RHEUMATOLOGIC COMPLICATONS OF IMMUNE CHECKPOINT BLOCKADE

And other things we should know

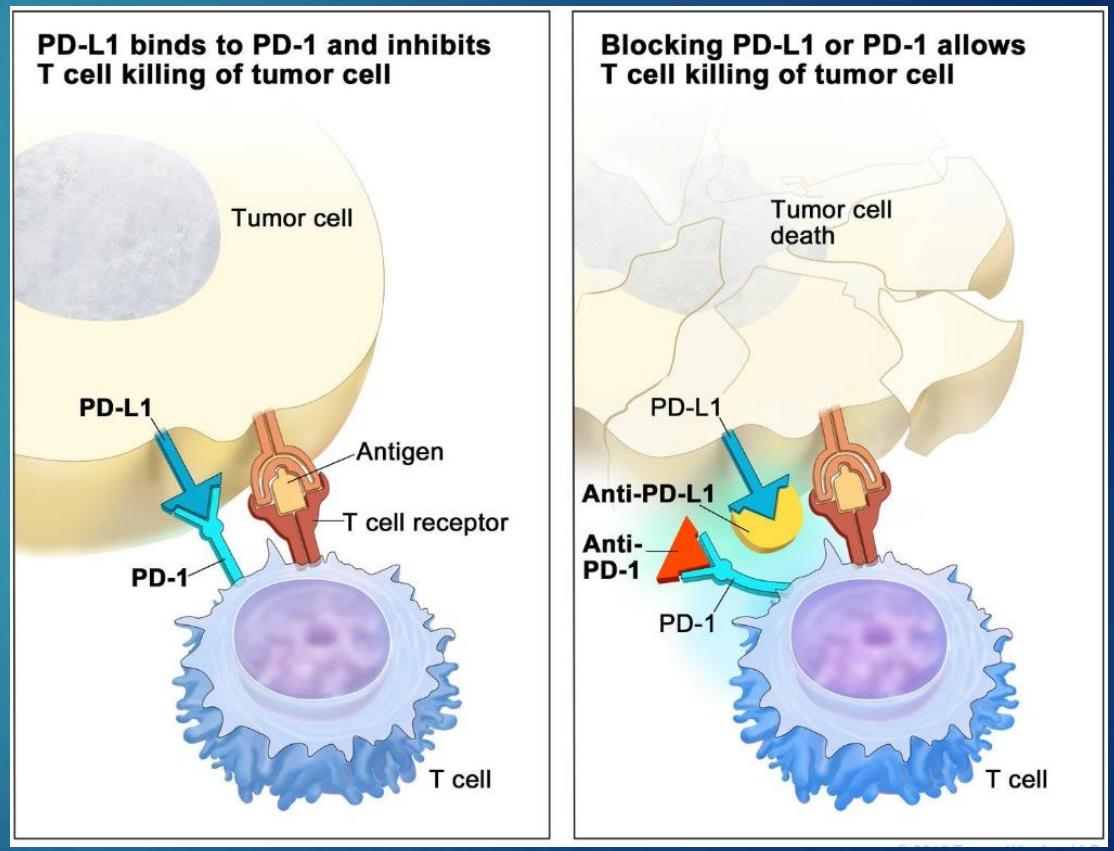
What happens when you "release the brakes"?

OSCAR ARILL, M.D.

Immune Checkpoint Inhibitors

Pembrolizumab

Metastatic melanoma



Rheumatologic Complications of Immune Checkpoint Blockade

- DISCLOSURES
  - Nothing to disclose
  - I am not an oncologist
  - Off-label use of DMARD's

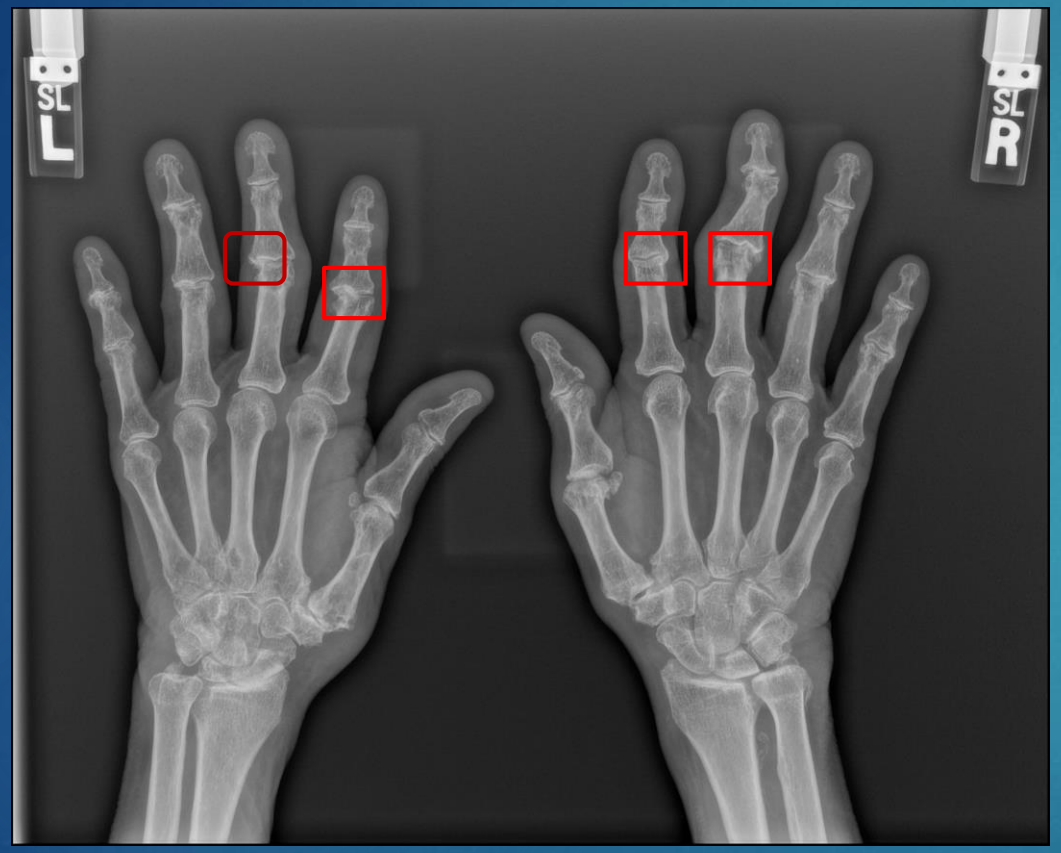
Rheumatology Consult

- A 74 y/o man followed in the Hema-Onco Clinic for a right upper lobe sarcomatoid epithelioid lung carcinoma with adenocarcinoma component, stage IIIB
- A rheumatology consult was requested due to persistently severe inflammatory arthritis affecting his hands, along with a scalp rash
- The patient was evaluated in the Rheumatology clinic 10-27-2017
- His previous therapy included two cycles of immune checkpoint inhibitor, **Nivolumab (anti-PD-1)** during May/June/ 2017
- After two cycles severe pain and edema involving both hands developed along with a scaly rash on his occiput area
- His labs showed a negative RF and a negative ANA, ESR 50, CRP 6.7 mg/L

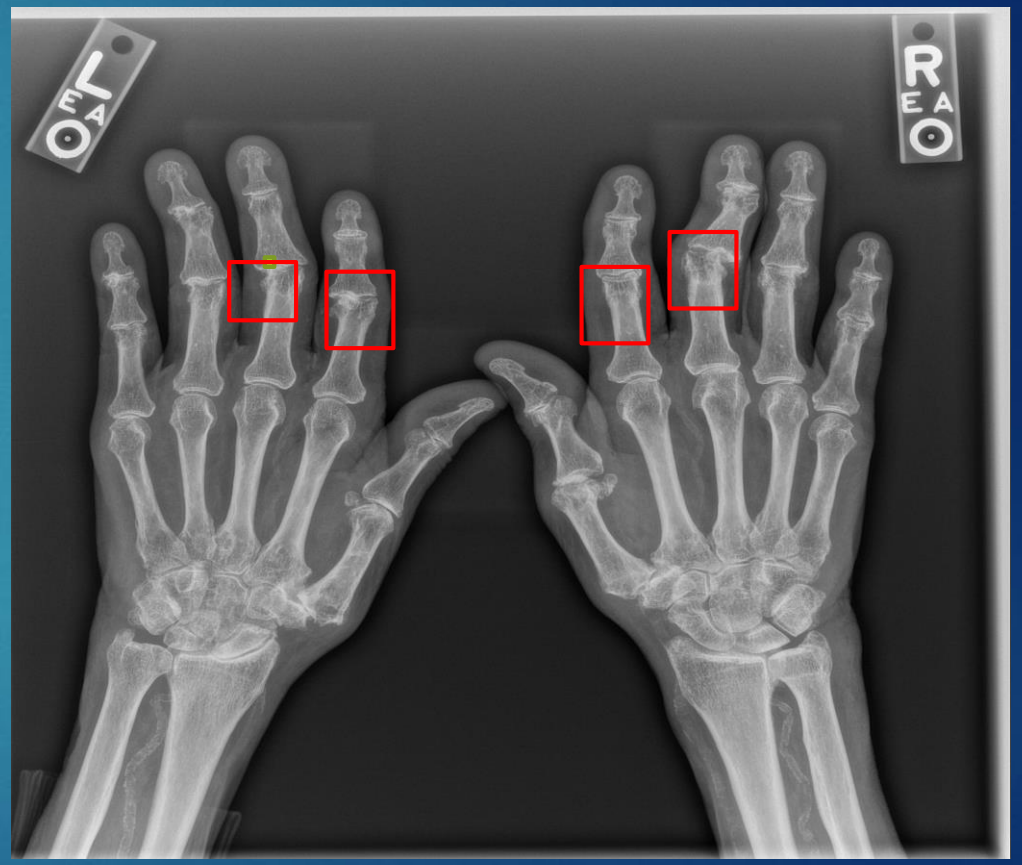
Rheumatology Consult

- When evaluated the patient presented findings of erosive osteoarthritis with severe superimposed inflammatory changes which were worse in his PIPs and DIPs
- The patient had been treated in the Hema-Onco Clinic with steroids with significant improvement, but the inflammatory arthritis recurred upon tapering and discontinuation of the steroids
- Radiographs of the hands done 19.5 months apart showed erosive changes that had progressed
- The rheumatology recommendation was to re-start corticosteroids, starting at 30mg/day with a slow tapering and clinic follow up

Rheumatology Consult



March 8, 2016



Oct. 23, 2017

Rheumatology Consult

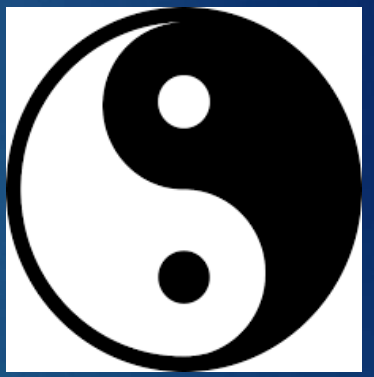
- Dermatology staff evaluated the patient's oxiput rash and categorized it as seborrheic dermatitis with psoriatic features
- Topical corticosteroid therapy was recommended
- When reevaluated on 12-14-2017, the patient presented the previously observed deformities in his PIPs and DIPs, but without active synovitis and he complained only of arthralgias that he was able to manage
- The scalp rash had also subsided
- Immune checkpoint therapy had been permanently discontinued and the patient was treated had begun therapy with pemetrexed/carboplatin 11-13-2017

Rheumatologic Complications of Immune Checkpoint Blockade

- Objectives
  - Describe immune checkpoints and their role as **targets for cancer treatment**
  - Recognize the spectrum of **immune related adverse events** associated with immune checkpoint blockade
  - Discuss the rheumatologic and other **autoimmune adverse events** associated with the use of checkpoint inhibitors
  - Discuss the current recommended **treatment interventions** for immunologic adverse events
  - Appreciate the need for **collaborative management** of patients presenting autoimmune adverse events associated with the use of checkpoint inhibitors and considerations about **concurrent medications**

