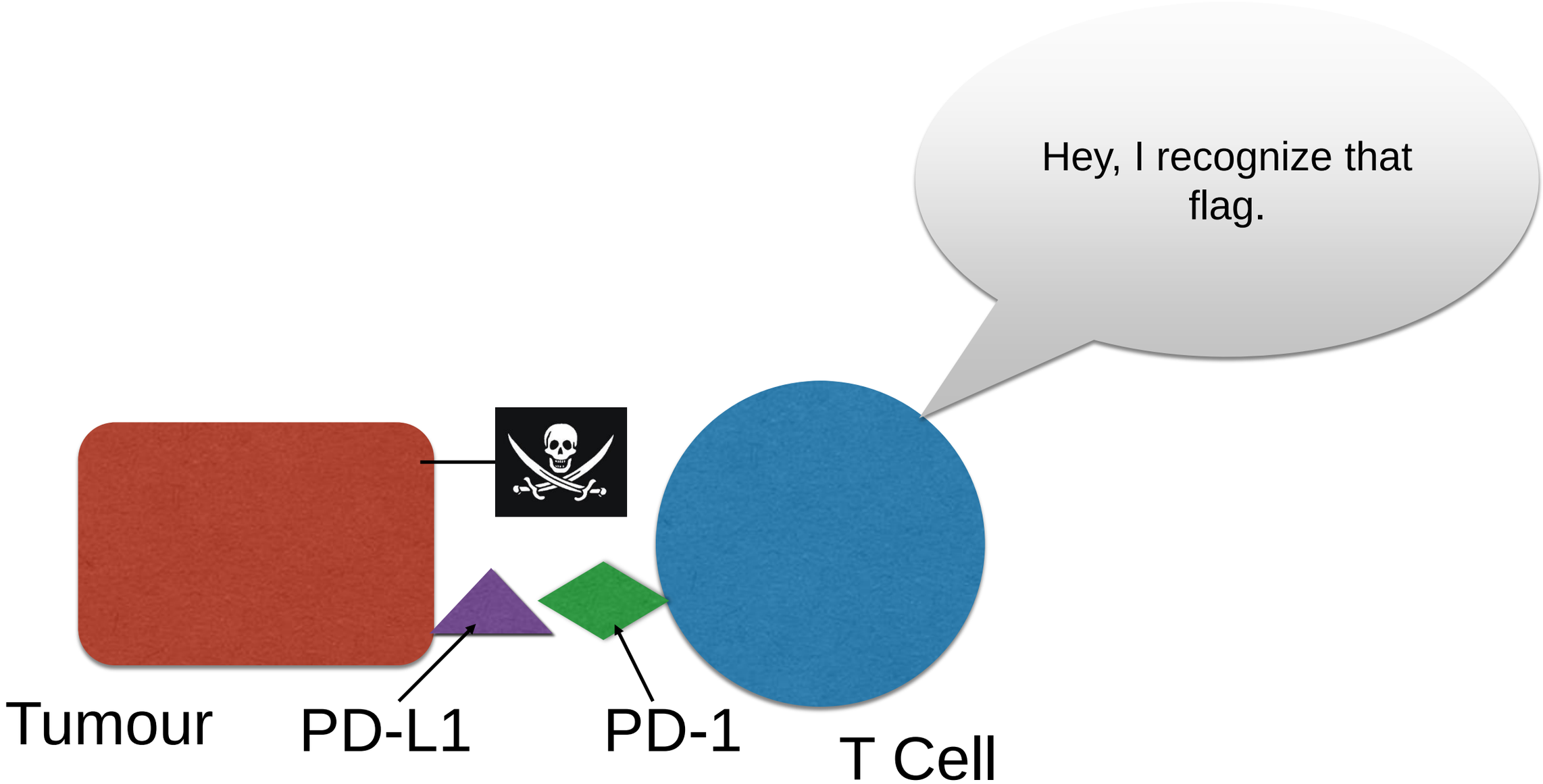
Immune activation and checkpoint inhibition

