Immunotherapy- What the Primary Care Doctor Needs to Know

Anna C. Pavlick, DO, MBA

Weill Cornell Medicine Professor of Medicine
Founding Director, WCM Melanoma and Cutaneous Oncology Program
WCM-Meyer Cancer Center Oncology Service Line Medical Director

Weill Cornell Medicine
Meyer Cancer Center

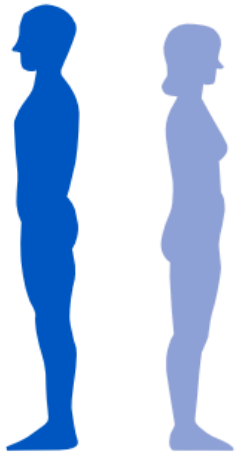
WHY this lecture??

- Immunotherapy is part of most cancer therapies now
- Immunotherapy had a unique toxicity profile and patients can present to their primary care physicians with these toxicities
- Boy Scout Motto-Always Be Prepared! You can save their life.

Cancer in America

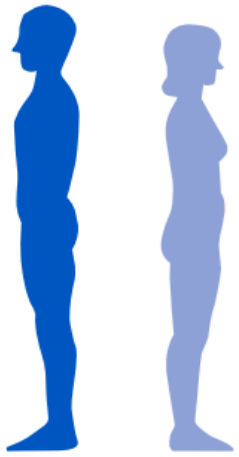
Estimated New Cases

Male			Female		
Prostate	313,780	30%	Breast	316,950	32%
Lung & bronchus	110,680	11%	Lung & bronchus	115,970	12%
Colon & rectum	82,460	8%	Colon & rectum	71,810	7%
Urinary bladder	65,080	6%	Uterine corpus	69,120	7%
Melanoma of the skin	60,550	6%	Melanoma of the skin	44,410	4%
Kidney & renal pelvis	52,410	5%	Non-Hodgkin lymphoma	35,210	4%
Non-Hodgkin lymphoma	45,140	4%	Pancreas	32,490	3%
Oral cavity & pharynx	42,500	4%	Thyroid	31,350	3%
Leukemia	38,720	4%	Kidney & renal pelvis	28,570	3%
Pancreas	34,950	3%	Leukemia	28,170	3%
All sites	**1,053,250**		**All sites**	**988,660**	



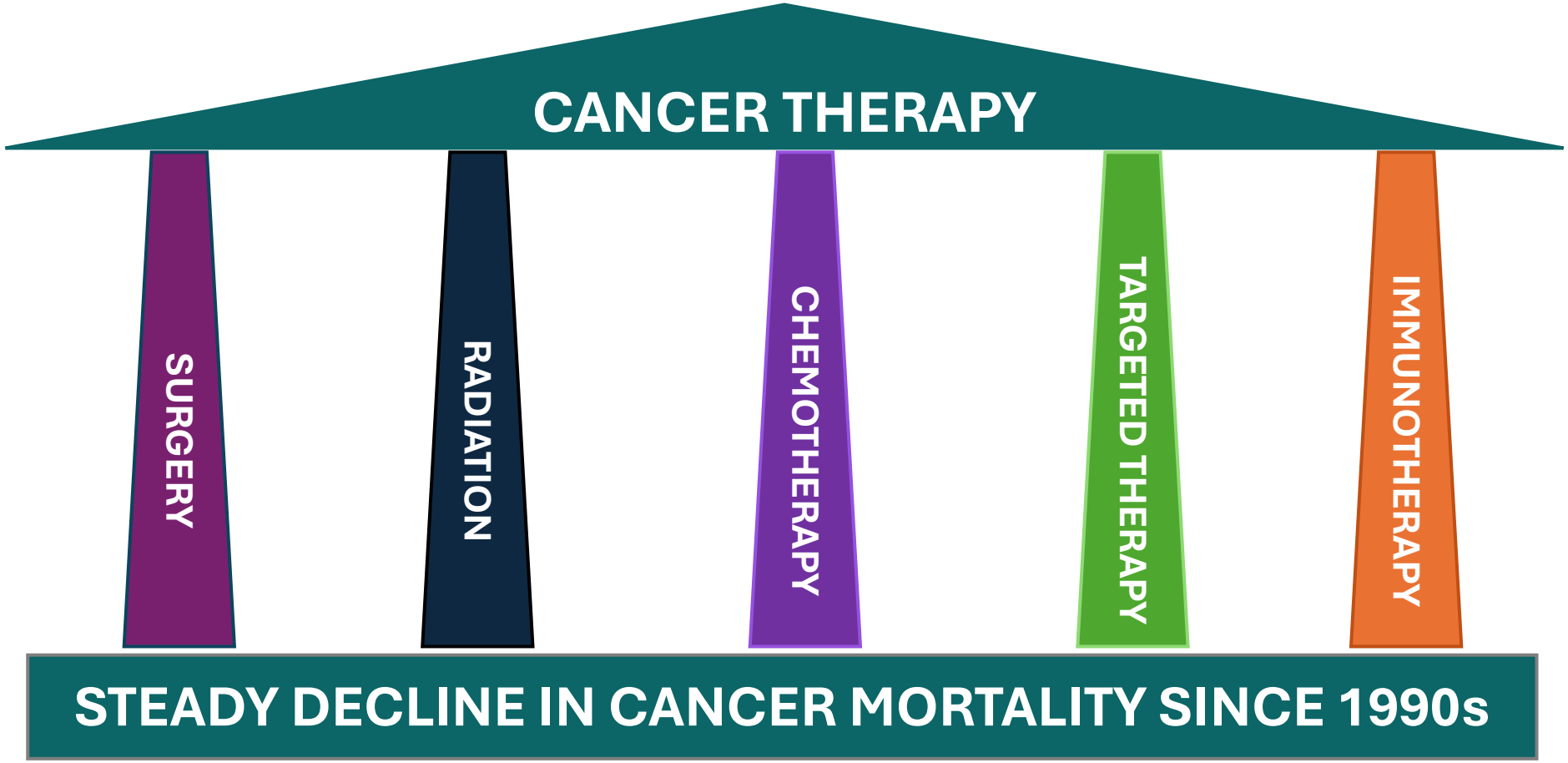
Estimated Deaths

Male			Female		
Lung & bronchus	64,190	20%	Lung & bronchus	60,540	21%
Prostate	35,770	11%	Breast	42,170	14%
Colon & rectum	28,900	9%	Pancreas	24,930	8%
Pancreas	27,050	8%	Colon & rectum	24,000	8%
Liver & intrahepatic bile duct	19,250	6%	Uterine corpus	13,860	5%
Leukemia	13,500	4%	Ovary	12,730	4%
Esophagus	12,940	4%	Liver & intrahepatic bile duct	10,840	4%
Urinary bladder	12,640	4%	Leukemia	10,040	3%
Non-Hodgkin lymphoma	11,060	3%	Non-Hodgkin lymphoma	8,330	3%
Brain & other nervous system	10,170	3%	Brain & other nervous system	8,160	3%
All sites	**323,900**		**All sites**	**294,220**	



Estimates exclude US territories and are rounded to the nearest 10; cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from observed data.

Cancer Treatment Modalities



www.cancer.gov/about-cancer/understanding/statistics.

Toxicities from Cancer Therapy

- Surgery-infection, wound healing issues
- Radiation- skin breakdown, dry mouth, lymphedema
- Chemotherapy- “cytopenias”, hair loss, fatigue, weight loss, N/V
- Hormone Therapy- weight gain, edema, hot flashes
- Targeted therapy- arthralgias, myalgias, skin tox, hepatitis
- IO-”itis”

What is the Difference Between Immunotherapy and Chemotherapy?