Checkpoints and Autoimmunity

- Genetic and epigenetic alterations in tumor cells result in diverse antigenic expression that can elicit an immune response, primarily mediated by **T-cells**
- **The immune response is regulated by stimulatory, costimulatory and inhibitory (checkpoint) signals**
- Inhibitory signals play an important role in **self-tolerance** under normal conditions
- Checkpoints are regulatory inhibitory pathways that contribute to **immune homeostasis** by modulating the intensity and duration of the immune response
- Checkpoints are essential in **preventing autoimmunity** and avoiding tissue damage



Arthritis Rheum 2017; 69; 687-99

ICs – Tumor Immunity
Immune Surveillance Theory

- Phase 1 – Elimination
  - Tumor infiltrating lymphocytes within the tumor microenvironment – CD4, CD8 T-cells, NK cells, macrophages, dendritic cells, interferon, IL-12, TNF and others
- Phase 2 – Equilibrium
  - Immune system is able to control tumor growth but does not completely eliminate it
  - Tumor cells gradually loose immunogenicity
- Phase 3 – Escape
  - Tumor cells exhibit less tumor specific antigens
  - Enhance expression of **inhibitory factors (checkpoints)**
  - Treg cells and others suppress antitumor immunity

Science 2011: 331: 1565-70
Arthriitis Rheumatol 2017: 69: 667-99

Immune Checkpoints

- Austrian Physicians' observations about serum from cancer patients preventing destruction of cancer cells- Freund/Kaminer 1920'ties
- The molecular mechanisms of T-cell antigen recognition, regulation and function were described in the 1980's and 1990's
- PD-1 discovered by Dr. Tasuku Honjo at Kyoto University -1992
- Immunologist Dr. James P. Allison hypothesized that blocking **negative immune regulators (checkpoints)** would give the human immune system the power to fight cancer –role of CTLA-4 1995
- Pre-clinical models led to the clinical development of a new generation of active agents for cancer treatment which have provided a realistic chance of long-term remissions
- "Releasing the brakes on cancer immunotherapy"

N Engl J Med 373; 2016: 1490-92

Immune Checkpoints

- In the presence of tumor cells, immune checkpoint (IC) pathways contribute to tumoral immune resistance
- Monoclonal antibodies, against regulatory checkpoint molecules that inhibit T-cell activation, enhance host anti tumor responses
- The result is **upregulation** of the immune function by blocking checkpoint inhibition
- The use of ICIs results in **durable anti-tumor responses** in patients with metastatic disease that are not seen with traditional chemotherapy
- **Due to the upregulation of the immune function, undesirable inflammatory and immune related adverse events (irAEs) can occur and their severity can limit the use of checkpoint inhibitors**

Arthritis Rheum 2017; 69: 687-99

Immune Checkpoint Inhibitors (ICIs)

- Immunotherapy enhances the immune system's defenses to fight disease
  - Source of promising new cancer treatments
- Immune checkpoint blockade has provided remarkable benefits in the treatment of various cancers by increasing anti-tumor immunity through the blocking of these intrinsic downregulators of immunity:
  - **Cytotoxic T-Lymphocyte Associated Antigen 4 (CTLA-4)**
  - **Programmed Cell Death 1 (PD-1)**
  - **Programmed Cell Death Ligand 1 (PD-L1)**

N Engl J Med 2018; 378: 158-68

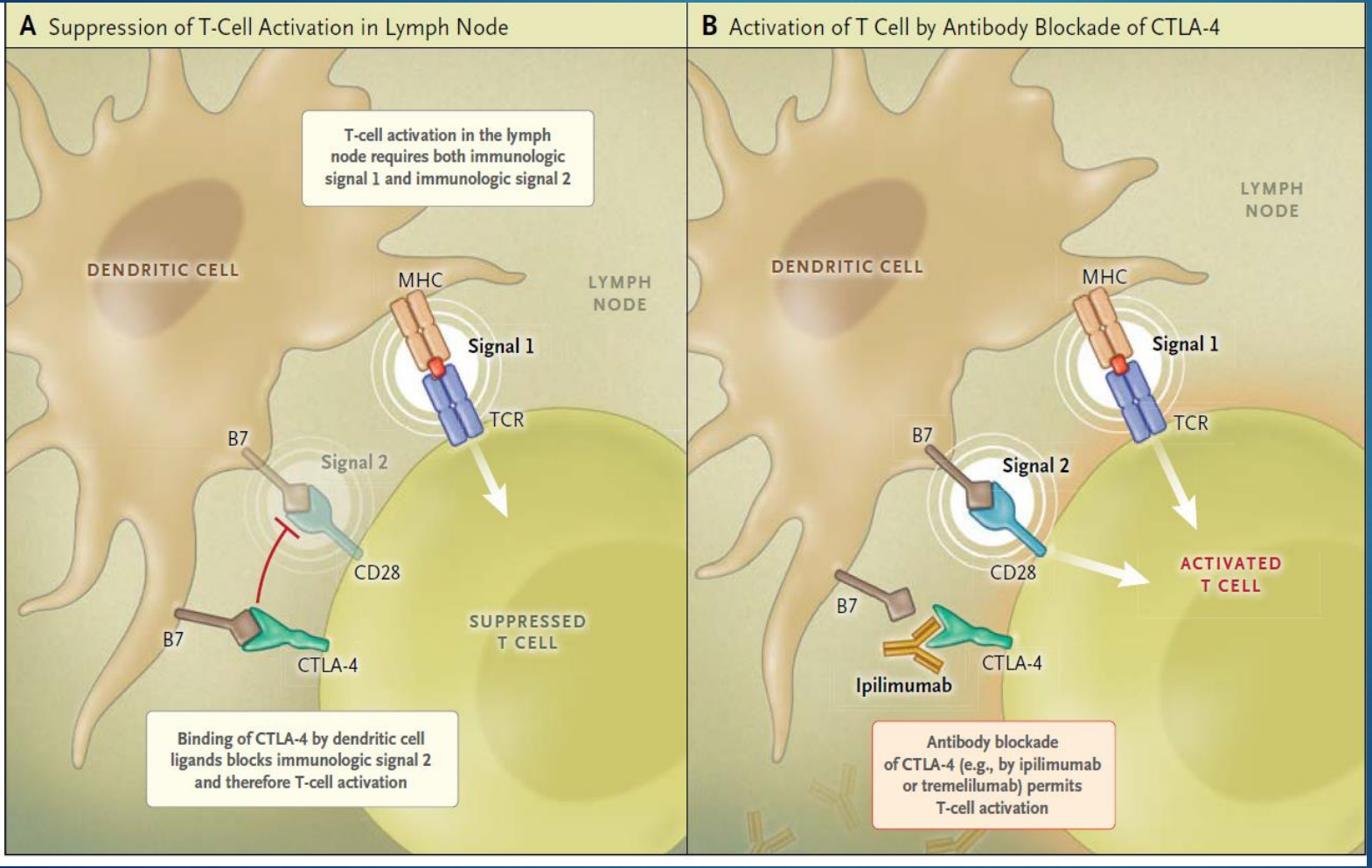
ICIs

Anti-CTLA-4

- Full activation of T-cells require two signals
  - Binding of the T-cell receptor to the antigen presented by MHC on APC
  - Costimulation by engagement of the CD28 on T cell to CD80/86 on APC
- Activated T-cells then express negative immune regulators (checkpoints) on the cell surface to regulate activation and prevent tissue injury
- CTLA-4 is a receptor that inhibits T-cell activation by blocking CD80/86
- Treg cells also express CTLA-4

Arthritis Rheumatol 2017; 69: 687-99

ICIs Mechanism
Anti-CTLA-4 Ipilimumab



-T cells require 2 signals for activation:
-TCR---AG/MHC on APC
-CD80/86 onAPC—CD28 Tcell
-CTLA-4 on Tcell downmodulates
-Treg express CTLA4
-Anti-CTLA-4-stimulate Tcells and deplete Treg

N Engl J Med 2015;373: 1490-92
Arthritis Rheumatol 2017; 69: 687-99

ICIs

Anti-CTLA-4

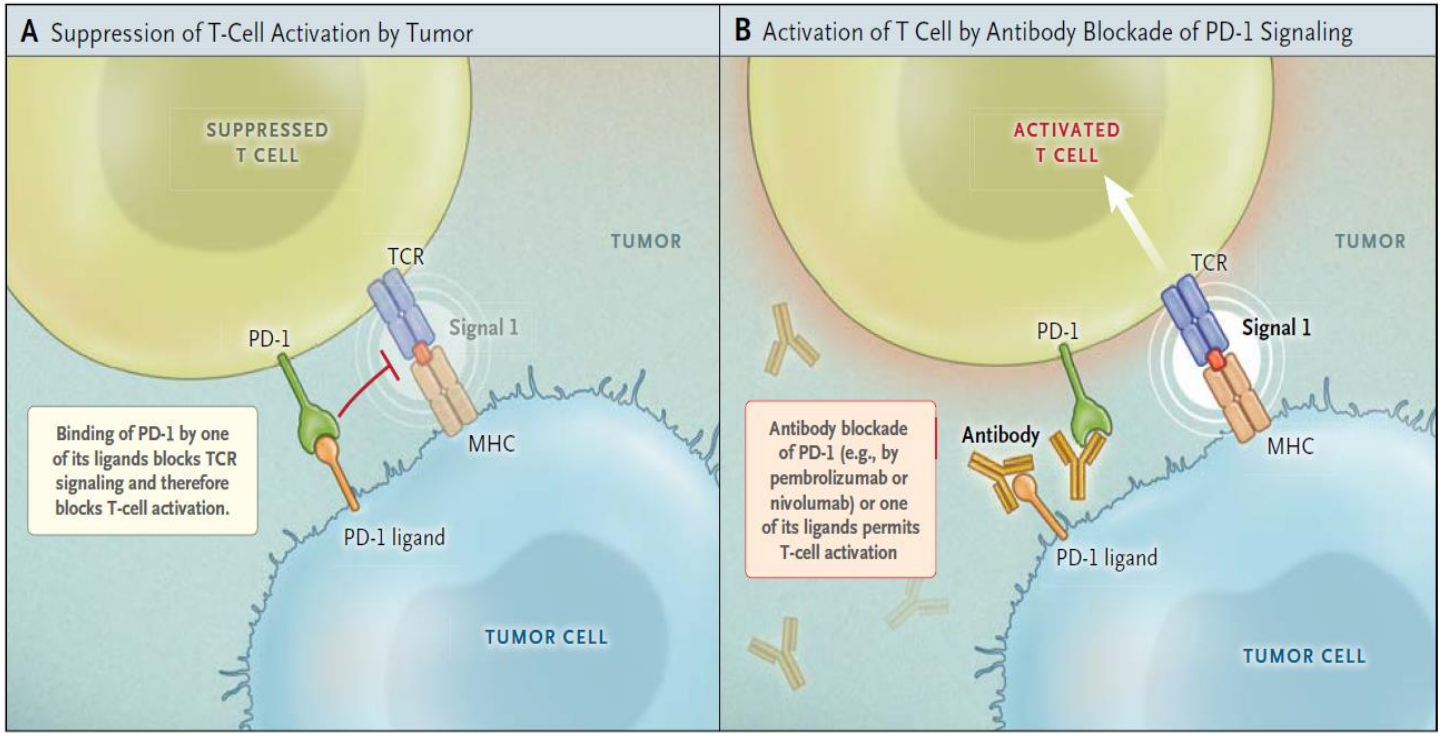
- **Ipilimumab (Yervoy)– anti CTLA-4**
  - First checkpoint inhibitor approved by FDA -2011
  - Impressive benefits against advanced melanoma