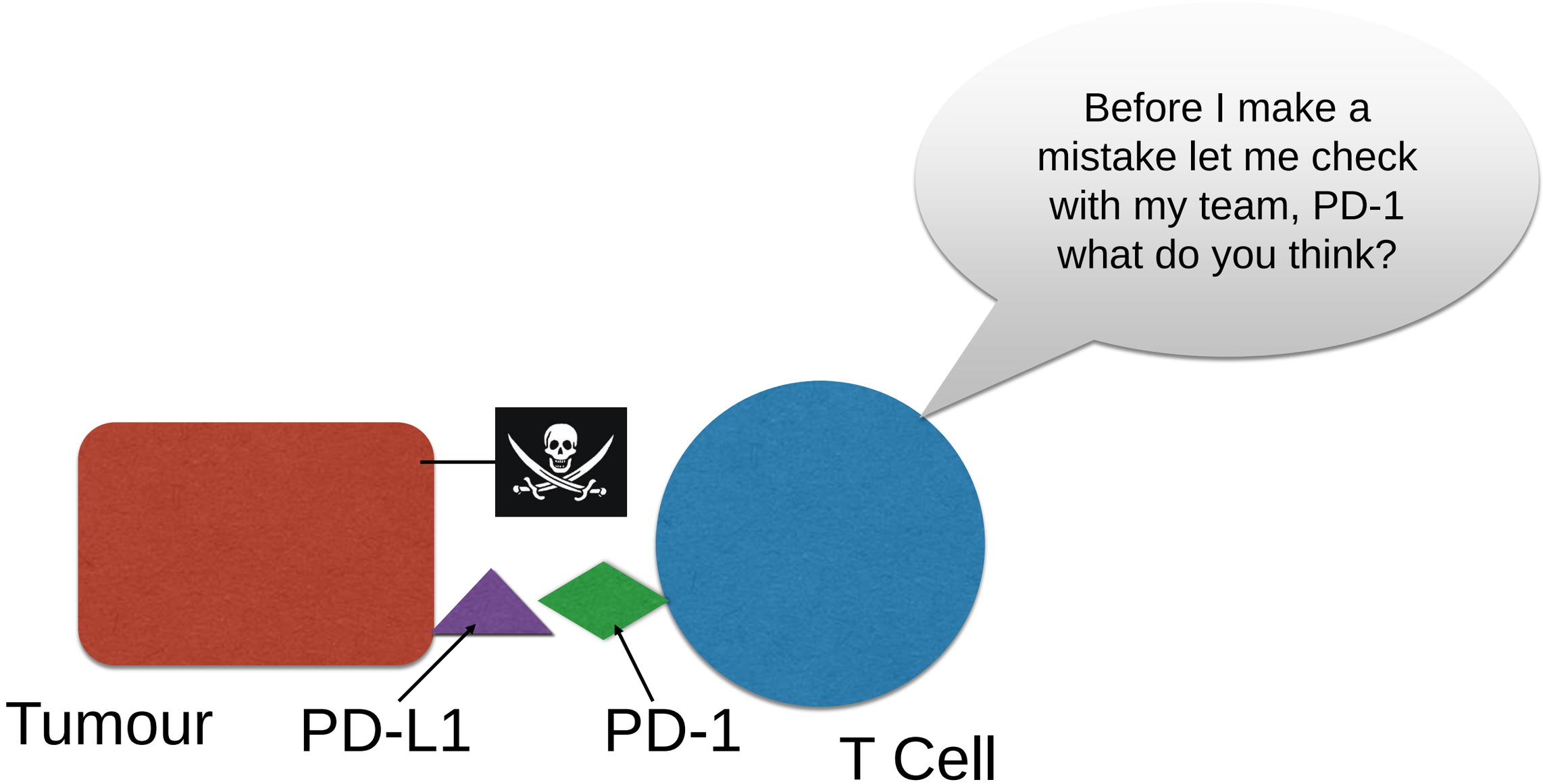


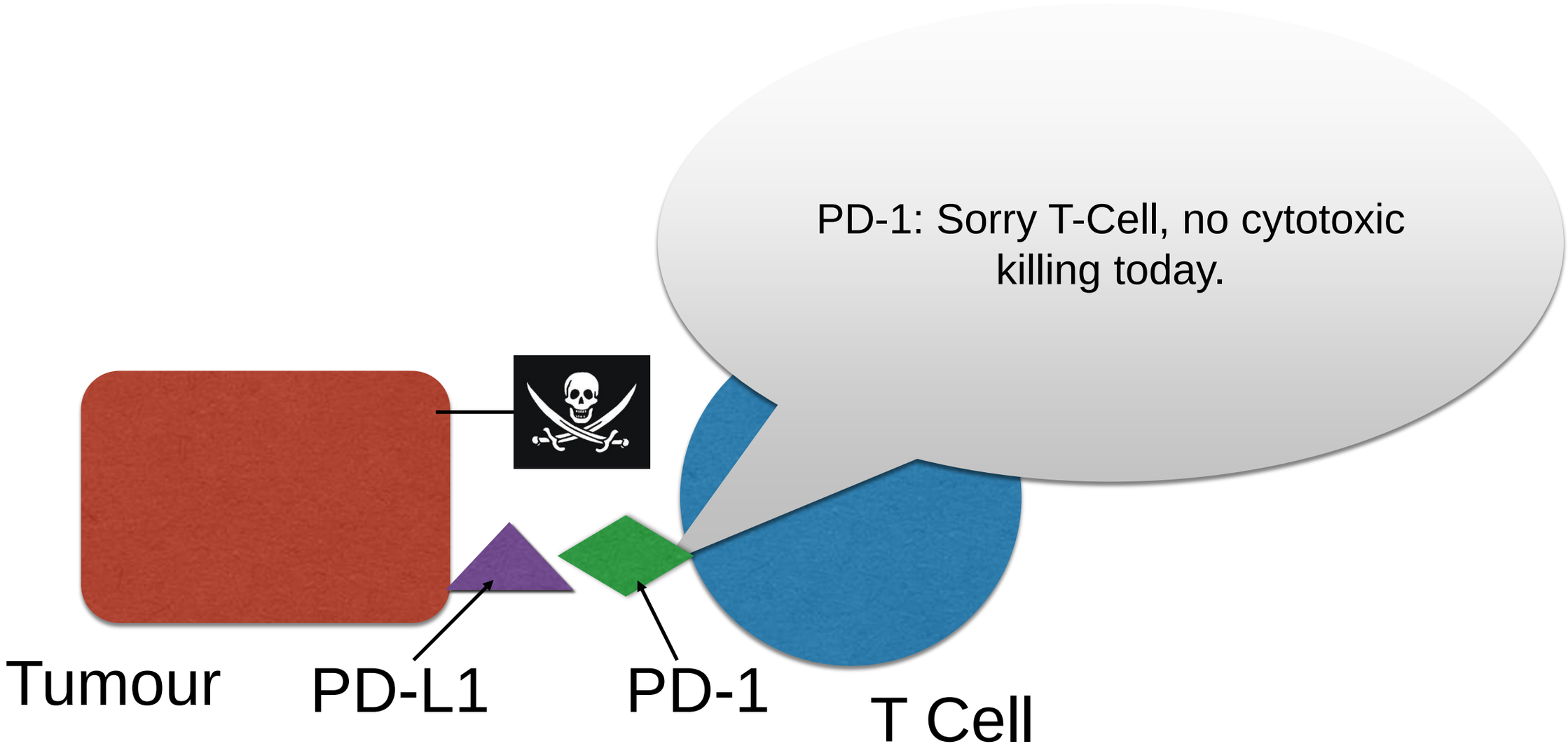
Reproduced with permission from: Scott Gettinger, MD.