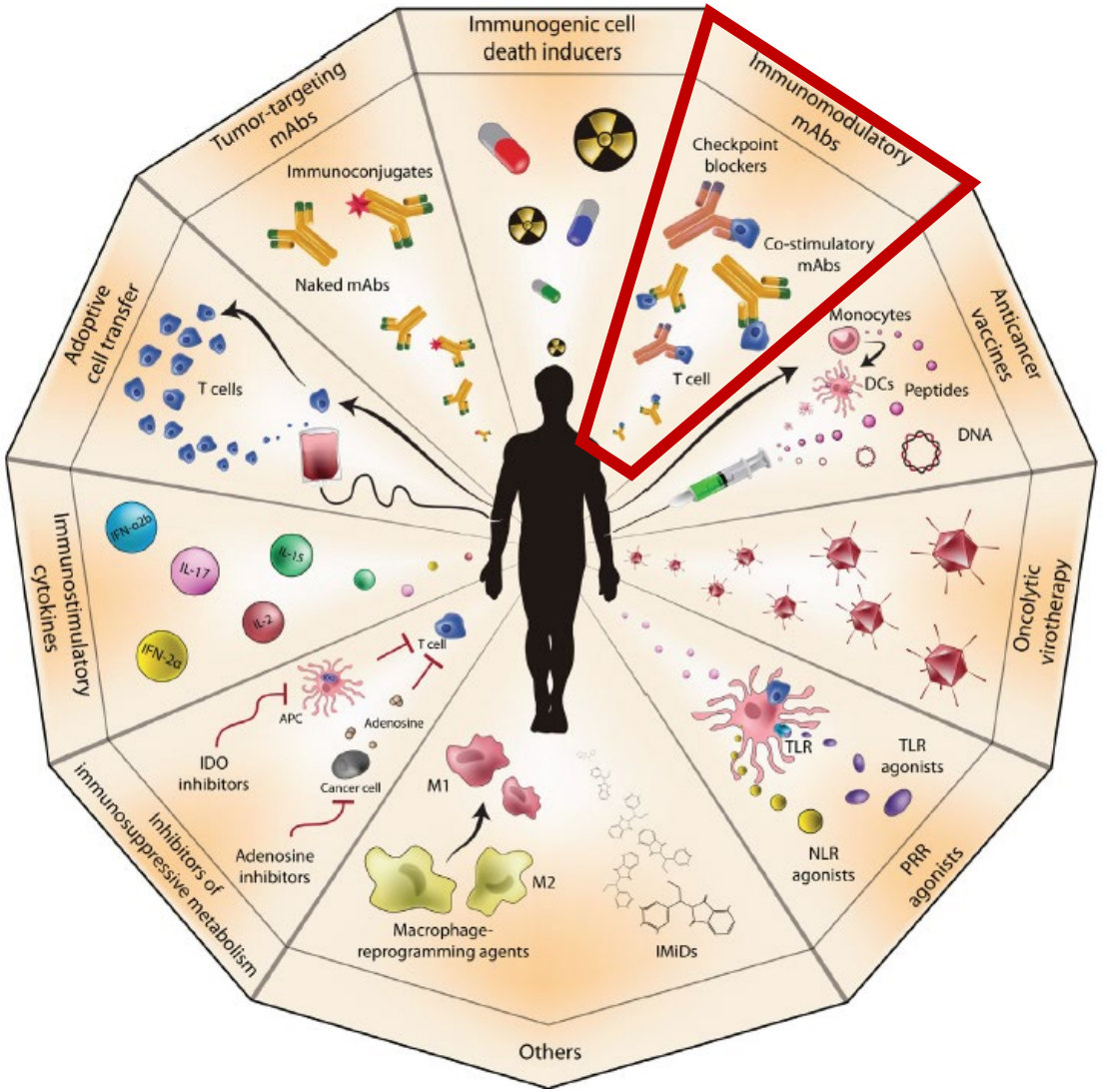
Immunotherapy builds up the immune system

Increased T-cells

Chemotherapy destroys rapidly dividing cells

Immune system Is weakened

Types of Cancer Immunotherapy

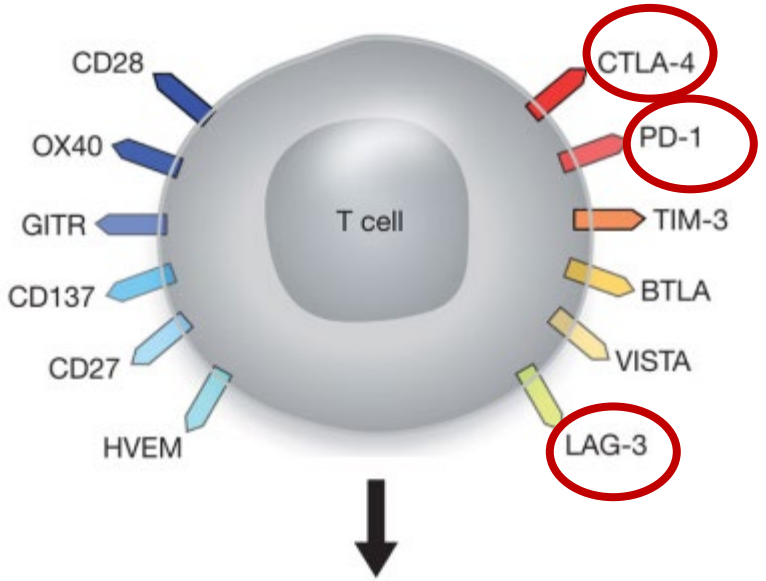


Galluzzi L, et al. *Oncotarget*. 2014.

Immuno-Regulatory Receptors

Activating Receptors

Inhibitory Receptors
(Immune Checkpoint Molecules)



T-Cell Regulation

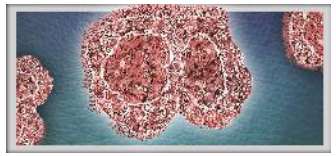
Immune checkpoint molecules: inhibitory receptors on immune cells

- Modulate the duration and amplitude of immune responses and maintain self-tolerance
- Usurped by cancer cells to suppress and evade anti-tumor immune response

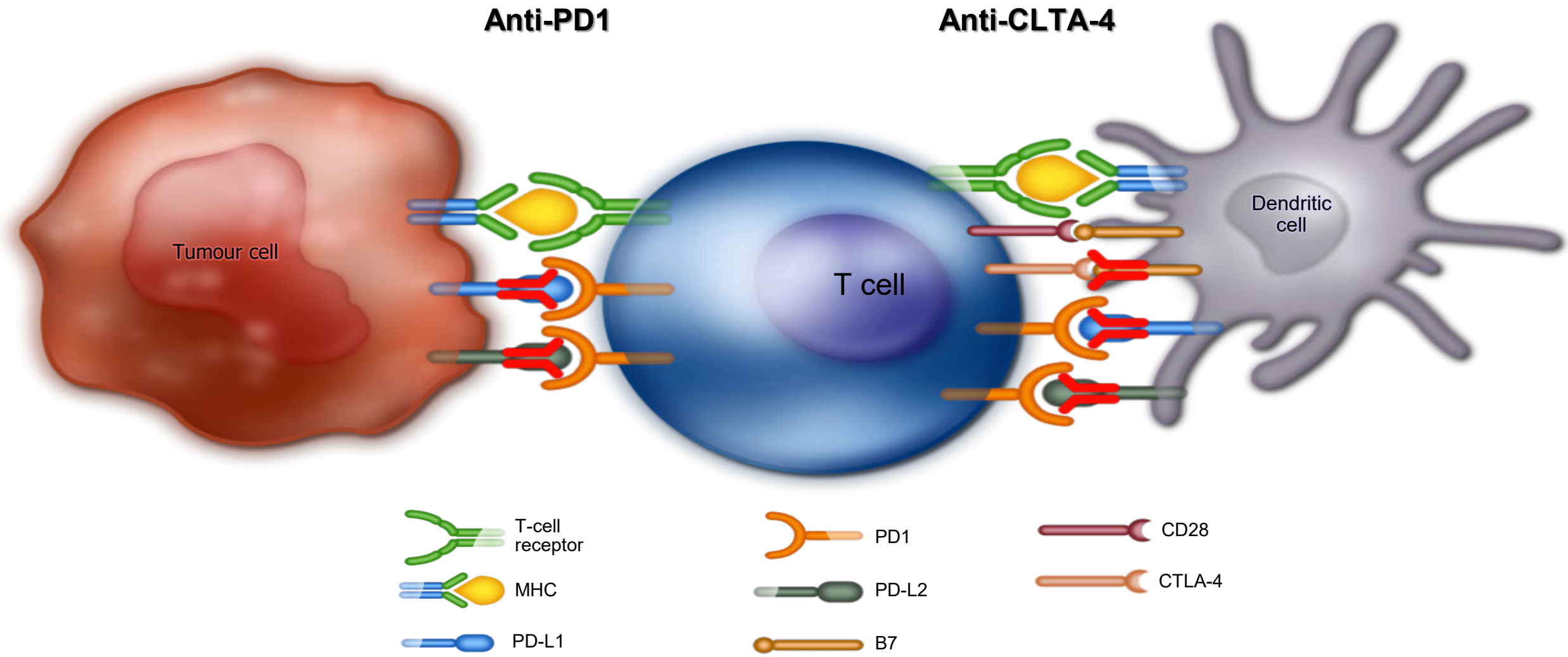
Mellman I, et al. *Nature*. 2011.