- In contrast to Ipilimumab effects -
  - **Abatacept (Orencia)** – soluble form of CTLA-4 that downregulates immune response and is used for the treatment of rheumatoid arthritis (2005)

Arthritis Rheumatol 2017; 69: 687-99

ICIs Mechanism of action Anti-PD1/PD1L

- Engagement of PD-1 and PD-L1 downmodulate TCR signaling
- Anti-PD-1/PD-L1 restore TCR signaling and stimulates Tcells



New Engl J Med2015;373:1490-92

ICIs

Anti-PD-1

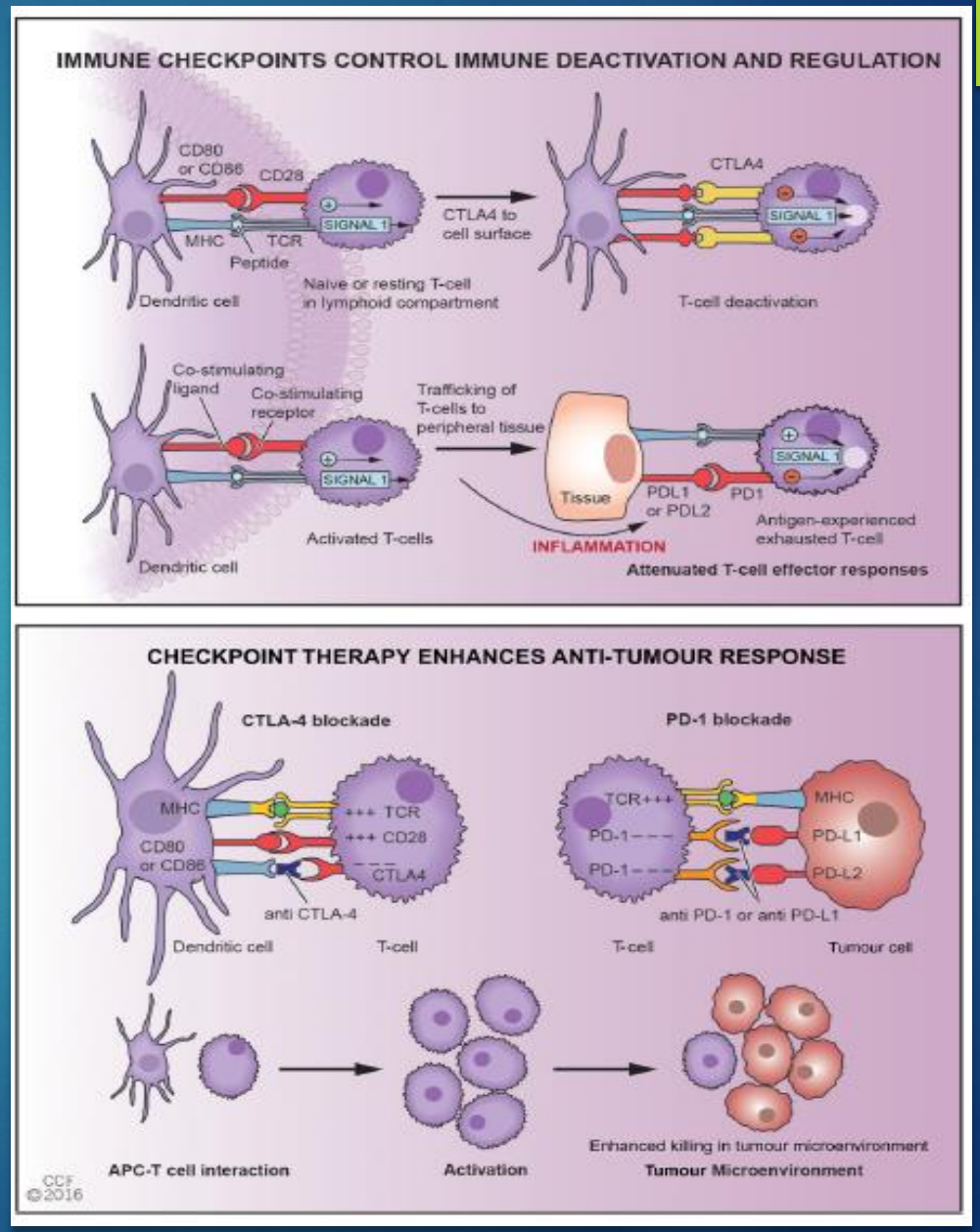
- **Pembrolizumab (Keytruda)** and **Nivolumab (Opdivo)**
  - Treatment of melanoma, NSCLC, head and neck cancer
- **Atezolizumab (Tecentriq) – anti PD-L1**
  - **Treatment of urothelial carcinoma and NSCLC, bladder ca, breast ca**
- **Avelumab (Bavencio)- anti PD L1**
  - **Merkel Cell cancer, urothelial ca, renal cell cancer**
- **Durvalumab (Imfinzi)- anti PD L1**
  - **Urothelial cancer, NSCLC**
- **Cemiplimab-rwlc (Libtayo) –anti-PD-1**
  - **Advaced cutaneous squamous cell carcinoma**

Arthritis Rheumatol 2017; 69: 687-99
Drugs .com Oct, 2019

Immune checkpoint blockade

- ICI's Reactivate T cells that emigrate from lymphoid compartments to seek out and engage tumors
- In peripheral tissues, "exhausted" T cells are energized for an enhanced anti-tumor response, but are also capable of participating in autoimmune, autoinflammatory reactions

Ann Rheum Dis 2017; 76: 1-3



ICIs

Immune related Adverse Events (irAEs)

- Up to **80%** of patients treated with ICIs can experience irAEs which may be severe and occasionally fatal
- Most are transient and not severe
- Most occur during the first three to four months of therapy with ICIs but may occur after a single dose or at later stages
- Rash and colitis are recognized promptly
- Endocrinopathies or pneumonitis can be insidious
- Endocrinopathies and neurologic syndromes can have lasting effects

Arthritis Rheum 2017; 69: 687-99

ICIs – irAEs
Organs affected

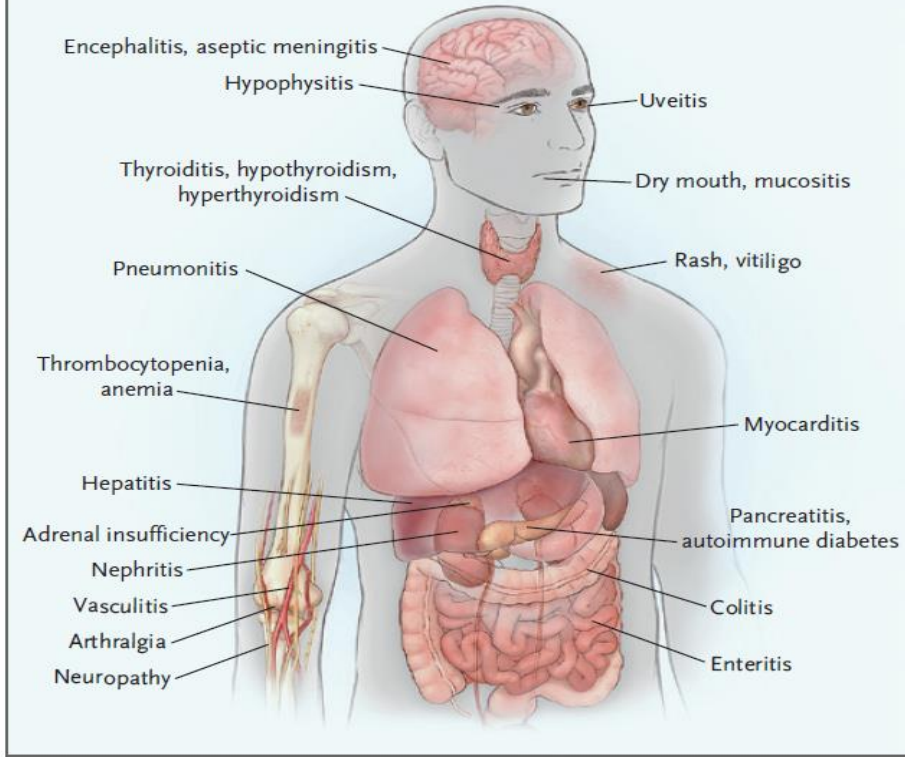
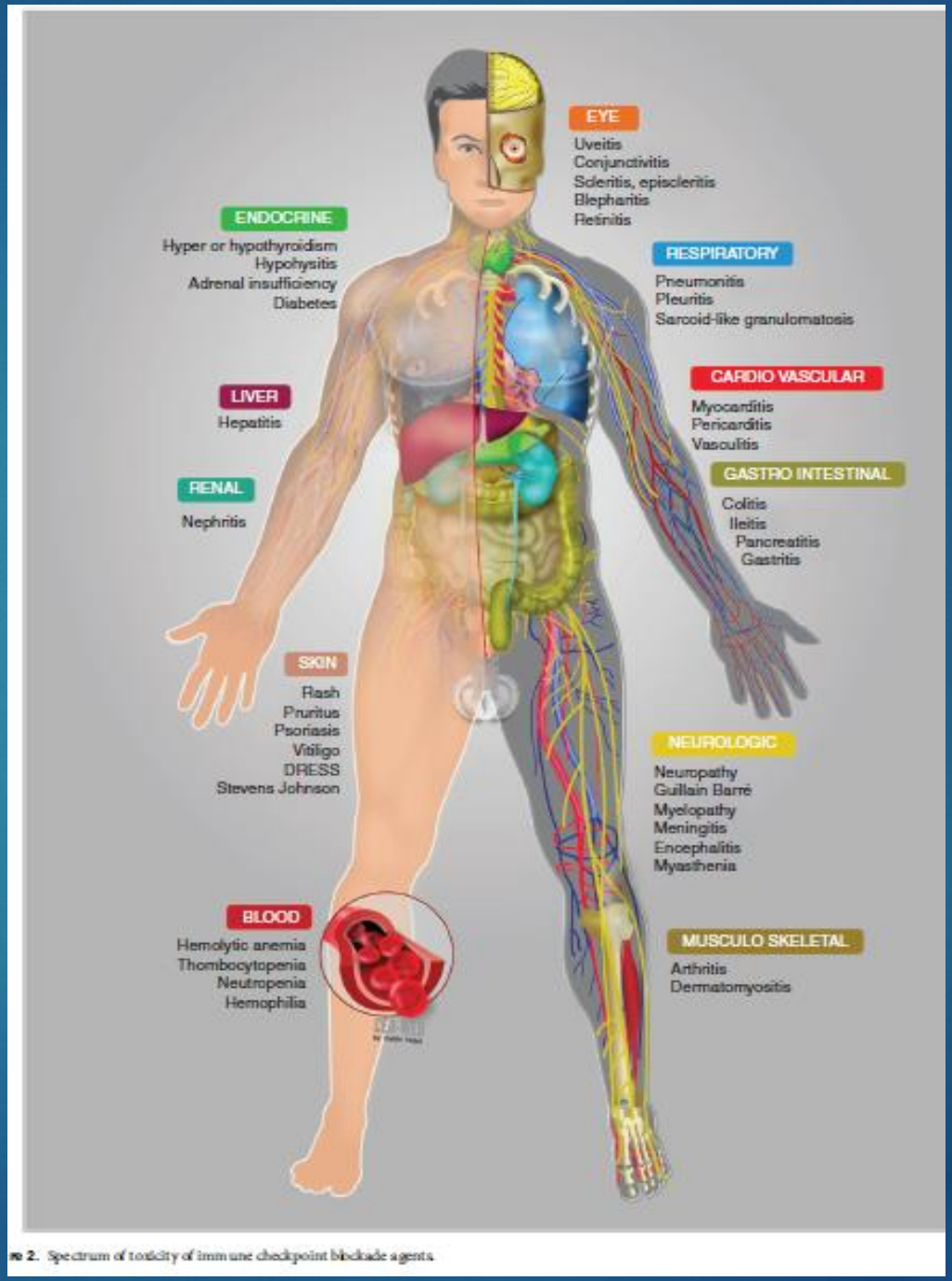


Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

N Engl J Med 2018; 378: 158-67

Immune Checkpoint Inhibitors – Spectrum of toxicity



Annals Oncol 2016;27: 559-74

ICIs –Immune-related adverse events –Dermatologic (irAE)

The most common irAE

- 50% Ipilimumab, 30-40% nivolumab or pembrolizumab
- Average 3.6 weeks after treatment initiation
- Reticular, maculopapular, mildly erythematous, trunk or extremities
- Perivascular lymphocytic infiltrates deep into the dermis
- Oral mucositis and dry mouth reported with antiPD-1 agents

Ann Oncol 2015;26: 2375

ICIs –Immune-related adverse events – Dermatologic (irAE)

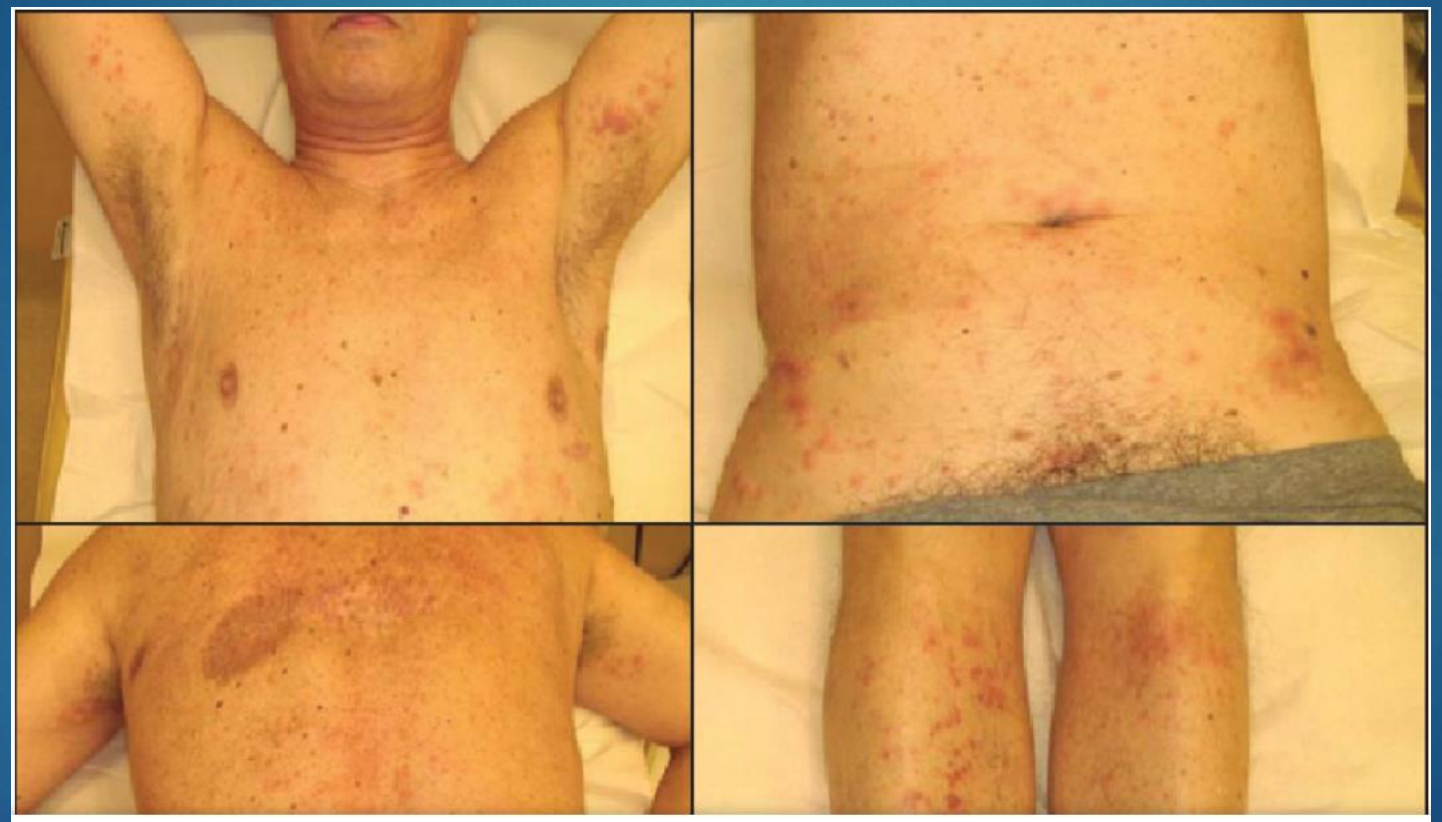


Figure 2. Patient presenting a diffuse papular erythematous rash.

Euro J of Dermatol 2017; 27:266-70

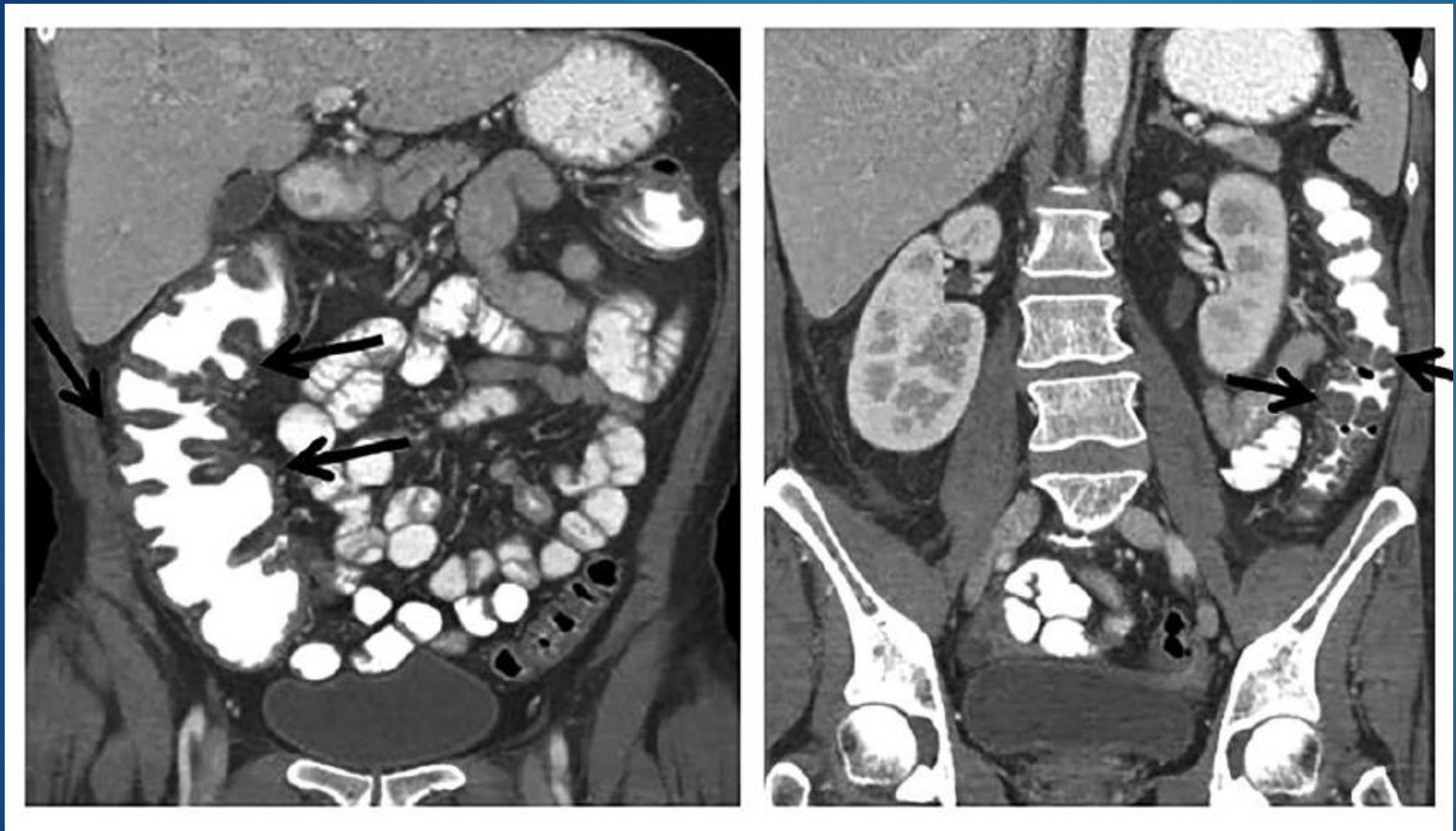
ICIs

Immune related Adverse Effects (irAEs)

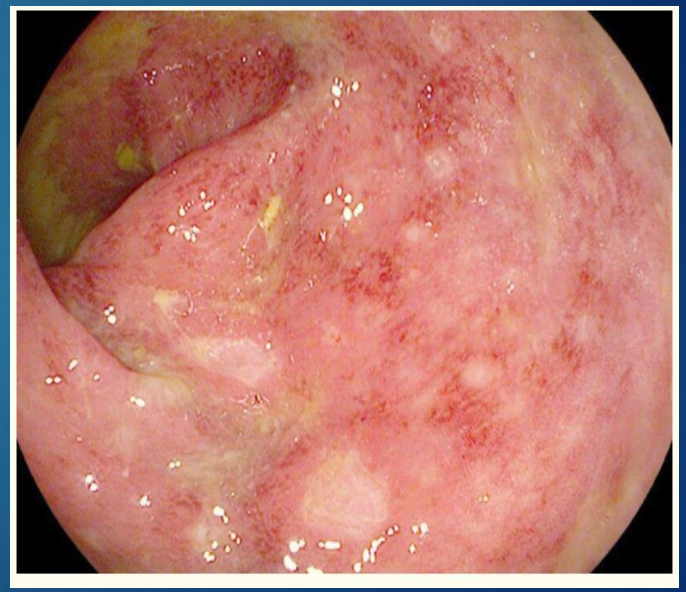
- **Enterocolitis / Colitis**
  - 30% of patients, receiving anti-CTLA-4 (Ipilimumab), less in anti-PD-1
  - Increased in combination therapy
  - Colonoscopy and histology – resemble idiopathic IBD
  - Bowel perforation has been reported
  - Influence of microbiome – increased representation of Bacteroides phylum may decrease incidence of enterocolitis

Arthritis Rheum 2017; 69: 687-99

ICIs – irAEs
Colitis



Ipilimumab-induced colitis – 3 weeks after receiving the first dose



Arthritis Rheum 2017; 69: 687-99
World J Clin Cases 2019 February 26; 7(4): 405-418