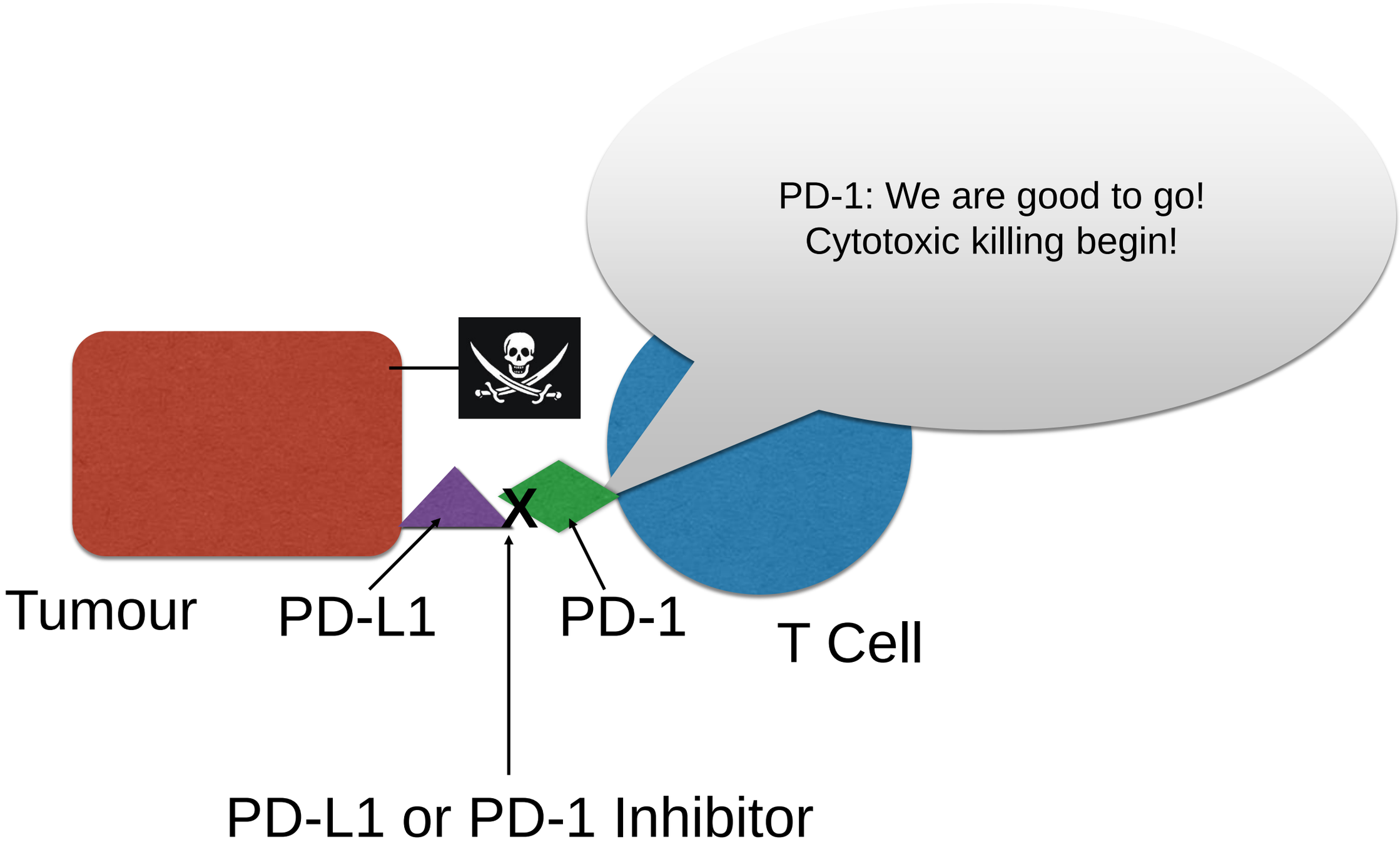
UpToDate®

Would a poorly drawn cartoon help?