Common Checkpoint Inhibitors

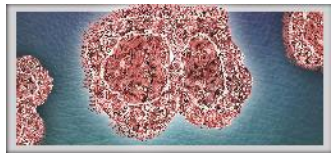
- CTLA-4 inhibitor- ipilimumab (YERVOY)
- PD-1 inhibitors- nivolumab (Opdivo), pembrolizumab (Keytruda), cemiplimab (Libtayo)
- PD-L1 inhibitors- avelumab (Bavencio)
- PD-1 and LAG3 inhibitor combo-nivolumab and relatlimab (Opdualag)



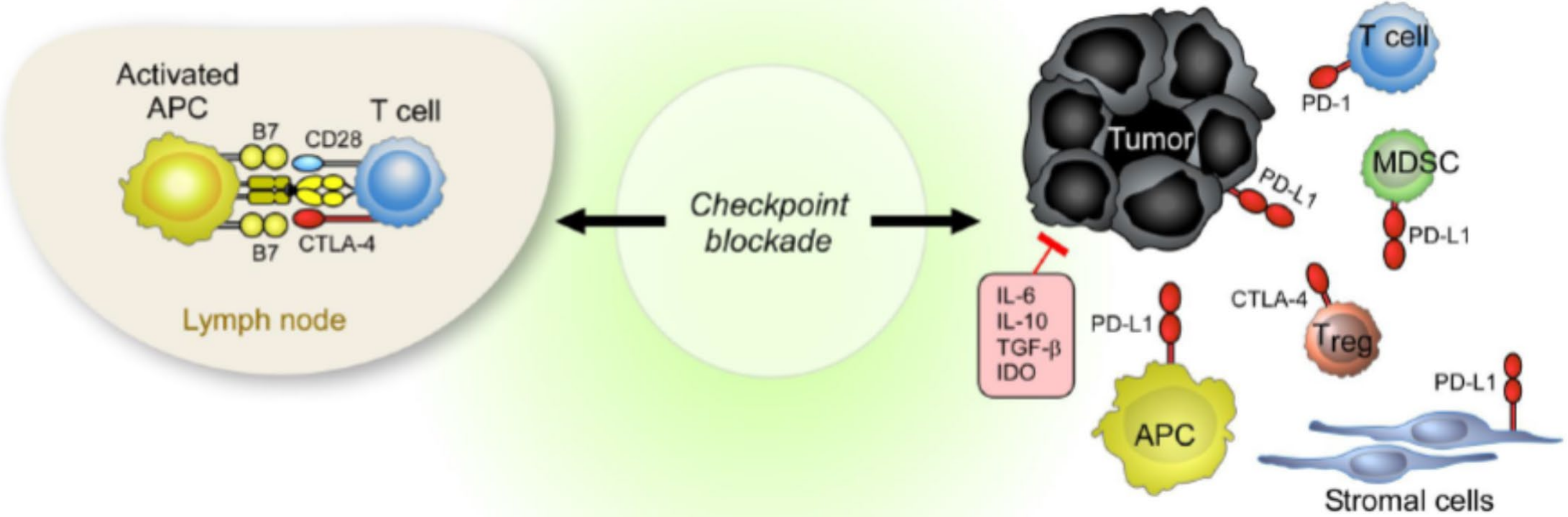
Players in Immune Checkpoint Inhibition



Adapted from Sznol M, et al. Presented at ASCO 2013: oral presentation CRA9006



Where Does Checkpoint Blockade Function?



CTLA-4 in the lymph node

CTLA-4 in the Lymph Node

PD-1 in the tumor

PD-1 in the Tumor

Adapted from Sznol M, et al. Presented at ASCO 2013: oral presentation CRA9006

Cancer Evading The Immune System

Rockets cannot penetrate forcefield

AKA

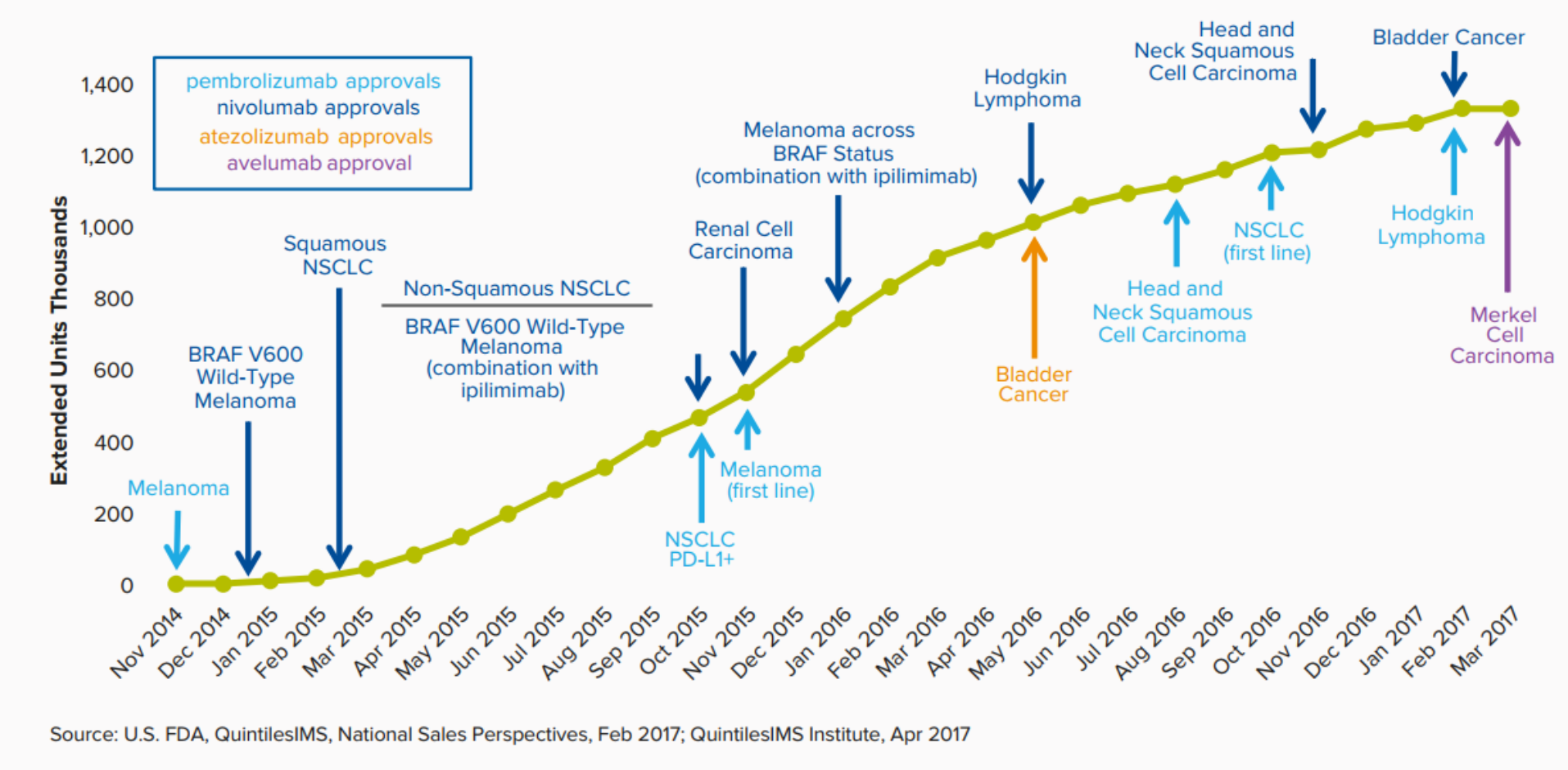
T cells cannot infiltrate the tumor

Activated Immune System and Blocked PD-1 Receptors Can Penetrate Tumor Cells Leading to Cell Death