ICIs

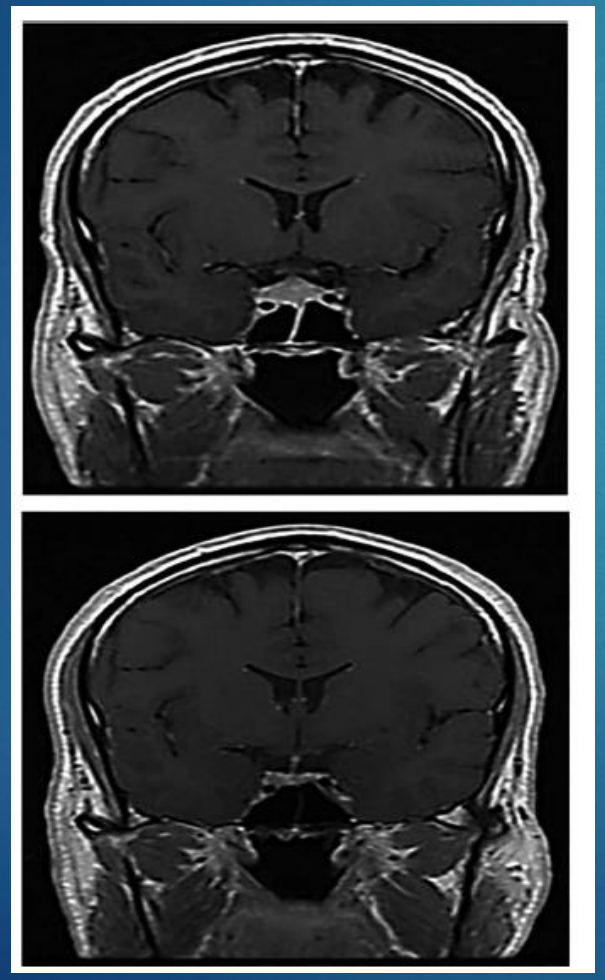
Immune related Adverse Effects (irAEs) Endocrinopathies

- **Thyroiditis most commonly reported**
  - Hypothyroidism, occasionally hyperthyroidism
  - Anti-PD-1 > anti-CTLA-4
  - Baseline thyroid function should be assessed
- **Hypophysitis**
  - Mainly anti-CTLA-4
  - 5% of patients
  - Men > Women
  - Lymphocytic infiltration resembling idiopathic autoimmune hypophysitis
- **Hypogonadism**
- **Primary adrenal insufficiency**
- **Type I DM**
- **Pancreatitis**

- **Hypothyroidism and adrenal insufficiency** are reported to have the most long term sequelae

Arthritis Rheum 2017; 69: 687-99

ICIs – irAEs – Endocrinopathy
Hypophysitis



- Ipilimumab-induced hypophysitis
- The patient presented with persistent headache, nausea and generalized fatigue after the fourth dose
- Resolution of the pituitary inflammation 6 weeks after onset of symptoms

Arthritis Rheum 2017; 69: 687-99

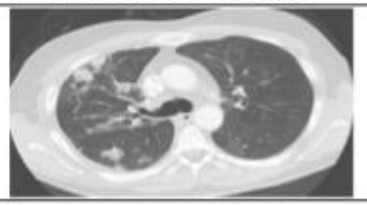
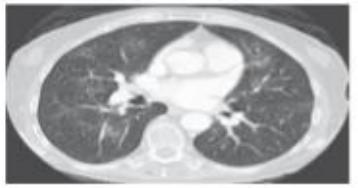
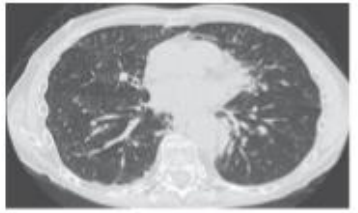
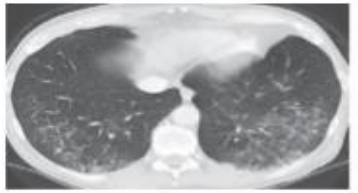
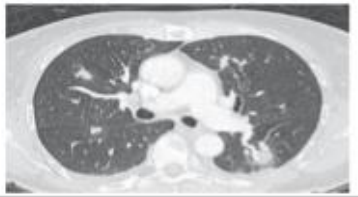
ICIs - irAEs

- **Autoimmune hepatitis**
  - Elevation of hepatic enzymes
  - Approx. 5% of patients
  - Mostly combination therapy
  - Abdominal pain, nausea, jaundice
- Pneumonitis
  - Most common with Nivolumab
  - Treatment of NSCLC
  - Pre-existing pulmonary disease
  - Dry cough, shortness of breath, fine crackles
  - CT imaging - ground glass lesions or small nodular infiltrates +
    - Other phenotypes

Arthritis Rheum 2017; 69: 687-99

ICIs Immune-related adverse events

Pneumonitis

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

J Clin Oncol 2016; 35:709-717

ICIs – irAEs
Frequency

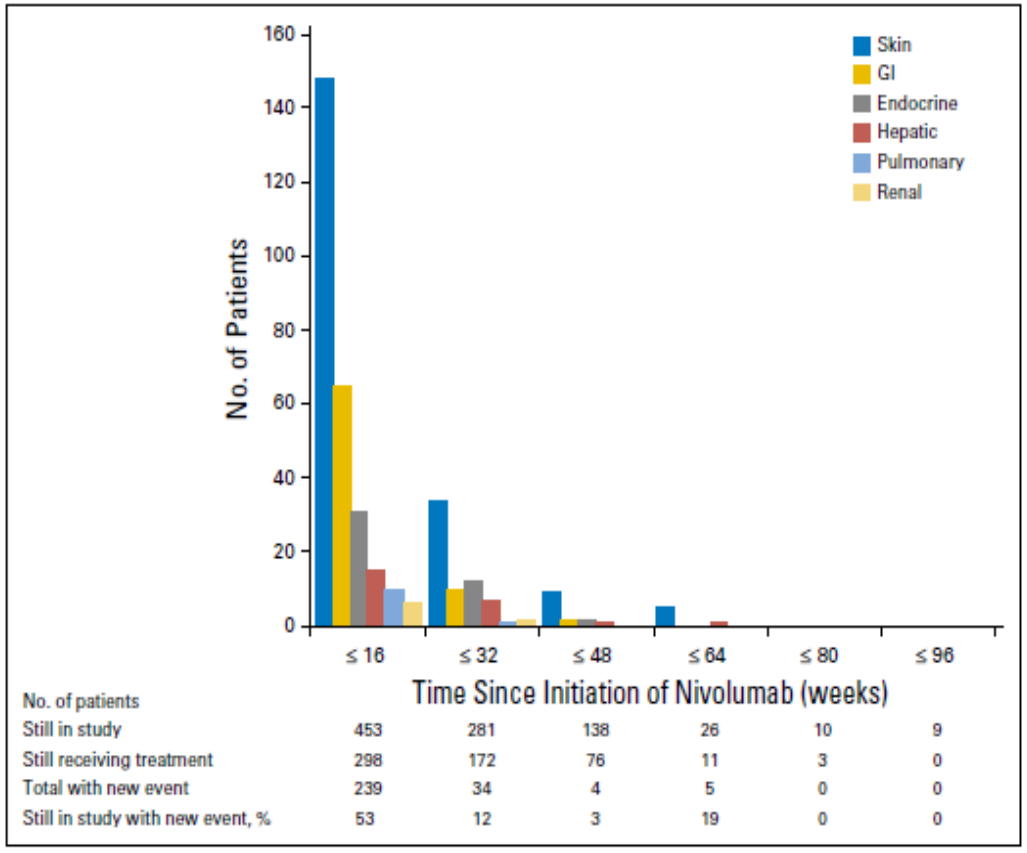
Table 1. Frequency of selected immune-related adverse events associated with immune checkpoint inhibitor treatment*

	Anti–CTLA-4 (ipilimumab) (refs. 21, 96, 97)	Anti–PD-1 (nivolumab or pembrolizumab) (ref. 99)	Anti–PD-L1 (atezolizumab) (ref. 23)	Combination therapy (ipilimumab + nivolumab) (ref. 21)
Any adverse event	72/25	82/14	69/16	88/40
Dermatologic				
Pruritus	24/0	23/<1	10/<1	33/2
Rash	19/1	21/2	7/<1	28/3
Gastrointestinal				
Colitis	8/5	1/1	1/1	12/8
Diarrhea	28/5	20/<1	8/<1	44/9
Endocrine	6/2		–	30/5
Thyroiditis	2/0	10/<1	–	25/1
Hypophysitis	2/2	2/1	–	8/2
Hepatitis	4/2	6/1	3/1	30/19
Pneumonitis	<1	7/<1	2/1	6/1
Arthralgia	6/0	11/<1	7/1	10/<1
Arthritis	–	2/0	–	–

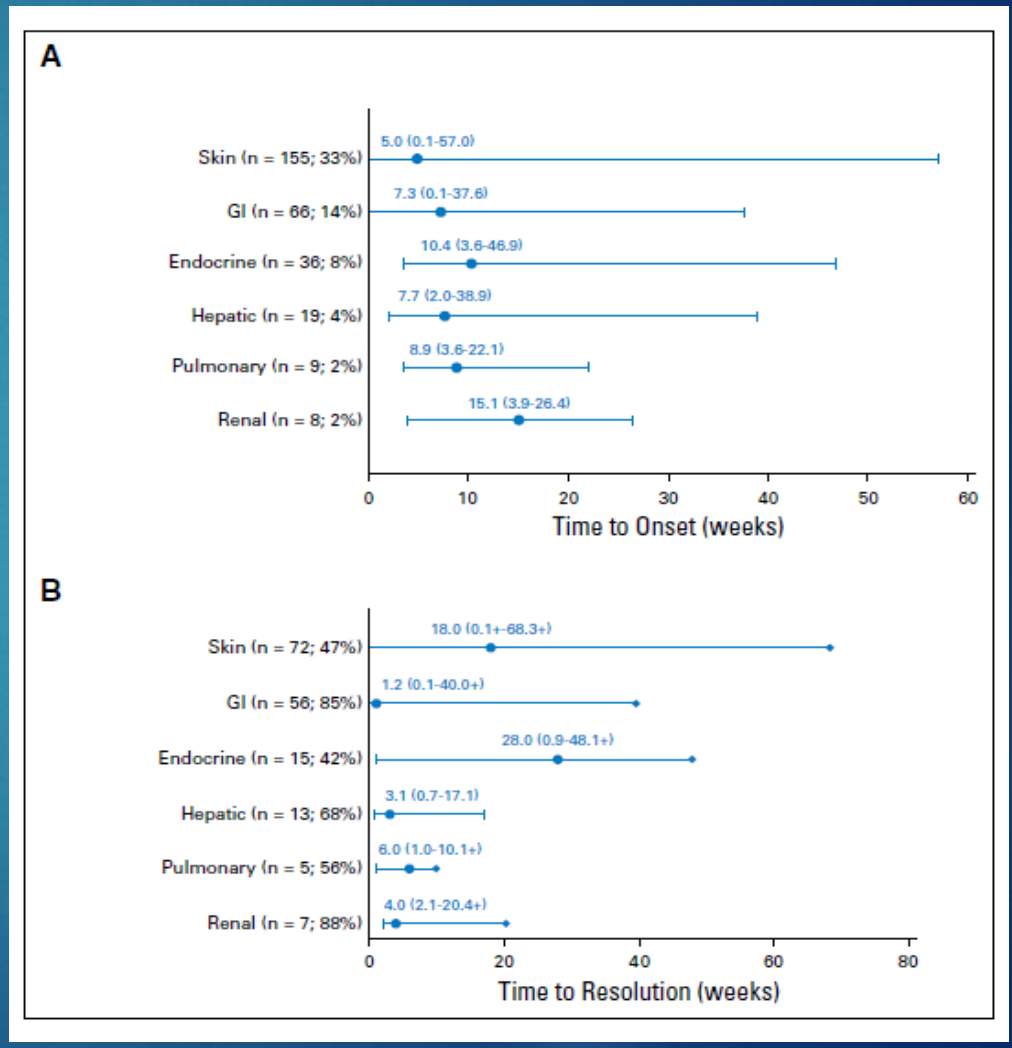
* Values are the percentage of treated patients who experienced adverse events of any grade/high-grade (based on the Common Terminology Criteria for Adverse Events grading system). Anti–PD-1 = anti–programmed cell death 1; anti–PD-L1 = anti–PD ligand 1.