Hey, I recognize that flag.
Tumour
PD-L1
PD-1
T Cell


Before I make a mistake let me check with my team, PD-1 what do you think?
Tumour
PD-L1
PD-1
T Cell


PD-1: Sorry T-Cell, no cytotoxic killing today.
Tumour
PD-L1
PD-1
T Cell

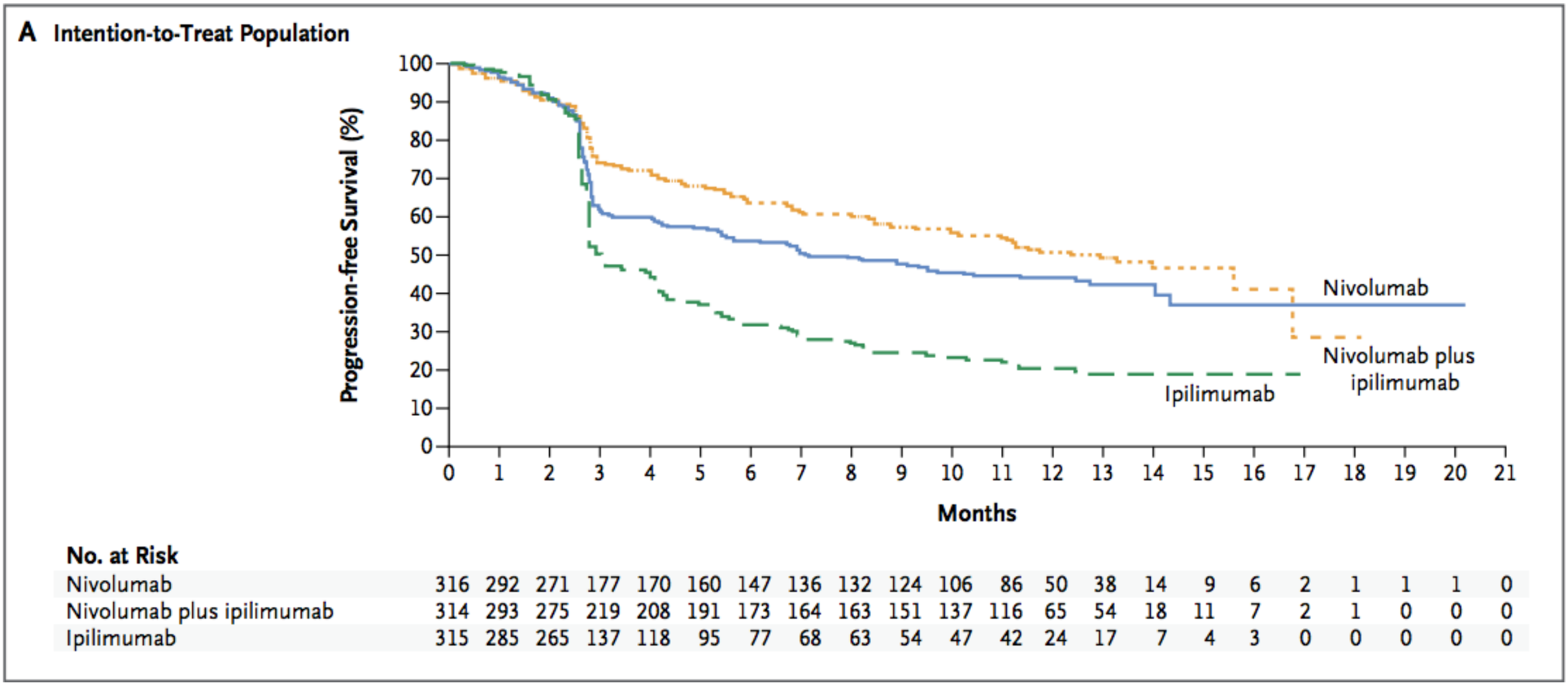

PD-1: We are good to go!
Cytotoxic killing begin!
Tumour
PD-L1
PD-1
T Cell
PD-L1 or PD-1 Inhibitor

What are the names of these drugs?

Name	Drug Class	Indications (Canada)	Location of T-Cell Activation
Ipilimumab (Yervoy)	CTLA4 Inhibitors	Metastatic Melanoma	Lymph Nodes
Nivolumab (Opdivo)	PD-1 Inhibitors	Metastatic Melanoma, Metastatic NSCLC (2nd Line), Metastatic Renal Cell Ca (2nd Line)	Tumour Tissue
Pembrolizumab (Keytruda)	PD-1 Inhibitors	Metastatic Melanoma, Metastatic NSCLC (2nd Line)	Tumour Tissue
In Clinical Trials - No Health Canada Indication as of April 12, 2017			
Atezolizumab	PD-L1 Inhibitor		Tumour Tissue
Durvalumab	PD-L1 Inhibitor		Tumour Tissue
BMS-936559	PD-L1 Inhibitor		Tumour Tissue
Avelumab	PD-L1 Inhibitor		Tumour Tissue
Tremelimumab	CTLA4 Inhibitor		Lymph Nodes

Why is this exciting?