https://images.app.goo.gl/kvdT85eNwepnpfjg6

Rapid Growth of Immunotherapy

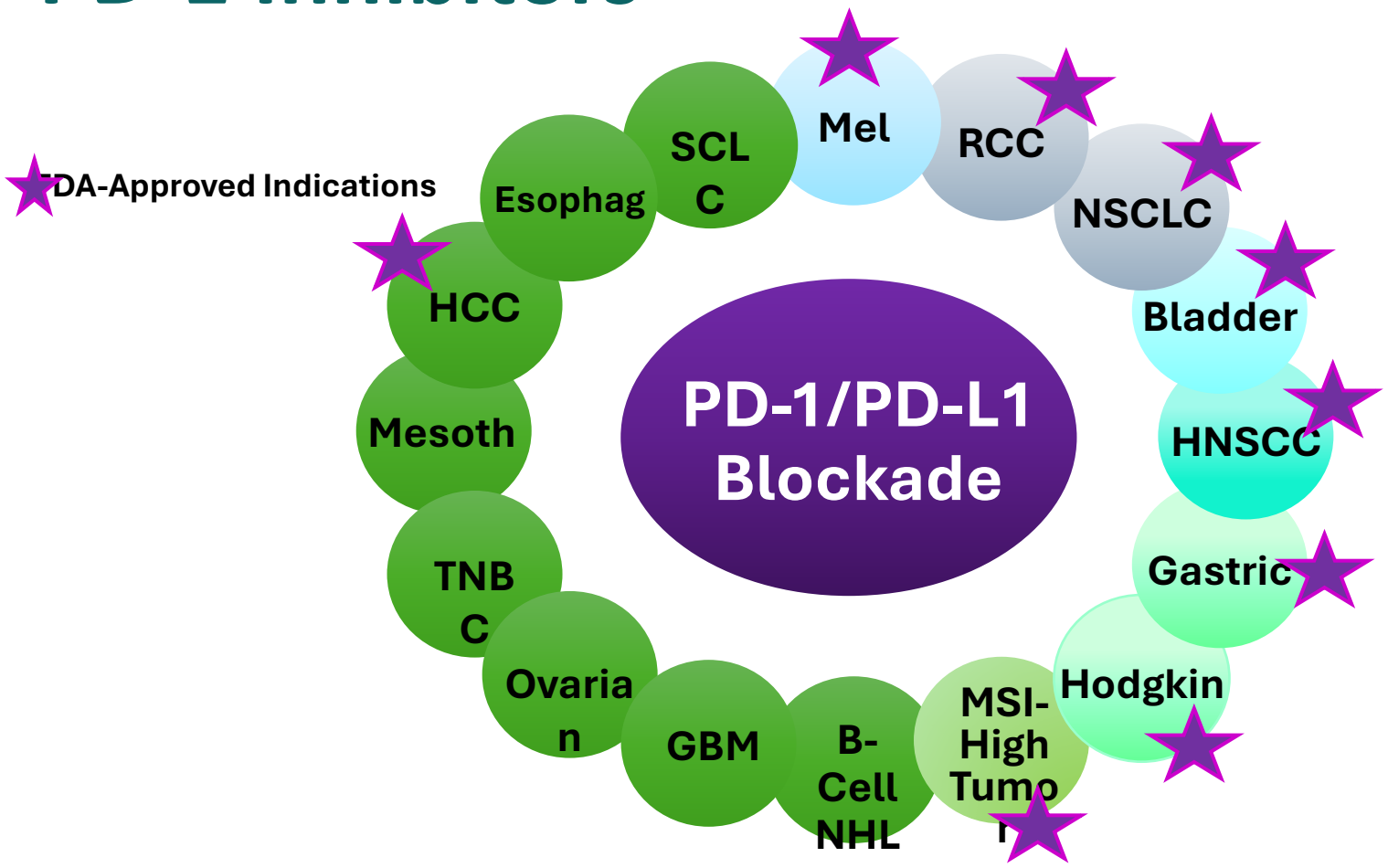
November 2014 – March 2017



Source: U.S. FDA, QuintilesIMS, National Sales Perspectives, Feb 2017; QuintilesIMS Institute, Apr 2017

Rapid Growth of Immunotherapy

Approved and Emerging Indications of PD-1 Inhibitors



NHL=Non-Hodgkin lymphoma; MSI=Microsatellite instability; SCLC=Small cell lung cancer; TNBC=Triple-negative breast cancer; Mesoth=Mesothelioma; HCC=Hepatocellular carcinoma; Oesophag=Esophageal carcinoma; GBM=Glioblastoma

Adapted from Michot JM. *Eur J Cancer*. 2016.

What Makes IO Management So Challenging?

- Loss of immunologic tolerance to self antigens
- Tissue damage associated with inflammatory T-cell infiltrates
  - Can involve any organ system
  - Mostly mild to moderate and reversible
  - **Can be life-threatening**
  - **Represent a new type of oncologic emergency**

Benefits of therapy outweigh potential risks, particularly when IRAEs are recognized early and treated quickly

Weber JS, et al. *J Clin Oncol*. 2012; Spain L, et al. *Cancer Treat Rev*. 2016; Horvat TZ, et al. *J Clin Oncol*. 2015; Downey SG, et. *Clin Cancer Res*. 2007; Freeman-Keller M, et al. *Clin Cancer Res*. 2016.

Immune Related Adverse Effects (IRAEs)
General Issues

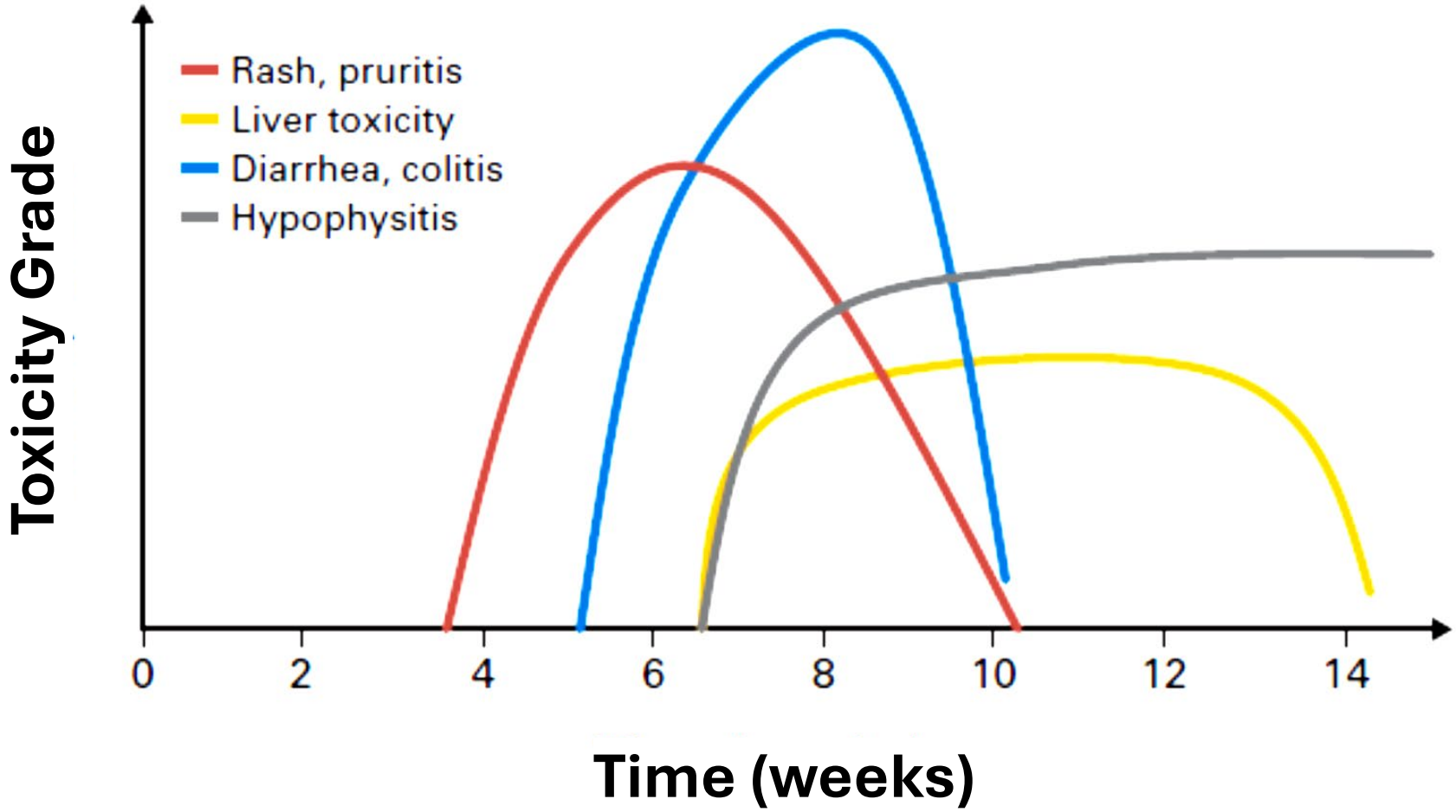
- Most irAEs occur during the first 3-4 months of therapy
  - Late irAEs, however, also can occur (eg, one episode has been seen at month 47 during maintenance phase of therapy)
  - Each irAE has different kinetics of onset and some can wax and wane, particularly colitis

- Corticosteroids and other immunosuppressants can be used to manage almost all irAEs
  - Prolonged steroid tapers are usually required

Weber JS, et al. *J Clin Oncol*. 2012;
Weber JS, et al. ASCO 2015. Abstract 261; Weber JS, et al. *J Clin Oncol*. 2015.