Arthritis Rheumatol 2017; 69:687-99

ICIs – irAEs
Onset and resolution



No. of patients						
Still in study	453	281	138	26	10	9
Still receiving treatment	298	172	76	11	3	0
Total with new event	239	34	4	5	0	0
Still in study with new event, %	53	12	3	19	0	0



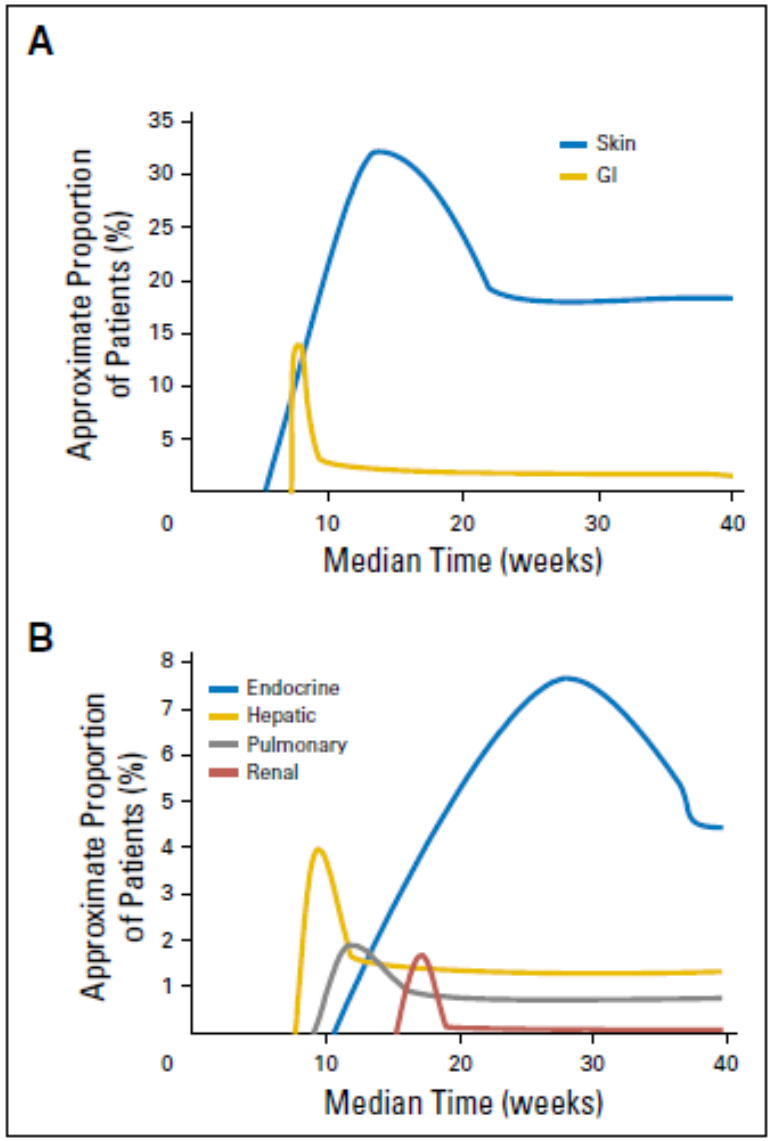
J Clin Oncol 2017; 35:785-91

ICIs – irAEs
Onset and resolution

- Median times to onset and resolution of select irAEs of all grades by organ category

- Safety pooled data on 576 patients with advanced melanoma treated with Nivolumab monotherapy

J Clin Oncol 2017; 35: 785-91



ICIs – irAEs
Other diseases

- Sicca syndrome – may have + ANAs, anti-SSB abs
- Lupus like syndrome
- Acute granulomatous interstitial nephritis
- Acute tubular necrosis
- Renal transplant rejection
- Myositis
- Polymyalgia rheumatica
- Giant Cell Arteritis
- Sarcoidosis
- Uveitis
- Episcleritis
- Celiac disease
- Myocarditis
- Cytopenias
- Myasthenia Gravis
- Transverse myelitis

Arthritis Rheumatol 2017; 69: 687-99

ICIs - irAEs
Pathophysiology – Contributing Factors

- Enhanced Th1 and Th17 cell responses leading to enhanced production of IL-6 and IL-17
- Increased levels of IL-17 described in Ipilimumab (anti-CTLA-4)-induced colitis, spondyloarthritis
- Abnormal Treg/Teff ratio → ↑ Teff cells
- Altered T cell – B cell interactions
- Abnormal autoantibodies – ANCAs, anti-dsDNA, anti-factor VIII, anti-pituitary, anti-thyroid peroxidase, anti-thyroglobulin
- Pathogenic antibodies production may be more critical in irAEs induced by anti-PD-1agents
- Dysfunctional Treg and Th17 cell mediated immunity may be more relevant in anti-CTLA-4 toxicity

J Immunother 2012; 35: 169-78
Autoimmun Rev; 2014; 13: 668-77

ICIs – irAEs
Possible mechanisms

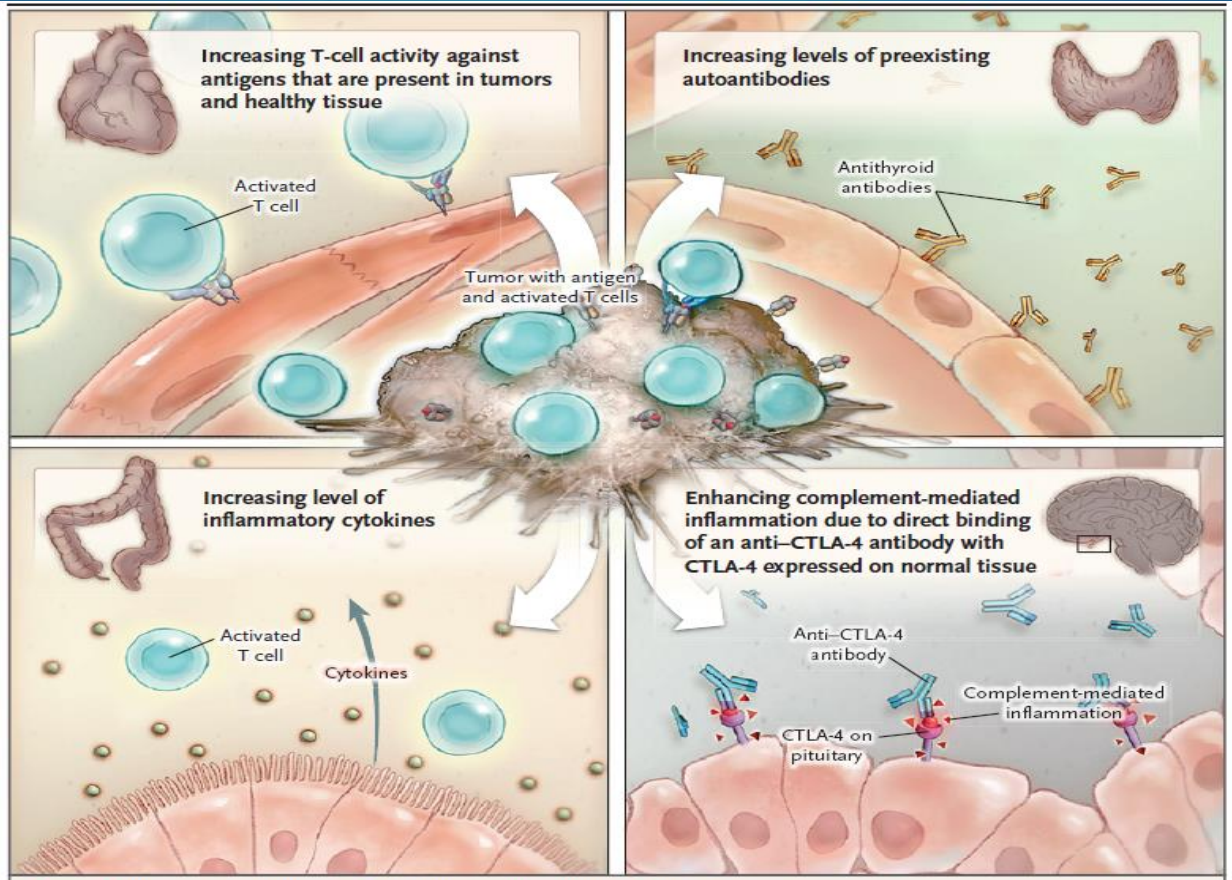


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.
The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

N Engl J Med 2018; 378:158-68

ICIs – irAEs
Management

- **Multidisciplinary approach, collaborative management**
- Consider differential diagnosis which may include the effects of other medications and possible infections
- Scant information as to whether some approaches may blunt tumor immunity more than others
- Unclear whether the use of high dose immunosuppressant therapies such as corticosteroids are more appropriate than more targeted approaches such as anti-TNF therapies

Ann Oncol 2016; 27: 559-74

ICIs

General approach to toxicity management

- US Food and Drug Administration Risk Evaluation and Management Strategies for Ipilimumab
- The management approach to irAEs is based on clinical experience
- No retrospective trails have been conducted to guide the treatment of irAEs
- Most data is derived from patients with advanced melanoma who were treated with Ipilimumab, Nivolumab and Pembrolizumab
- In general, treatment of moderate or severe irAEs requires interruption of the ICI and the use of corticosteroids

Arthritis Rheum 2017; 69: 687-99
FDA Downloads Drug Safety UCM249168

ICIs

Toxicity Management

- For patients with grade 2 (moderate) immune-mediated toxicities, treatment with the ICI should be withheld and should not be resumed until symptoms or toxicity are graded as grade 1 or less
  - Corticosteroids – prednisone 0.5mg/kg/d or equivalent, should be started if symptoms do not resolve within a week
- For patients experiencing grade 3 or 4 (severe or life threatening) immune-mediated toxicities, treatment with ICI should be permanently discontinued
  - Corticosteroids at higher doses – prednisone 1-2mg/kg/d or equivalent should be given; dose can be tapered once symptoms subside to grade 1 or less
  - Anti-TNF therapy (Infliximab 5mg/kg) may be considered if CS are not effective; dose should be repeated in 2 weeks

Annals Oncol 2016; 27: 559-74

ICIs – Rheumatologic irAEs

- Rheumatologic irAEs have been less consistently reported than other types of irAEs
- A large number of other rheumatologic irAEs have been reported
- Rate of "arthralgia" has ranged from 1-43%
- Dry eyes and dry mouth 3-24%, myalgia 2-21%
- Rheumatologic irAEs are rarely life-threatening and are thus recognized or reported less often
- There are multiple ways in which a given clinical finding is reported
- The more extreme cases have been described in case reports
- It is common for patients with rheumatologic irAEs to also develop other non-rheumatologic irAEs

Arthritis Care Res 2017; 69: 1751

ICIs – irAEs
Arthralgia/Arthritis

- Incidence of inflammatory arthritis has not been systematically reported
- Probably underrepresented – most series on ICIs AE report grade 3 or higher AE
- Large and small joints may be involved
- RA-like symmetric polyarthritis, with and without erosions
- Reactive arthritis, urethritis, conjunctivitis also reported
- Co-development of colitis in some patients
- RF/anti-CCP abs mostly negative

Arthritis Rheum 2017; 69: 687-99

ICIs – irAEs
Inflammatory Arthritis - Therapy

- No clear guidelines
- Recommendations based on consensus and case reports
- Effective doses of corticosteroids higher than the usual recommended doses
- Most patients respond to 20-30 mg/d prednisone which can be tapered if ICI therapy is discontinued
- DMARDs, biologic or non-biologic, have been used to taper corticosteroids more rapidly

Ann Rheum Dis 2017; 76: 43

ICIs – irAEs Rheumatologic

Inflammatory arthritis – most common

Can develop at any time – 2 weeks, >year

Joint damage and erosions can occur within months

Small joints, polyarticular, RA-like

Larger joints, +/- inflammatory back pain, reactive features

New onset psoriatic arthritis - family history of psoriasis

Labs: Seronegative for RF/anti-CCP

ESR/crp limited value

Imaging helpful in assessing progression

X-rays - MRI

Always consider differential dx: paraneoplastic, metastatic bone disease

Ann Rheum Dis 2017; 76:43/ RMD Open 2017; 3:e00412 /N Engl. J Med2009; 361; 211/ Ann Rheum Dis 2017; 76: 1747