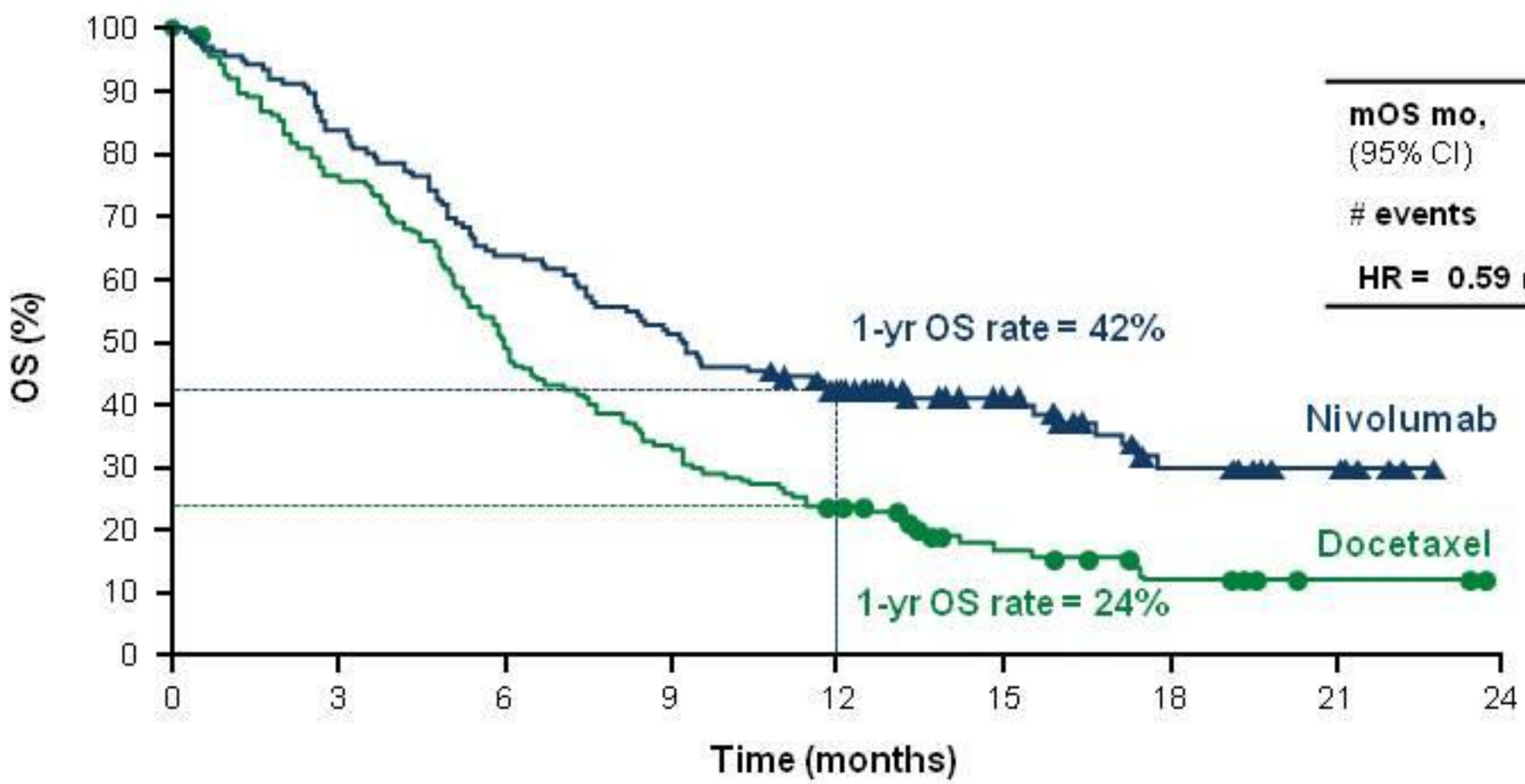
Metastatic Melanoma



Maio JCO April 1, 2015

2nd Line Squamous Non-Small Cell Lung Cancer

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

Tip of the iceberg?