CTLA-4 Blockade With Ipilimumab

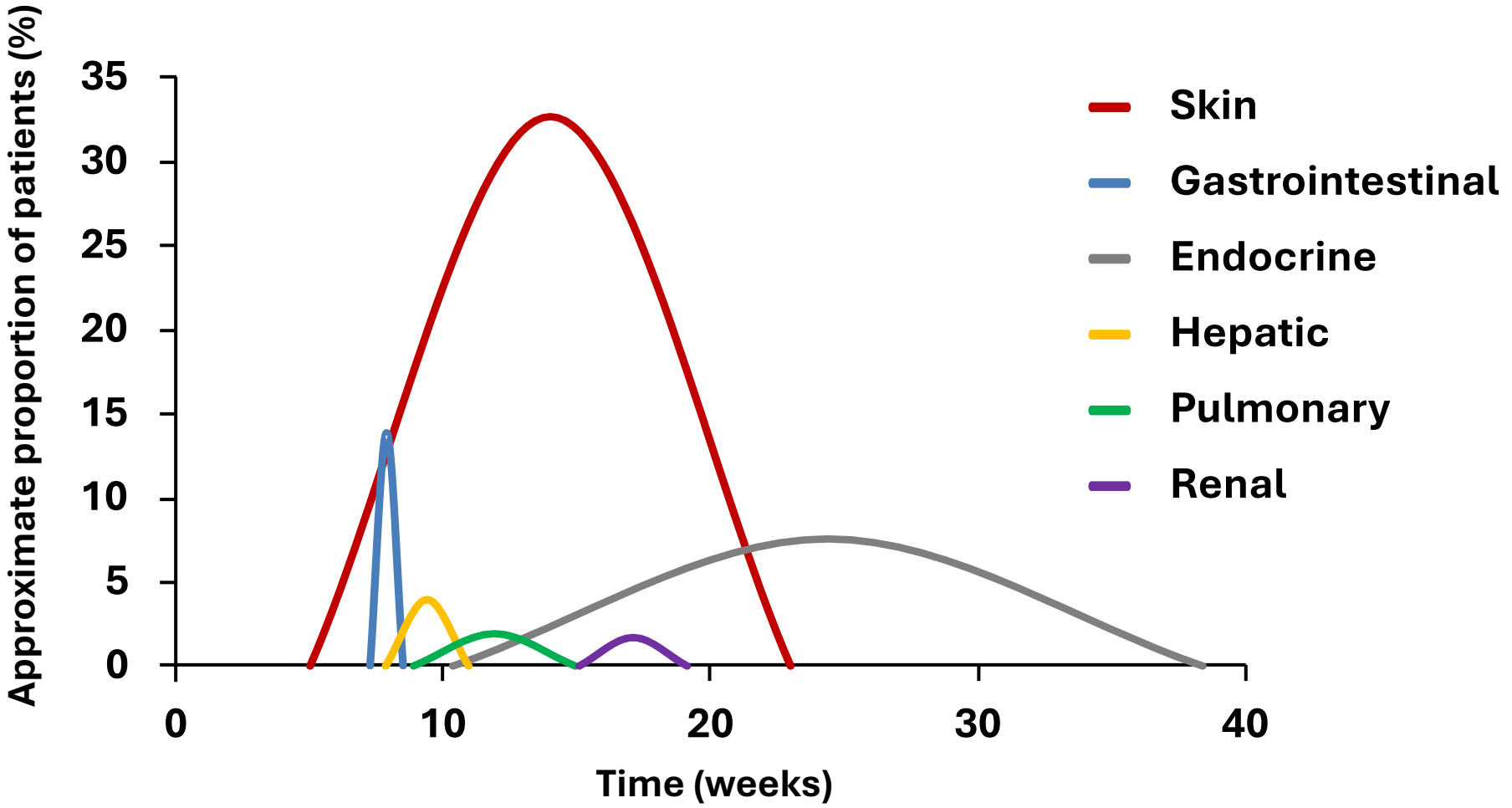
Kinetics of IRAEs in Melanoma



Weber JS, et al. *J Clin Oncol*. 2012.

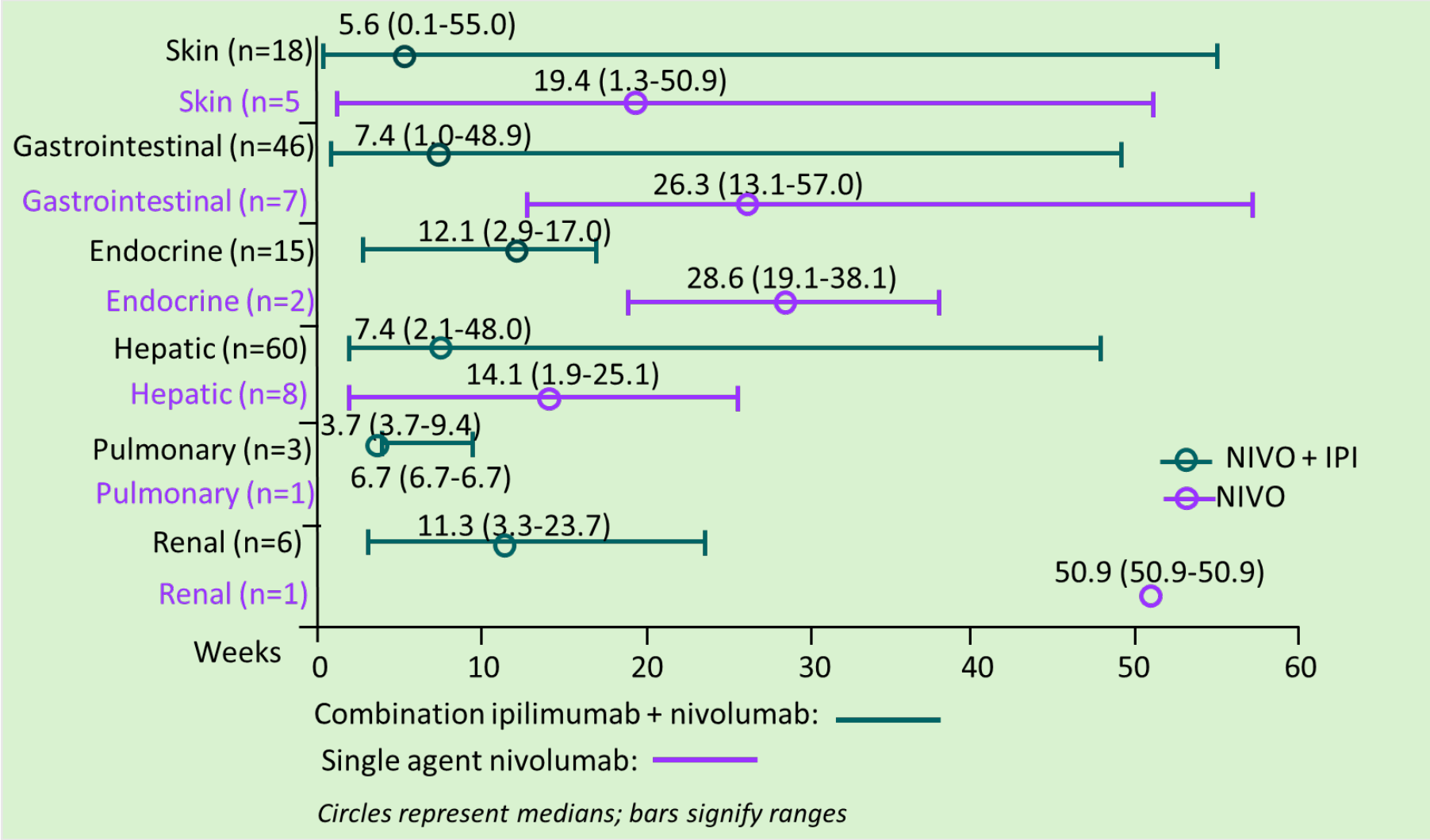
PD-1 Blockade With Nivolumab

Kinetics of IRAEs in Melanoma



Weber JS, et al. *ASCO*. 2015.

Combined Checkpoint Blockade
Kinetics of IRAEs



Larkin J, et al. *Eur J Cancer*. 2015.

Nonconventional Kinetics Are Most Apparent With Pseudo-Progression

Pseudo-progression may occur when T-cell infiltration causes tumors to flare or new lesions to appear upon imaging[1]

Considerations when evaluating true progression vs pseudo-progression

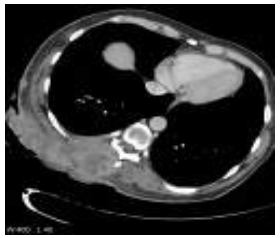
	May indicate progression	May indicate pseudo-progression
Performance status	Deterioration of performance	Remains stable or improves
Systemic symptoms	Worsen	May or may not improve
Symptoms of tumor enlargement	Present	May or may not be present
Tumor burden **Baseline** **New lesions**	Increase Appear and increase in size	Increase followed by response Appear then remain stable and/or subsequently respond
Biopsy may reveal	Evidence of tumor growth	Evidence of T-cell infiltration

1. Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420; 2. Topalian SL, et al. *N Engl J Med*. 2012;366:2443-2354; 3. Eisenhauer EA, et al. *Eur J Cancer*. 2009;45:228-247; 4. Chow LQ. Am Soc Clin Oncol Educ Book. 2013:280-285; 5. American Cancer Society. Lung Cancer. http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-diagnosis. Accessed September 30, 2013.

Ipilimumab: Response After Tumor Volume Increase

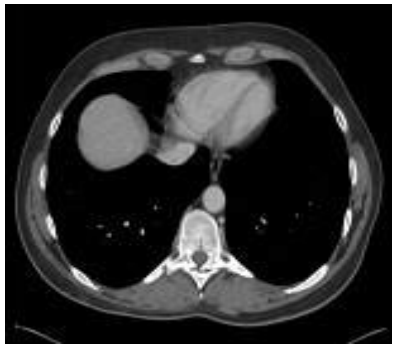
Screening

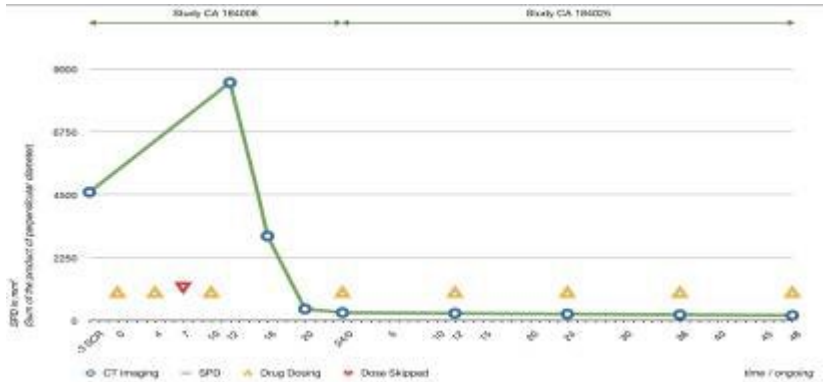

Week 12
Initial increase in total tumor burden (mWHO PD)