ICIs- irAEs
Inflammatory arthritis

Mild arthritis	• NSAID's low dose CS
ICI Tx	• Continue (limited data)
Larger joints	• Consider local injection(s)

Ann Rheum Dis 2017; 76: 43
RMD Open 2017; 3: e000412

ICIs - irAEs
Inflammatory arthritis

Moderate Severe

- Multiple joints impairment of functions
- 40 mg – 1mg /kg/d

ICI Hold

- May be held temporarily
- Prednisone dose tapered

ICI Restarted

- Prednisone dose < 20 mg/d
- Continue tapering, d/c trial

Ann Rheum Dis 2017; 76: 43
RMD Open 2017; 3: e000412

ICIs - irAEs
Inflammatory Arthritis

Severe Arthritis

- Unable to taper steroids to 7.5 – 10 mg/d
- Consider the use of DMARDs concurrently with ICI
- No systematic studies on efficacy and outcome

Refractory Arthritis

- Use of anti-TNF agents – Infliximab, Etanercept, Adalimumab
- Tocilizumab – concerns about ICIs induced colitis and risk of perforation

ICIs

- Usually interrupted
- Only small number of patients reported

Ann Rheum Dis 2017; 76: 43
RMD Open 2017; 3: e000412

ICIs – irAEs
Rheumatologic

Sicca features resembling Sjogren's syndrome

- Dry mouth symptoms tend to be predominant
- Antibodies to Ro/SSA, La/SSB usually not present
- Avoid medications that may contribute
- Topical therapy with artificial tears and saliva substitute

Uveitis, keratitis, scleral ulcerations also reported

Ophthalmology referral

Ann Rheum Dis 2017; 76: 43

ICIs - irAEs
Rheumatologic

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)

- Age and clinical findings similar to patients who have not received ICIs
- TA biopsy findings also similar
- Since treatment for GCA requires high doses of steroids, ICIs are discontinued
  - Restarting ICI during steroid tapering? No data
  - Role of Tocilizumab?
- For PMR – therapy with lower dose steroids, ICIs could be continued

Arthritis Rheumatol 2014; 66: 768
Ann Rheum Dis 2017, 76: 1747

ICIs - irAEs
Rheumatologic

Inflammatory myopathies

- Dermatomyositis and polymyositis have been described (case reports)
- Muscle involvement similar to classic forms
- Atypical features have been described
- Muscle biopsy – similar findings based on one report
- Therapy with prednisone 30 mg/d up to 1 gm IV methylprednisolone
- ICIs have been discontinued in published cases

JAMA Dermatol 2015; 151; 195
Can J Neurol Sci 2009; 36: 518

ICIs

Pre-existing Autoimmune Disease

- Report from 13 academic centers in Australia included 119 patients treated with anti-PD-1 for advanced melanoma, of which 52 had pre-existing AI disorders
- 52% had rheumatologic conditions
- Flares observed in 20/52: 7/13 RA, 3/3 PMR, 2/2 Sjogren's, 2/2 ITP, 3/8 psoriasis
- No patients with GI (6) or neurological (5) disorders flared
- 15 patients (29%) developed other irAEs
- In general, flares of the autoimmune condition were mild, occurred in those with active symptoms or requiring immunosuppressants and the PD-1 agent was not discontinued
- Other irAEs that developed were also mostly mild and did not require d/c of the anti-PD-1 agent

Annals Onco 2017; 28: 368-76

ICIs

Pre-existing Autoimmune Disease

- Flares of pre-existing AI disorders were common, particularly with rheumatologic conditions
- Conventional irAEs were similar to other clinical trials
- The tumoral response rate of those who had a flare of the AI disorder was similar to those that did not flare
- Those that entered with more active AI disease flared more
- Response rate was lower in those on immunosuppression at the start of therapy with ICI
- Lower response appeared to be more closely related to steroids-sparing immunosuppressive drugs

Annals Onco 2017; 28: 368-76

ICIs

Pre-existing Autoimmune Disease

- Systematic review of the available literature using various databases (MedlinePlus, PubMed, Cochrane) reporting on 123 cases with pre-existing AI diseases treated with ICIs
- 92 patients (75%) had exacerbation of pre-existing AI disease(50 patients), denovo irAEs or both
- Colitis(17)and hypophysitis (6) were the most common de novo irAEs
- Renal transplant rejection occurred in 3 patients on anti-PD-1 agents
- There was no difference in irAEs between patients with active versus inactive AI disease

Ann Int Med 2018; 168: 121-30

ICIs

Pre-existing Autoimmune Disease

- Patients receiving immunosuppressive therapy had fewer adverse events, but AI disease exacerbations still occurred in some
- Most flares and irAEs were managed with corticosteroids (62% high dose); 16% required other immunosuppressive therapies
- Adverse events improved in more than 50% of patients without the d/c of ICI therapy
- More de novo irAEs developed with Ipilimumab therapy
- More exacerbations of AI disease developed with anti-PD-1 therapy

Ann Int Med 2018; 168: 121-30

ICIs

Impact of immunosuppression on efficacy

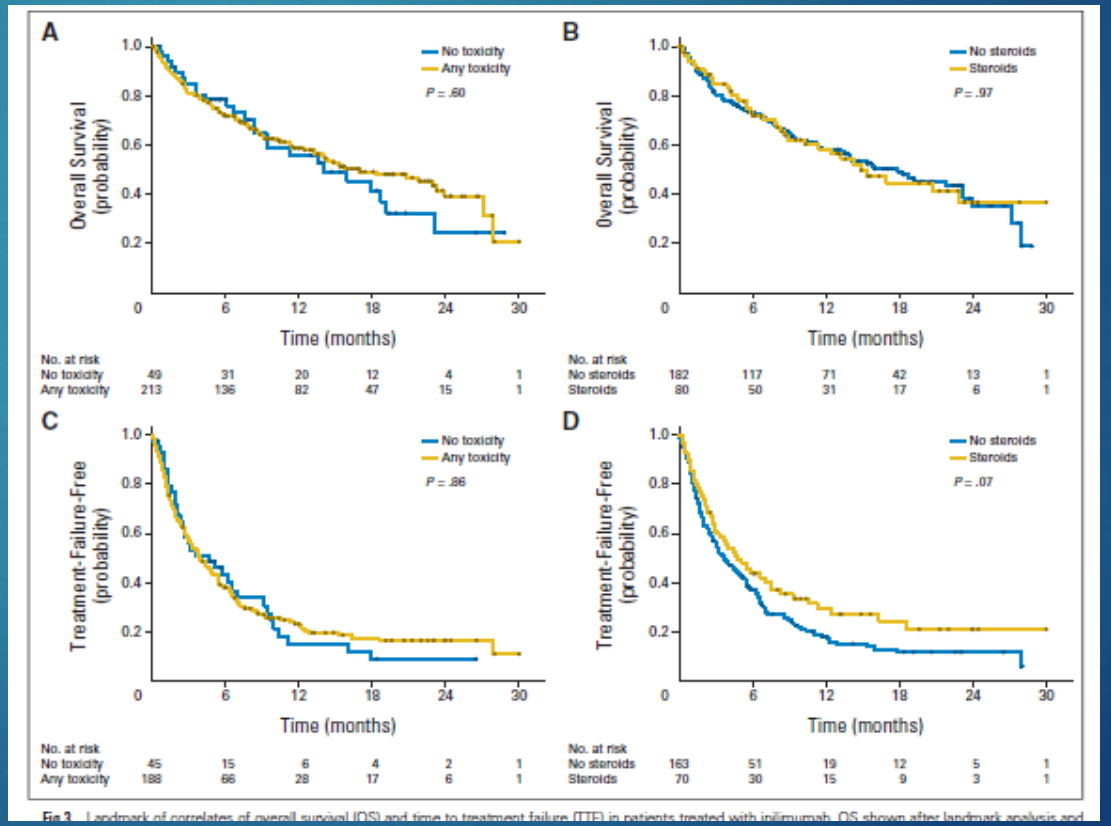
- Immunosuppression therapies for irAEs do not appear to affect the response to the ICI therapy
  - Study of 576 patients with advance melanoma in 4 clinical trials treated with ICIs
    - 24% received immunosuppressive therapy
    - No significant differences in objective response were observed
  - Study of 298 melanoma patients treated with Ipilimumab (anti-CTLA-4)
    - 85% of patients developed irAEs
    - 35% of patients required corticosteroids
    - 10% of cases had treatment with anti-TNF
    - No significant difference in overall survival

J Clin Oncol 2016; 35: 785-91
J Clin Oncol 2015; 33: 3193-98

ICIs – irAEs
Impact of Immunosuppression

Overall Survival (OS)
Time to TX Failure (TTF)

- Patients treated with Ipilimumab
- Developed irAEs
- Required systemic CS
- No impact presence/absence AE
- No impact of treatment with CS



J Clin Oncol 2017; 33; 3193-98

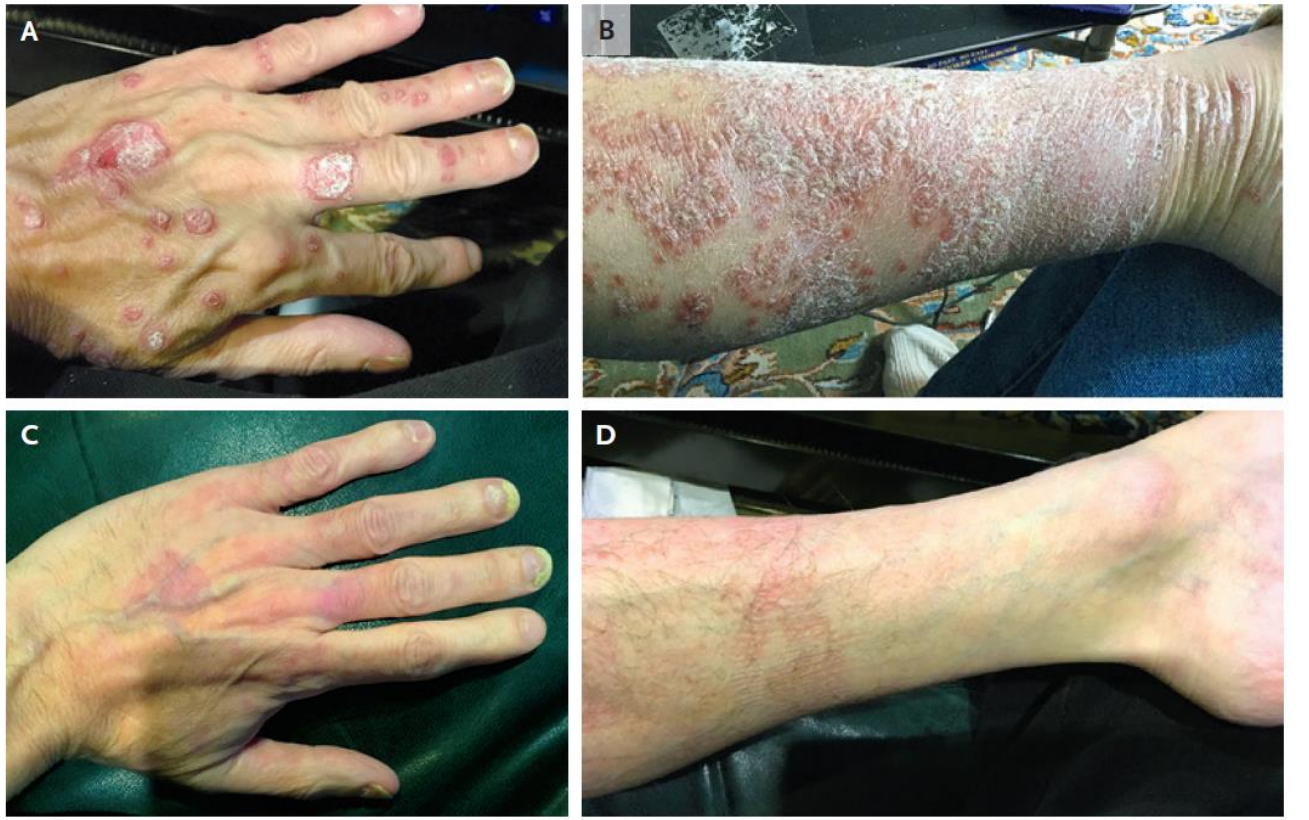
ICIs – irAEs

Inflammatory arthritis and other AI diseases

How do steroids vs other immunosuppressive agents affect tumor responses?	• Most observations regarding treatment with CS of patients who develop irAE's during ICI tx suggest no significant impact
Difference between immunosuppressive agent used - steroids vs other conventional steroid-sparing DMARDs vs more targeted therapies?	• Anti-TNF/ IL-1/IL-6/ IL-17
Is timing of the Immunosuppressive therapy important for tumor responses vs tx of AI disease?	• Active therapy before ICI is started vs after ICI therapy has been started?