Immune Checkpoint Inhibitors-The Future

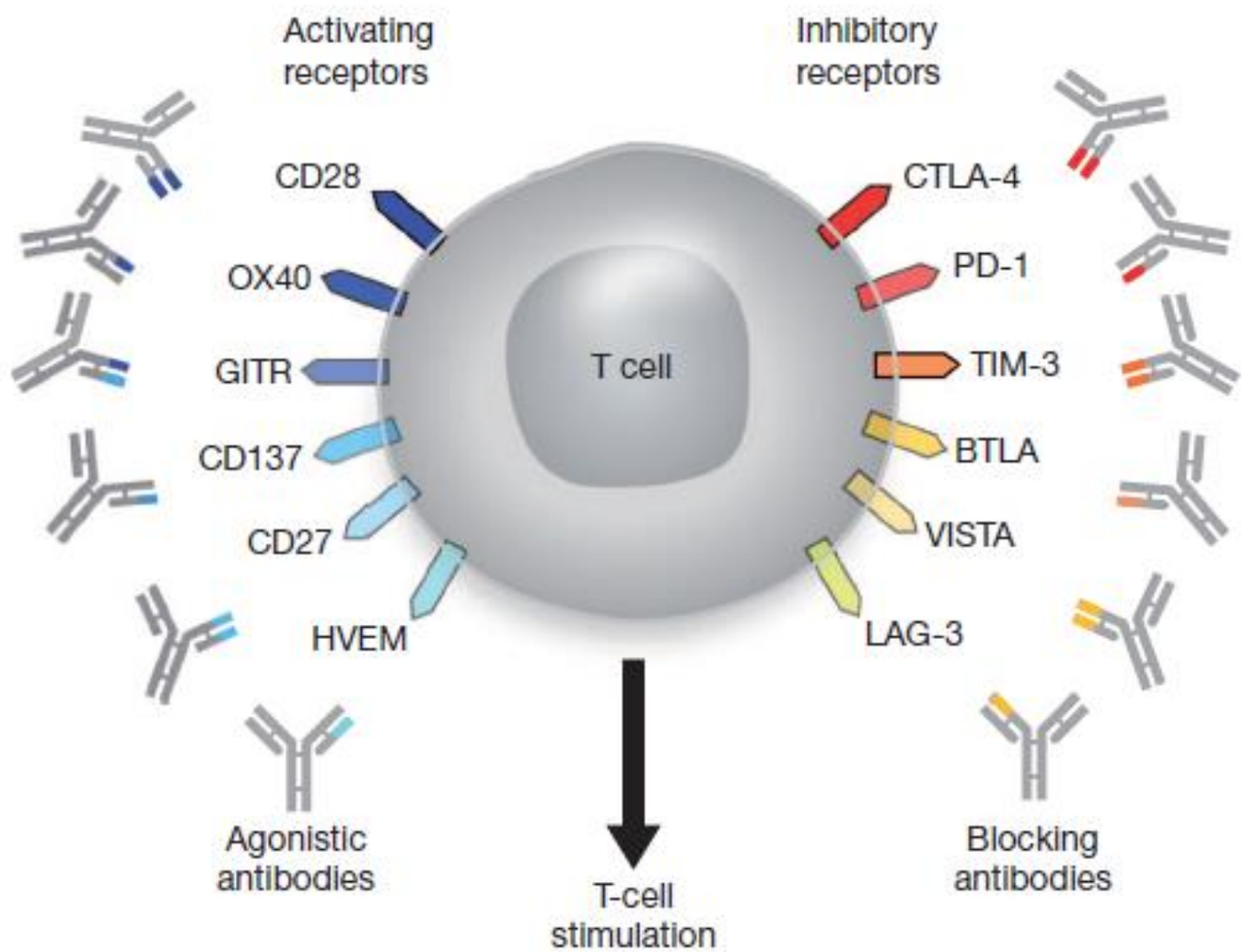


Figure 3 | T cell targets for immunoregulatory antibody therapy. In addition to specific antigen recognition through the TCR, T-cell activation is regulated through a balance of positive and negative signals provided by co-stimulatory receptors. These surface proteins are typically members of either the TNF receptor or B7 superfamilies. Agonistic antibodies directed against activating co-stimulatory molecules and blocking antibodies against negative co-stimulatory molecules may enhance T-cell stimulation to promote tumour destruction.

Toxicity

Toxicity Grading

- National Cancer Institute Common Terminology Criteria for Adverse Events
  - mild (Grade 1),
  - moderate (Grade 2),
  - severe (Grade 3),
  - life-threatening (Grade 4)
  - Specific Parameters exist for each organ system.

Immune Related Adverse Events (irAE)

- Adverse effects result from “un-inhibited” immune response (ie. irAE)
  - T-cell mediated
- Can theoretically effect any organ system
  - Toxicity can be fatal if not treated

Potential Immune Related Adverse Events

1 | 2 EDUCATION | 3 MONITORING | 4 EARLY RECOGNITION | 5 irAE Management

Skin
- Dermatitis exfoliative
- Erythema multiforme
- Stevens Johnson Syndrome
- Toxic Epidermal Necrolysis
- Vitiligo
- Alopecia

Eye
- Uveitis
- Iritis

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

Hepatic
- Hepatic, autoimmune

Gastointestinal (GI)
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

Renal
- Nephritis, autoimmune
- Renal failure

Neurologic
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barré
- Myasthenia Gravis-like syndrome