Week 16
Responding


Week 72
Durable & ongoing response without signs of IRAEs

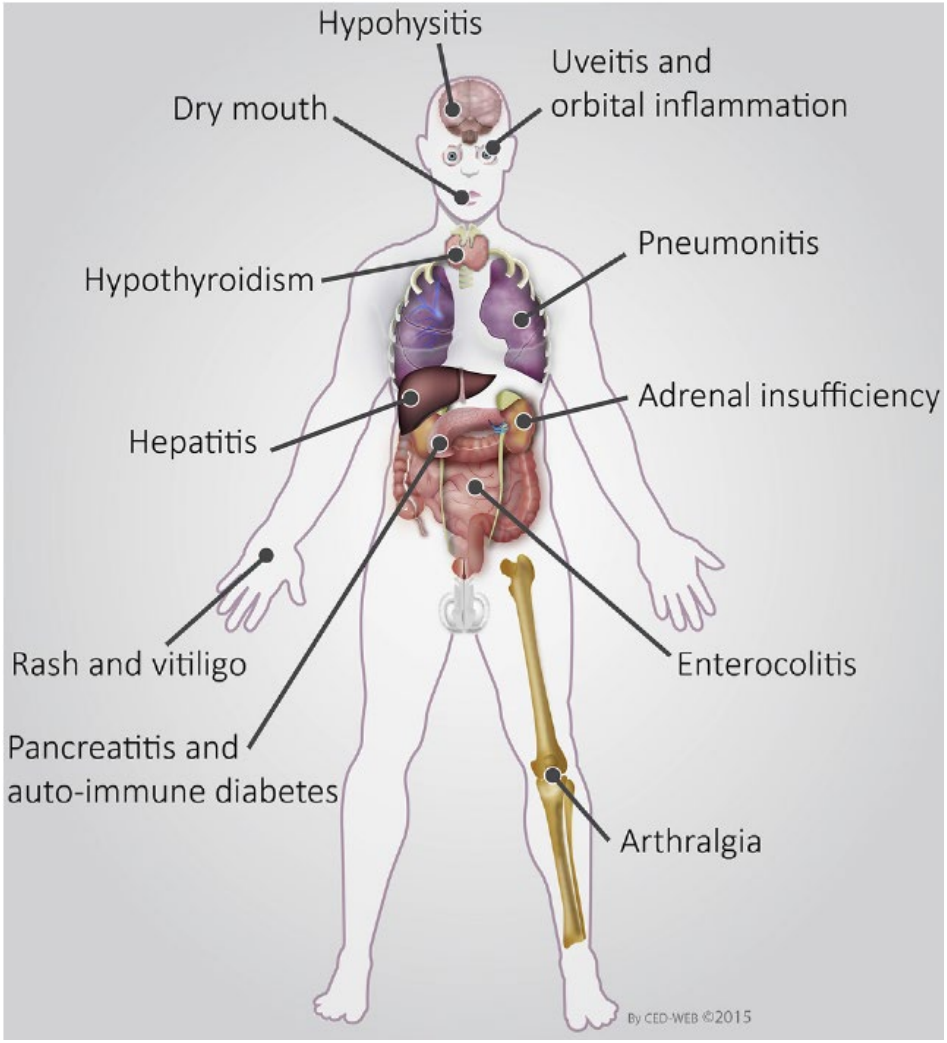


Courtesy of K. Harmankaya and S. Hodi

Toxicity Identification

- Most IRAE's are reversible
- Vast majority of endocrinopathies are permanent
- If you don't know/think about them, you'll miss them

IRAEs *Clinical Spectrum*



Michot JM, et al. *Eur J Cancer.* 2016.

Skin

Dermatitis *Management*

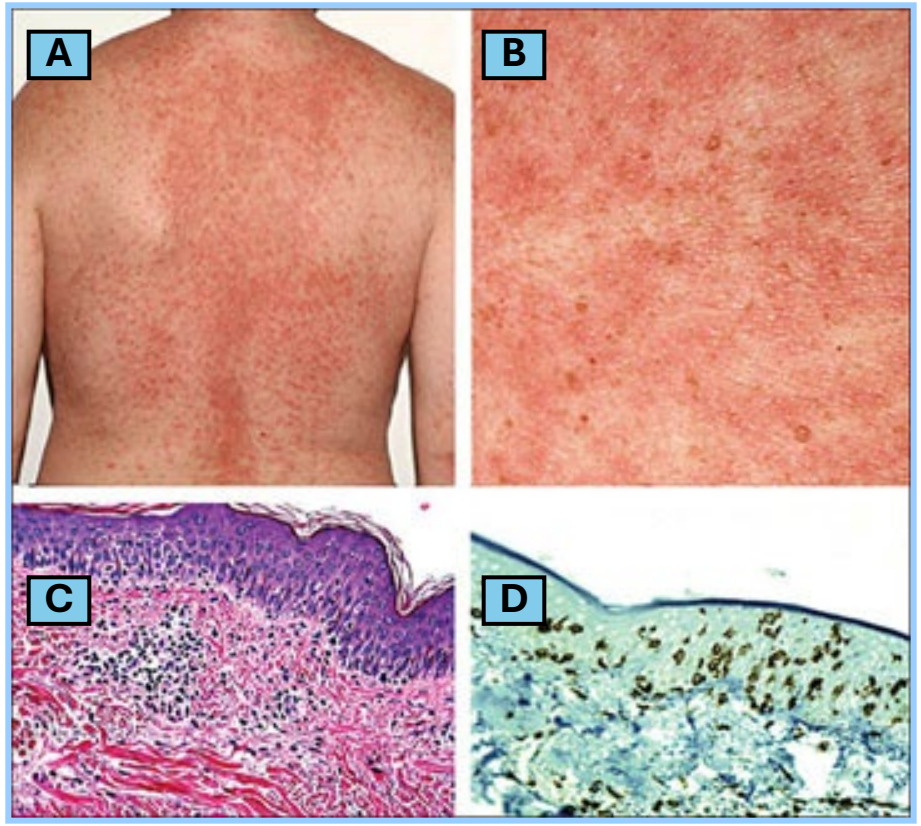
- Encourage the preventative use of moisturizers
- Photograph, document, and follow
- Mild (grade 1)
  - Topical therapies including emollient skin creams, oral anti-histamines, mild strength topical steroid creams
- Moderate (grade 2)
  - Check patient weekly for improvement
  - Consider holding immunotherapy
  - Topical emollients, medium-high strength topical steroids, oral anti-histamines
- Severe (grade 3+)
  - Hold/discontinue immunotherapy until back to grade 1
  - Topical emollients, oral antihistamines and high strength topical steroids Consider systemic corticosteroids 0.5–1 mg/kg
  - Stevens-Johnson- discontinue therapy permanently and treat SJS

Haanen JBAG, et al. *Ann Oncol*. 2017.

Dermatitis
Presentation and Findings

Back:

Confluent red rash



Back:

Papular lesions (Close up)

Right upper arm:

Vacuolar changes (magnification x20)

Anti-CD8 staining:

Extensive epidermal exocytosis (magnification x20)

Jaber SH, et al. *Arch Dermatol*. 2006.

Pulmonary

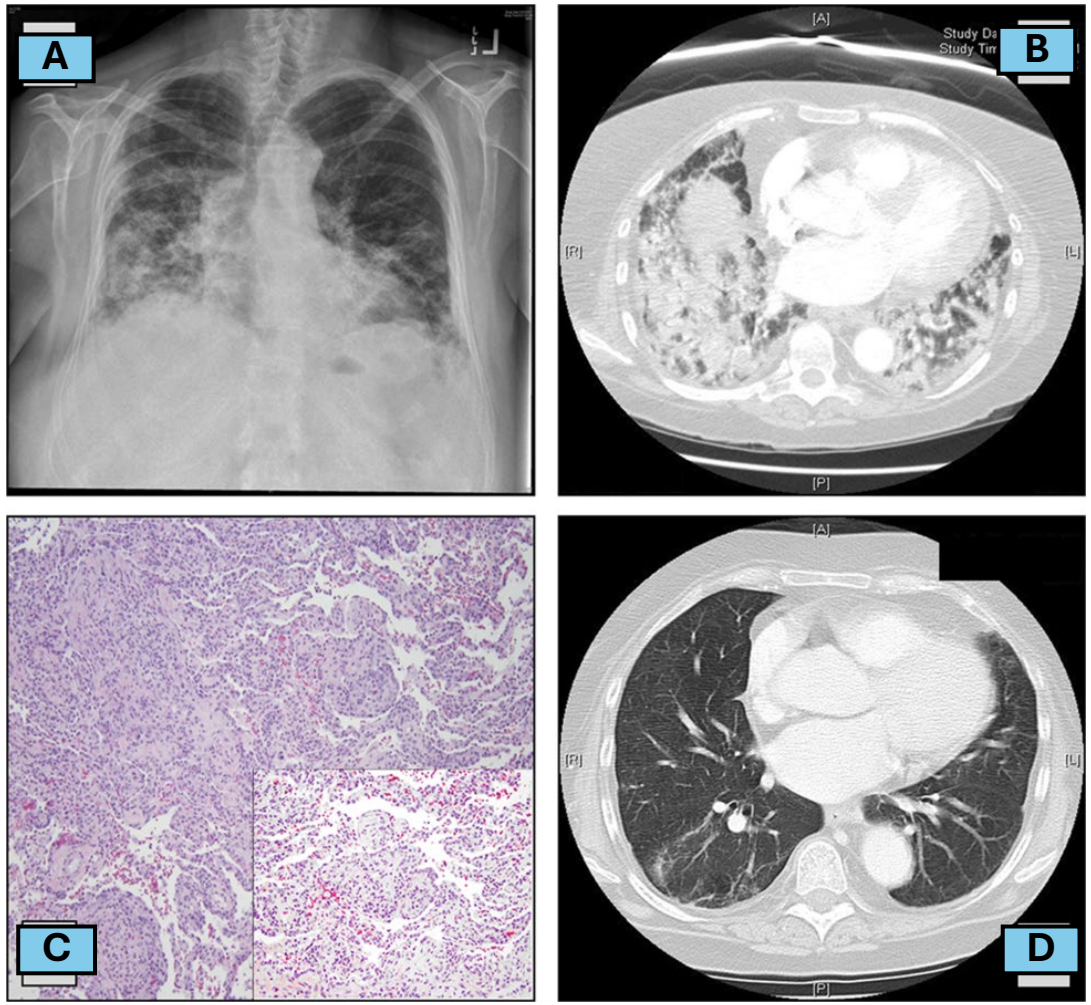
IRAE-*Pneumonitis*

- Uncommon, 2-4% all grades, 1-2% grades ≥3
  - Higher incidence with combined checkpoint blockade
  - Higher frequency in smokers
- Check pulse oximetry in all patients at baseline and before each cycle of checkpoint inhibitor(s)
- Obtain chest X-ray in anyone with SOB, chronic cough, increased sputum, and have a low threshold for CT chest
  - Radiographic findings may lag behind the patient's symptoms
- Rule out infectious etiology and disease progression
- Call the oncologist
- Consider empiric anti-infectives
- Start corticosteroids

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015; Haanen JBAG, et al. *Ann Oncol*. 2017.

Pneumonitis

Radiographic and Histopathology Findings



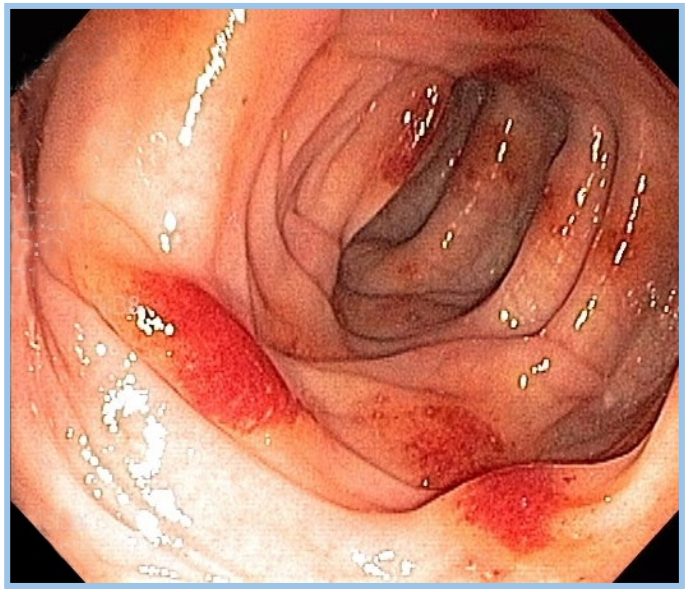
Barjaktarevic IZ, et al. *Chest*. 2013.

GI tract

Colitis and Enteritis

Colonoscopy and Histopathology Findings

- Colonoscopy
  - Multifocal circumscribed erythematous lesions
- Histopathology
  - Predominantly chronic inflammation
  - Eosinophils and focal active cryptitis



Colitis and Enteritis

- Rule out other causes
  - Bacterial (ie, *clostridium difficile*)
  - Parasitic
- Treat symptomatically (antidiarrheals, fluid and electrolyte supplementation)
- Diet Modification
- Use systemic corticosteroids if persistent
- Follow closely for resolution

Haanen JBAG, et al. *Ann Oncol*. 2017.

Diarrhea, Colitis and Enteritis

- Typical presentation is quick escalation of uncontrollable diarrhea not responsive to typical anti-diarrheal therapies
- Early intervention with corticosteroids is essential to prevent escalation and bowel perforation
- Infliximab is used in steroid-refractory cases
- Endoscopic evaluation
- Supportive care
  - Dietary modification, fluid repletion, electrolyte supplementation, anti-motility agents

Postow MA. *Am Soc Clin Oncol Educ Book*. 2015;
Weber JS, et al. *J Clin Oncol*. 2015; Haanen JBAG, et al. *Ann Oncol*. 2017.

Uncommon Toxicities

- Cardiac-myocarditis
- Ocular-uveitis
- Neuro-neuropathy, Guillian-Barre, Myasthenia Gravis, encephalitis
- Renal- nephritis
- Muscular-myositis

IRAE-*Endocrinopathies*

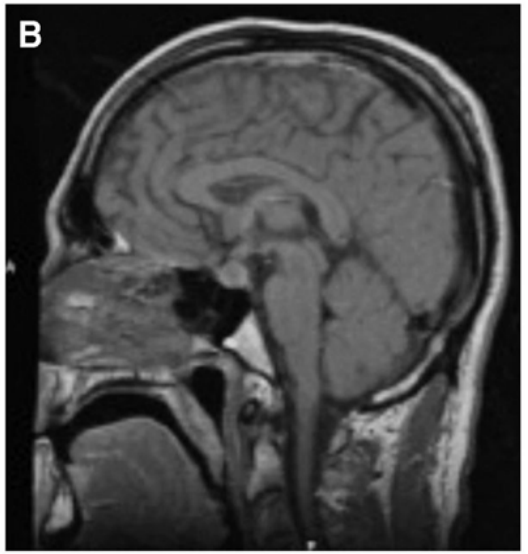
- Thyroid dysfunction-incidence 10%
  - Hypothyroidism > hyperthyroidism
- Adrenal insufficiency- incidence <2%
- Panhypopituitarism (hypophysitis)-incidence <1%
- Type 1 diabetes mellitus-incidence <1%

Weber JS, et al. *J Clin Oncol*. 2012; Postow, *Am Soc Clin Oncol Educ Book*. 2015;
Villadolid J, et al. *Transl Lung Cancer Res*. 2015; Naidoo J, et al. *Ann Oncol*. 2015; Haanen JBAG, et al. *Ann Oncol*. 2017.

Endocrinopathies- *Hypophysitis*

- Can present with severe headache, fatigue, weakness, memory loss, impotence, personality changes, and visual impairment
- Pituitary dysfunction can cause downstream effects on all hormone levels
- Differential includes CNS metastases
- Monitor TSH before each dose and intermittent cortisol levels
- Diagnostic MRI with pituitary cuts (not required) and laboratory evaluation of hormone levels
- **IF the patient has combined adrenal insufficiency and hypothyroidism, replace corticosteroids FIRST!! Giving levothyroxine first can enhance cortisol clearance and precipitate an adrenal crisis.**

6/30/04 - Baseline (4.5 mm)



12/3/04 - Headache/fatigue (10.8 mm)

Blansfield JA, et al. *J Immunother* 2005; Attia P, et al. *J Clin Oncol* 2005; Phan GQ, et al. *Proc Natl Acad Sci USA*. 2003; Haanen JBAG, et al. *Ann Oncol*. 2017.

Endocrinopathies
Type 1 Diabetes Mellitus

- Rare, <1%, more common with anti-PD-1/PD-L1
- May occur with rapid onset anytime during therapy
- Monitor serum glucose at baseline and prior to each cycle of checkpoint inhibitor
- Obtain endocrine consult
  - C-peptide and diabetes related autoantibodies*
- Require life-long insulin therapy
- No role of high-dose steroids
  - Exacerbate hyperglycemia
  - No data to suggest high-dose steroid can prevent total β cell loss
- Resume checkpoint inhibitors once blood sugar well- controlled

*Glutamic acid decarboxylase 65 (GAD-65) antibody; Tyrosine phosphatase islet 2 antibody (IA-2); Insulin autoantibody (IAA)

Haanen JBAG, et al. *Ann Oncol*. 2017;Godwin JL, et al. *J ImmunoTher Cancer*. 2017; Mellati M, et al. *Diabetes Care*. 2015.

Immune Checkpoint Blockade
Treatment and Toxicity in Elderly Patients

- No difference in incidence of toxicity or grade of toxicity for patients under or over 65
- It appears that ipilimumab and PD-1/PDL1 antibodies can be safely given to those at any age
- Caution should be used in using IPI or IPI/NIVO in those functionally over 80 with co-morbidities, who will not tolerate the colitis or prolonged steroid taper very well
- I may hold the record for oldest patient treated with PD-1 inhibitor-Olive is 103!

Friedman CF, Wolchok JD. *J Geriatr Oncol*. 2017.