Figure courtesy of Glenn Myers

Toxicity

CTLA-4 Inhibitors

- Greater toxicity due to more “global” T-cell activation

PD-1/PD-L1 inhibitors

- Less toxic compared to CTLA-4 class

Common Side Effects of PD-1 Inhibitors

- Fatigue
- Decreased Appetite
- Rash
- Diarrhea

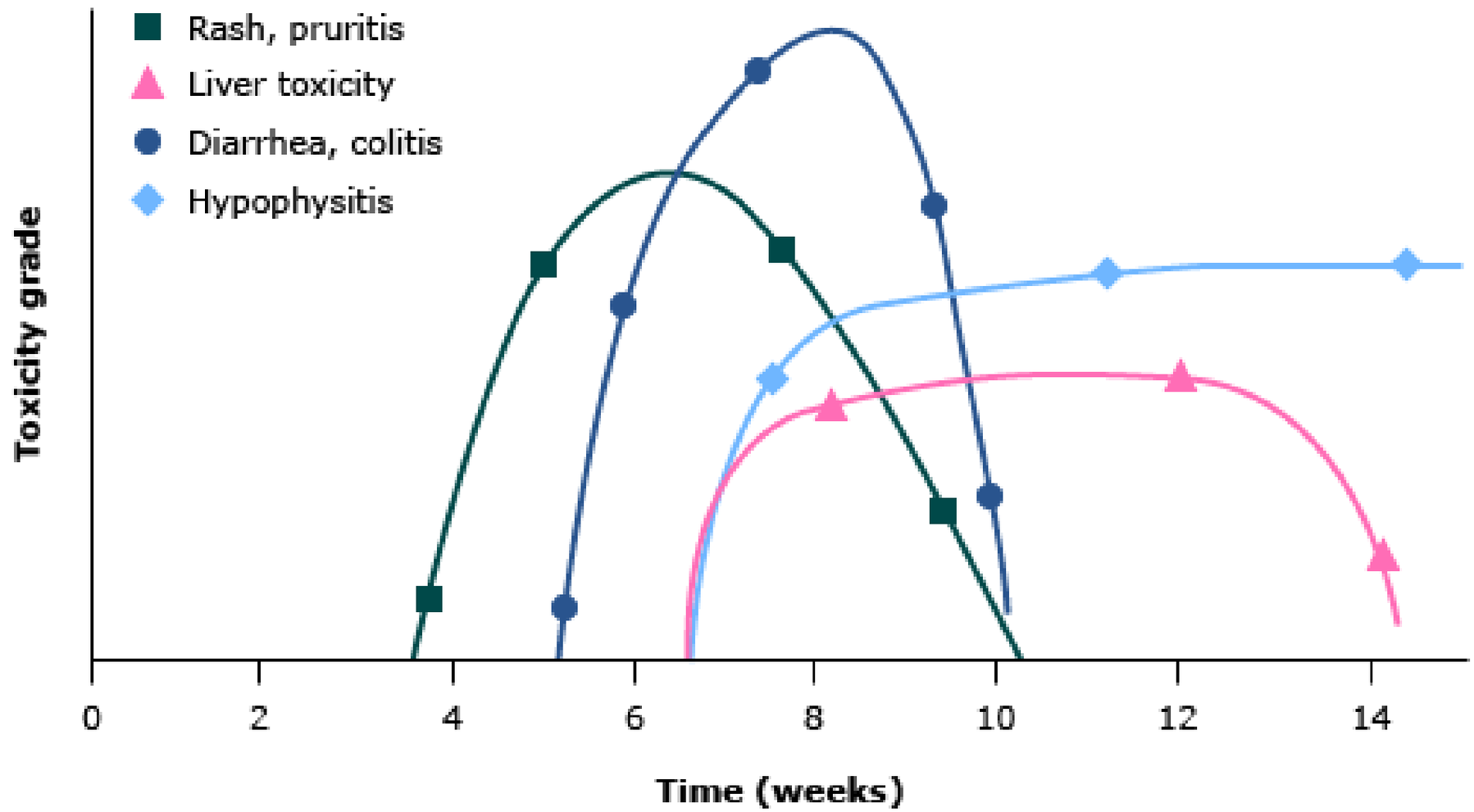
irAE

- Diarrhea/Colitis
- Pneumonitis
- Endocrinopathies
  - All axis of the pituitary gland (*ie. Hypophysitis)*
  - Thyroid gland (*ie. Hypo- or hyperthyroidism)*
  - Adrenal glands (*ie. Adrenal suppression)*
  - Pancreas (*ie*. *Diabetes Mellitus)*
- Dermatologic
- Liver Toxicity

More irAE….

- Myocarditis (<1%)
- Nephritis (1-3%)
- Pancreatitis (<1-2%)
- Ocular toxicity
- Neurological (<1%)

Kinetics of appearance of immune-related adverse event



From: Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with Ipilimumab. J Clin Oncol 2012; 30:2691-7. Reprinted with permission. Copyright © 2012 American Society of Clinical Oncology. All rights reserved.

irAE Management - General Principles

- Grade 1: Supportive Care; +/- withhold drug
- Grade 2: withhold drug, consider re challenge if toxicity resolves to <= Grade 1. **Corticosteroids** (prednisone 1mg/kg/day or equivalent tapered over a MONTH)
- Grade 3-4: discontinue drug; **high dose corticosteroids** (Methlyprednisilone 1-2 mg/kg/day or equivalent) tapered over 1 month or greater once toxicity resolves to <= Grade 1
- **Communicate with Oncology/Hematology for all Toxicities**

Soria ASCO 2016 Presentation

PD-1 vs Chemo Toxicity 2nd Line NSCLC

PD-1 Checkpoint Inhibition Phase III Trials -Toxicities

Trial	Agent	Rx-Related AEs– All & Grade 3/4	Most Common Rx-Related AEs	Pneumonitis Rate
Checkmate 017	Nivolumab	58% 7%	Fatigue – 16% ↓ appetite – 11% Asthenia – 10%	All – 5% Gr 3/4 – 0%
	Docetaxel	86% 55%	Neutropenia – 33% Fatigue – 33% Nausea 23%	0%
Checkmate 057	Nivolumab	69% 10%	Fatigue – 16% Nausea – 12% ↓ appetite – 10%	All – 3% Gr 3/4 – 1%
	Docetaxel	88% 54%	Neutropenia – 31% Fatigue – 29% Nausea – 26%	0%
Keynote 010	Pembrolizumab 2 mg/kg dose	63% 13%	Fatigue – 20% Pruritis – 11% ↓ appetite – 11%	All – 5% Grade 3-5 – 2% 2 deaths
	Docetaxel	81% 35%	Fatigue – 25% Diarrhea 18% ↓appetite – 16%	0%

Brahmer J et al NEJM 2015; Borgahi H et al NEJM 2015; Herbst R et al Lancet 2015

Presented By Jean-Charles Soria at 2016 ASCO Annual Meeting

Prolonged Steroid Course

- Adjunct therapies for steroid tapers to consider
  - Pneumocystis jirovecii (PCP) prophylaxis
    - >4 weeks @ >20mg/day
  - GI ulceration prophylaxis in patients on NSAIDS or ASA
  - Calcium + vitamin D for bone health

Take Home Points

- Drug induced autoimmunity ALWAYS included in differential, often diagnosed by exclusion
  - Rule out other Etiologies
  - Can affect ANY organ system
  - Early Recognition, evaluation and treatment are critical.
- **Communicate with Oncology/Hematology for all Toxicities**
- **PO/IV corticosteroids the preferred method for managing moderate to severe immune related adverse events.**

And something to take home ...