Patient and Provider Education

- Early identification and intervention are key
- Recommend a ”second set of ears” to be present during treatment and toxicity visit
- Provide written, take-home materials on therapy
- Provide patient wallet card
- Give family/friends permission to call about patient’s symptoms

Patient Education – Wallet Card

Name, Family name:

Immunotherapy drug(s):

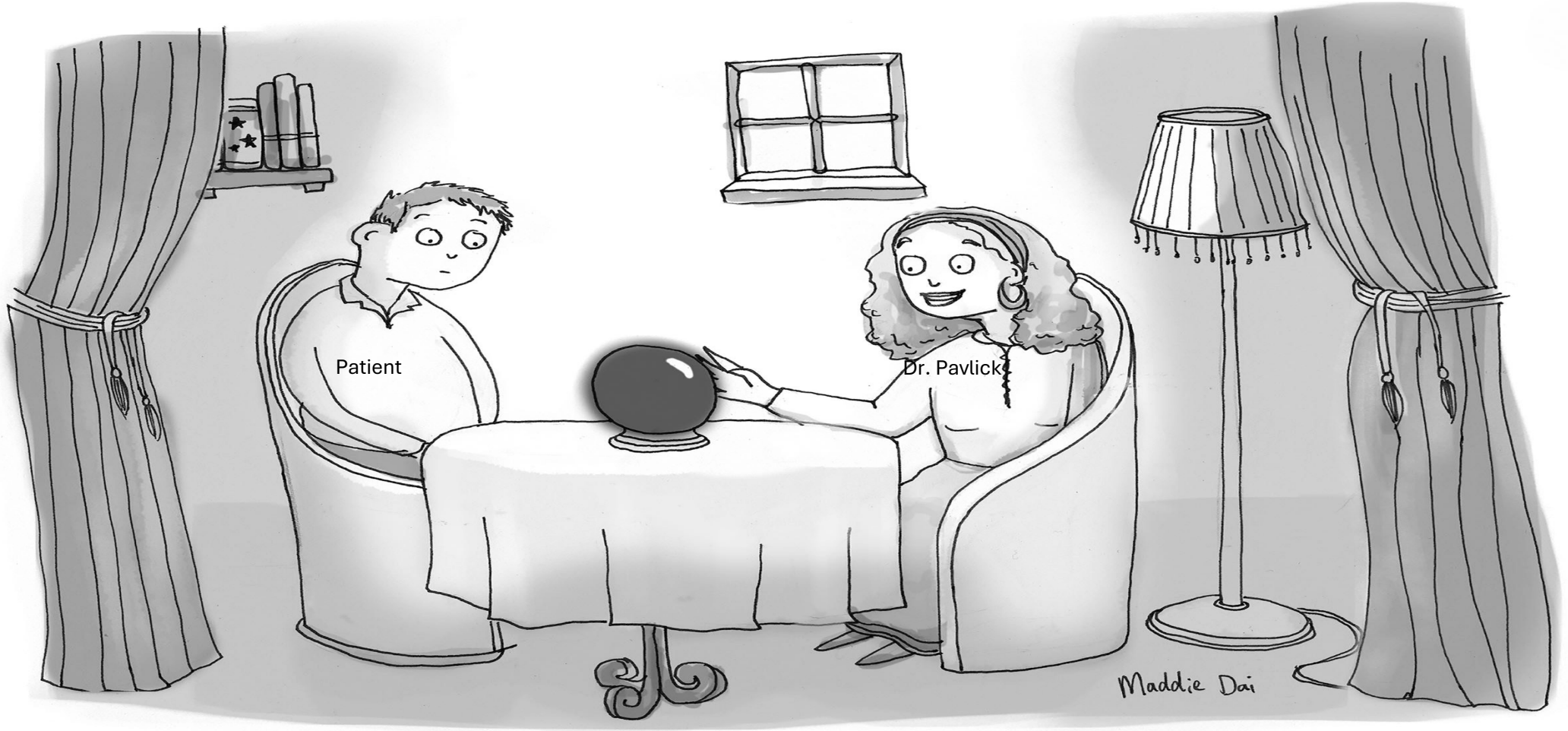
I am currently receiving an immunotherapy which may increase the risk of occurrence of autoimmune diseases and in particular:

- pneumonitis (inflammation of the lungs)
- colitis (inflammation of the gut)
- hepatitis (inflammation of the liver)
- nephritis (inflammation of the kidneys)
- endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,... **The management of these dysimmune adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team which has prescribed the treatment:**

Prescriber ID and contact information (reported at the back of this card)

Champiat S, et al. *Ann Oncol.* 2016.



“I left my crystal ball at home today”

Management of IRAEs

General Principles for Non-Oncology Clinicians

- Emergency department clinicians and primary care providers are often the first line of defense
- Maintain a high degree of suspicion
- Obtain thorough oncologic treatment history
  - Look beyond current therapy for late-onset or waxing/waning IRAEs
- Infections, disease progression/pseudo-progression and other etiologies should be ruled out or deemed unlikely as contributing to the IRAEs
- ***Early contact with primary oncologist***
- Be aware of management algorithm for IRAEs

Health Care Maintenance and Immunotherapy

- Vaccines can be and should be given while a patient is on immunotherapy, however, the timing is important.
- Vaccines should be administered 10-14 days AFTER the infusion of immunotherapy. Immunotherapy will not make the vaccine side effects worse but the vaccine can augment the toxicity of the immunotherapy.
- CT Scans/PET scans are NOT substitutes for routine mammograms and colonoscopies.
- Safe for dental work to be done since immunotherapy is not immunosuppressive.
- Recommend contraceptive use while on and for 3 months after immunotherapy.

Case 1

- A 65 year old male with stage IV lung cancer is receiving pembrolizumab.
- After 6 cycles (18 weeks), he presents to the ED with complaints of new-onset of SOB on exertion and a constant dry cough.
- Afebrile, BP stable, HR 116, O2 Sat 89% on room air
- Past social history: non-smoker

What’s Your Differential Diagnosis?

- Pneumonia
- Pulmonary Embolism
- Disease progression
- Pneumonitis from Immunotherapy

Work-up, Diagnosis and Treatment

- Work-up:
  - CXR, CT (PE protocol)
  - Blood and sputum culture, BNP
  - **CT (PE protocol): *ground glass opacities bilaterally***

  - ***Diagnosis: IO induced pneumonitis***

  - ***Treatment: IO interruption***
    - ***Corticosteroids with prolonged taper and O2 (if needed)***
    - ***PPI for GI protection while on steroids***
    - ***PCP prophylaxis while on 4-6 week taper***

Case 2

- A 78-year old male with recurrent metastatic melanoma involving multiple nodules in lungs as is treated with nivolumab.
- After cycle 3 cycles, he presents to the radiology department for a follow up PET/CT scan.
- Pre-scan glucose assessment demonstrates blood glucose of 375.
- He confirms he has been fasting for 12 hours and is not a known diabetic.
- The radiologist sends him to your office without the scan being done.

In the Office

- Lab results pertinent for Na 132, K 3.1, CO2 11, Cr 1.5, glucose 583, anion gap 18, venous pH 7.22, and positive urine ketones.
- Upon questioning, he admits to fatigue, extreme dry mouth, and polyuria.
- What caused this sudden onset DM and DKA?

Diagnosis and Treatment

- Diagnosis: Immunotherapy induced type I diabetes
- Treatment:
  - 911 to ED from office
  - Admit to intensive care unit for IV fluid, insulin drip, electrolyte replacement, and frequent lab monitoring
  - Endocrine consult
    - C-Peptide: 0.1 (ref range 0.9 - 7.1 ng/mL)
    - Insulin Level <2.0 (ref range: 2.0 - 29.1 mIU/mL)
    - Diabetes related autoantibodies* +
  - ***Do not use high-dose corticosteroid for this IRAE***
  - Life-long insulin therapy
  - Can resume immunotherapy once blood sugar under control

Case 3

- 76 year old woman with metastatic bladder cancer is being treated with pembrolizumab.
- She comes to your office for a routine well visit to get her flu shot.
- You notice her BP is 90/60 and her usual BP is 130/80.
- She has lost 10 pounds since her visit 3 months ago.
- Upon questioning, she states that she has lost weight because she has no appetite and is nauseated. She is also attributing her extreme fatigue and dizziness to her weight loss, poor appetite and cancer treatment.

What’s Your Diagnosis and What Tests Will You Do?

- Diagnosis- Adrenal Insufficiency
- Diagnostic Tests- Serum cortisol, serum ACTH and electrolytes
- Treatment- Steroid replacement-refer to endocrinologist
- Educate patient and family regarding instances needing increased steroid requirements
- Have patient purchase and wear medical alert bracelet-it can save their life in an emergency situation

Conclusions:

- Immunotherapy has changed the outcomes of many cancer patients but has unique toxicities.
- Primary care physicians may be the first person to recognize an IRAE.
- IRAE's can masquerade as other illnesses and they can be delayed in onset.
- Close communication with the patient and their oncologist is crucial once an IO induced toxicity is identified.
- Routine HCM is important to be continued while receiving immunotherapy.
- Despite sounding toxic, immunotherapy is very well tolerated and toxicities only happen in about 20% of patients!

THANK YOU

Weill Cornell Medicine
Meyer Cancer Center