Checkpoint Immunotherapy Quick Reference - Created by Glenn Myers BScPharm, ACPR & Michael LeBlanc BScPharm, PharmD

Generic Name (Brand)	Drug Class	Approved Indication	Off-Label	Dosing
Ipilimumab (Yervoy®)	CTLA-4 Inhibitors	Metastatic Melanoma (single or combo), Adjuvant melanoma	N/A	3mg/kg IV q3 weeks X 4 doses (10mg/kg for adjuvant)
Nivolumab (Opdivo®)	PD-1 Inhibitors	Metastatic Melanoma, mNSCLC (2nd line), mRCC, Head and Neck	Hodgkin's Lymphoma	3mg/kg IV q 2 weeks; 1mg/kg q3 weeks in combination with ipilimumab
Pembrolizumab (Keytruda®)	PD-1 Inhibitors	Metastatic Melanoma, mNSCLC (1st or 2nd line), Head and Neck	N/A	2mg/kg IV q 3 weeks

CTLA-4 = Cytotoxic T-Lymphocyte Antigen -4; PD-1 = Programmed Death-1; mNSCLC= metastatic Non-Small Cell Lung Cancer; mRCC = metastastic renal cell carcinoma

Mechanism of Action: Inhibition of CTLA-4 and PD-1 receptors on activated T-lymphocytes allows for increased T-lymphocyte activation in the lymph nodes and tumor tissue, respectively, to improve anti-tumor immune responses. This is not the same mechanism utilized by conventional cytotoxic chemotherapy or other targeted anti-cancer therapy.

Immune related adverse events (iRAE): Inhibition of T-lymphocyte deactivation increases risk for immune related toxicities that resemble that of autoimmune presentation. **The preferred method of managing ≥grade 2 iRAE is PO/IV corticosteroids**.

Grade 1 Adverse Event (mild, asymptomatic or minimally symptomatic)		
Dermatologic Toxicity • Maculopapular rash <10% of BSA (*+/- pruritis*)	Topical corticosteroid (ie. Betaderm) +/- antipruritic	• Communicate with Oncology/Hematology
Gastrointestinal Toxicity • <4 stools/day; no colitis symptoms	Anti-motility agent X 24-48hrs; Monitor by oncology	
Hepatic Toxicity • AST/ALT ≤2.5x ULN **OR** bilirubin ≤1.5x ULN	No therapy required; Monitor by oncology	
Nephrotoxicity • SCr ≤1.5x ULN	No therapy required; Monitor by oncology	
Pulmonary Toxicity • Asymptomatic; Radiographic changes only	No therapy required; Monitor q3 days by oncology	
Endocrine Toxicity • Asymptomatic	No therapy required; Monitor by oncology	
Grade 2 Adverse Event (Moderate severity toxicity that requires corticosteroids)		
Dermatologic Toxicity • Maculopapular rash 10-30% of BSA	• Communicate with Oncology/Hematology • Start prednisone 1mg/kg PO **OR** methylprednisolone 1mg/kg IV daily • Consider consultation of disease site specialist (ie. Gastrointestinal toxicity → Gastroenterologist)	
Gastrointestinal Toxicity • 4-6 stools/day; mild colitis symptoms†		
Hepatic Toxicity • AST/ALT >2.5-5x ULN **OR** bilirubin >1.5-3x ULN		
Nephrotoxicity • SCr >1.5-6x ULN		
Pulmonary Toxicity • New mild to moderate symptoms	• Same as above • CT Chest	
Endocrine Toxicity • Symptomatic **hypothyroidism**, **hyperthyroidism** or **hypophysitis** with laboratory changes	• TSH, T_4, cortisol and pituitary blood panel; Brain MRI **if hypophysitis** • Same as above (strongly consider endocrinologist consult)	
Grade 3/4 Adverse Event (Severe toxicity that requires admission and aggressive corticosteroids)		
Dermatologic Toxicity • Maculopapular rash >30% of BSA	• Communicate with Oncology/Hematology • Prednisone 1-2mg/kg PO daily as outpatient	
Gastrointestinal Toxicity • >7 stools/day; moderate-severe colitis symptoms‡	• Admission to hospital • Communicate with Oncology/Hematology • Start methylprednisolone 1-2mg/kg IV daily • Consultation with disease site specialist (ie. Gastrointestinal toxicity → Gastroenterologist)	
Hepatic Toxicity • AST/ALT >5x ULN **OR** bilirubin >3x ULN		
Nephrotoxicity • SCr >6x ULN		
Endocrine Toxicity • Adrenal crisis; Severely symptomatic hypophysitis		
Pulmonary Toxicity • New severe symptoms and worsening hypoxia	• Same as above only methylprednisolone 2-4mg/kg IV daily • CT Chest	

† = Abdominal pain, hematochezia, mucous in stool; ‡ = Abdominal pain with ileus or peritoneal signs, fever and potential life threatening consequences

Learning Objectives

- Review presentation and management of Malignant Epidural Spinal Cord Compression (MESCC)
- Introduce immune checkpoint inhibitors
- Provide a brief overview of the management immune related adverse events.

Three Key Messages

- MRI is the gold standard for diagnosis of malignant epidural spinal cord compression.
- If a patient is on an immune checkpoint inhibitor, drug induced autoimmunity should ALWAYS be included in the differential diagnosis.
- PO/IV corticosteroids the preferred method for managing moderate to severe immune related adverse events.

- Special thanks to Glenn Myers for the IO toxicity handout and access to his slides.

Thank you

Questions

Oncologic Emergencies Links

- Alberta: A Guide for Family Physicians
- Nova Scotia

Horizon Guidelines

- Febrile Neutropenia
- Penicillin Allergies
- Chemotherapy Induced Toxicity

British Columbia Cancer Agency (BCCA) Guidelines

- Hypercalcemia
- Febrile Neutropenia

Immune Checkpoint Inhibitors Links

- Ipilimumab
- Nivolumab
- Pembrolizumab