ICIs – irAEs – Reversal of autoimmunity/ Loss of Tumor response

Targeted therapy – anti-IL17



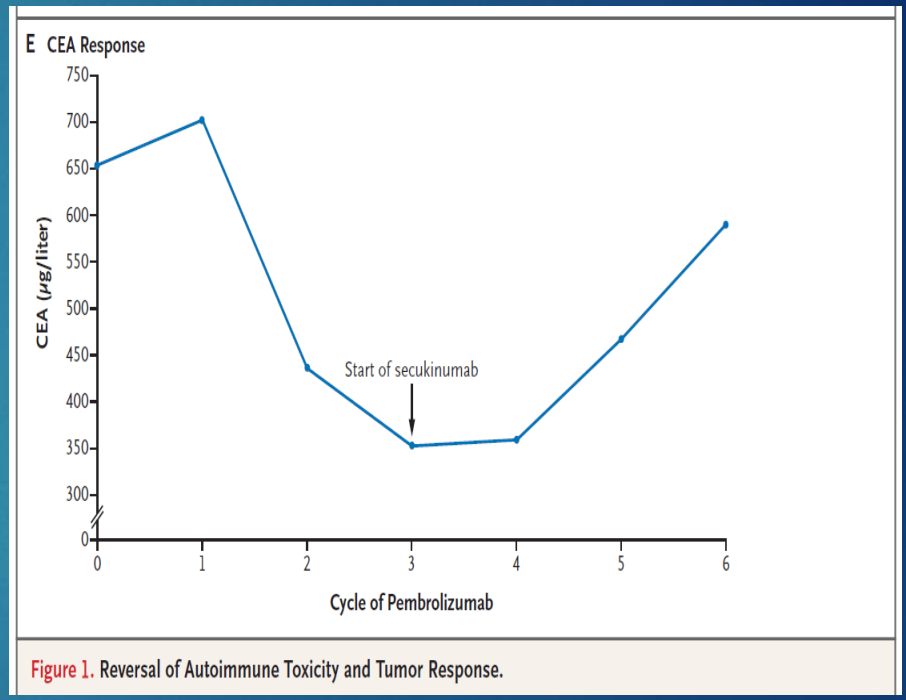


Figure 1. Reversal of Autoimmune Toxicity and Tumor Response.

Case of colon cancer with mismatch repair deficiency

N Engl J Med 2017;376: 1989-91

ICIs – irAEs
Management considerations

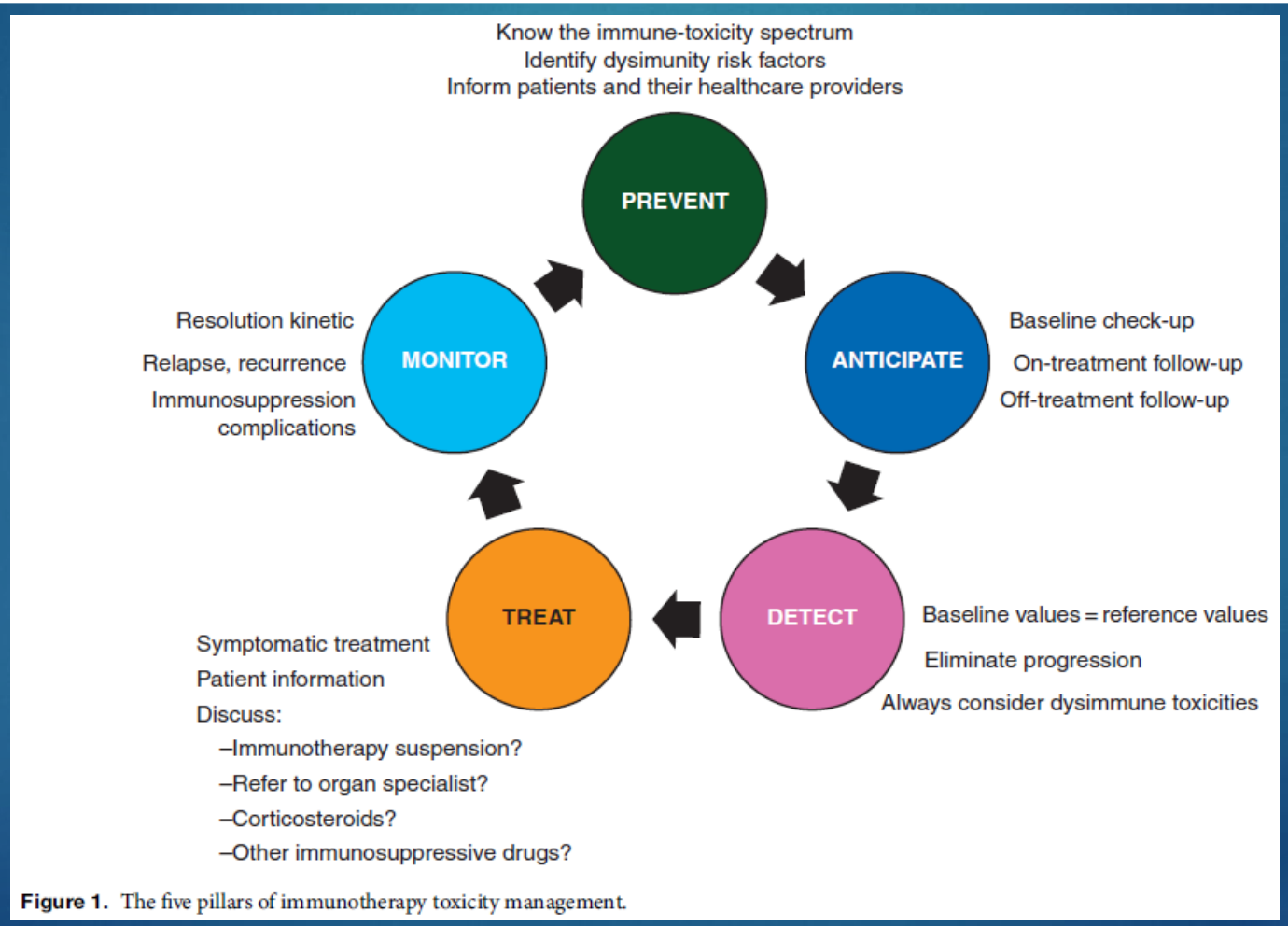


Figure 1. The five pillars of immunotherapy toxicity management.

Annals Oncol 2016;27: 559-574

ICIs

Immunotherapy baseline checklist

Table 2. Immunotherapy baseline checklist

- Physical examination
  - Performance status
  - Weight, size, body mass index
  - Heart rate and blood pressure
  - General symptoms such as asthenia or appetite should be evaluated as they are frequently affected
  - Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia
  - History of fever or recent infection must be checked and investigated appropriately
  - Baseline electrocardiogram
  - Ongoing treatment
- Laboratory test
  - Complete CBC
  - Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)
  - Glycemia
  - Total bilirubin, AST, ALT, GGT, PAL
  - Albuminemia, CRP
  - TSH, T4
  - Cortisol and ACTH at 8 am
  - LH FSH estradiol testosterone
  - Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria
  - Urinary sediment
  - Quantiferon tuberculosis or TST in case of anterior exposure
  - Virology: HIV, HCV and HBV serology
  - Antibody: ANA, TPO Ab, Tg Ab
  - If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker.
- Imaging
  - X-ray chest imaging reference is recommended at baseline
  - The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs.

Any other evaluation may also be necessary before starting immunotherapy depending on patient's history, symptoms or diseases detected at baseline.

Annals Oncol 2016; 27; 559-774

ICIs –Concurrent Medications

- Epidemiological studies have highlighted that exposure to antibiotic therapy influences the probability of response to ICIs and predict a shorter survival across malignancies
- Possible negative effects of proton pump inhibitors are also being investigated
  - **Perturbation of gut microbiota**

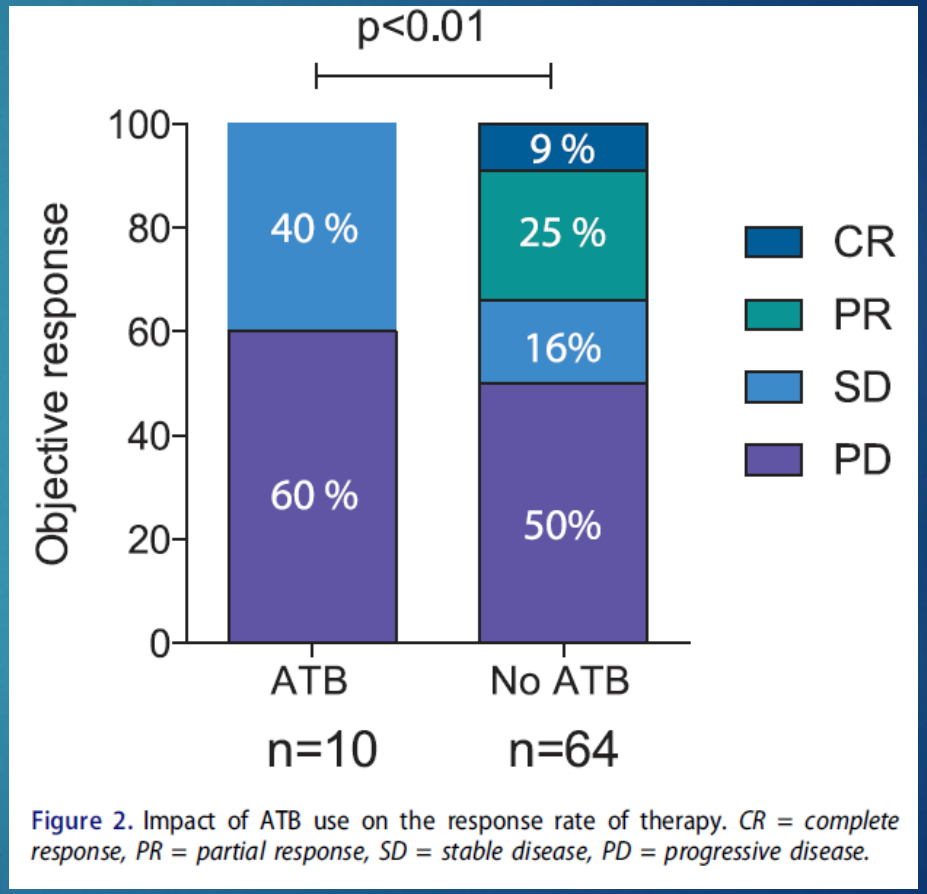
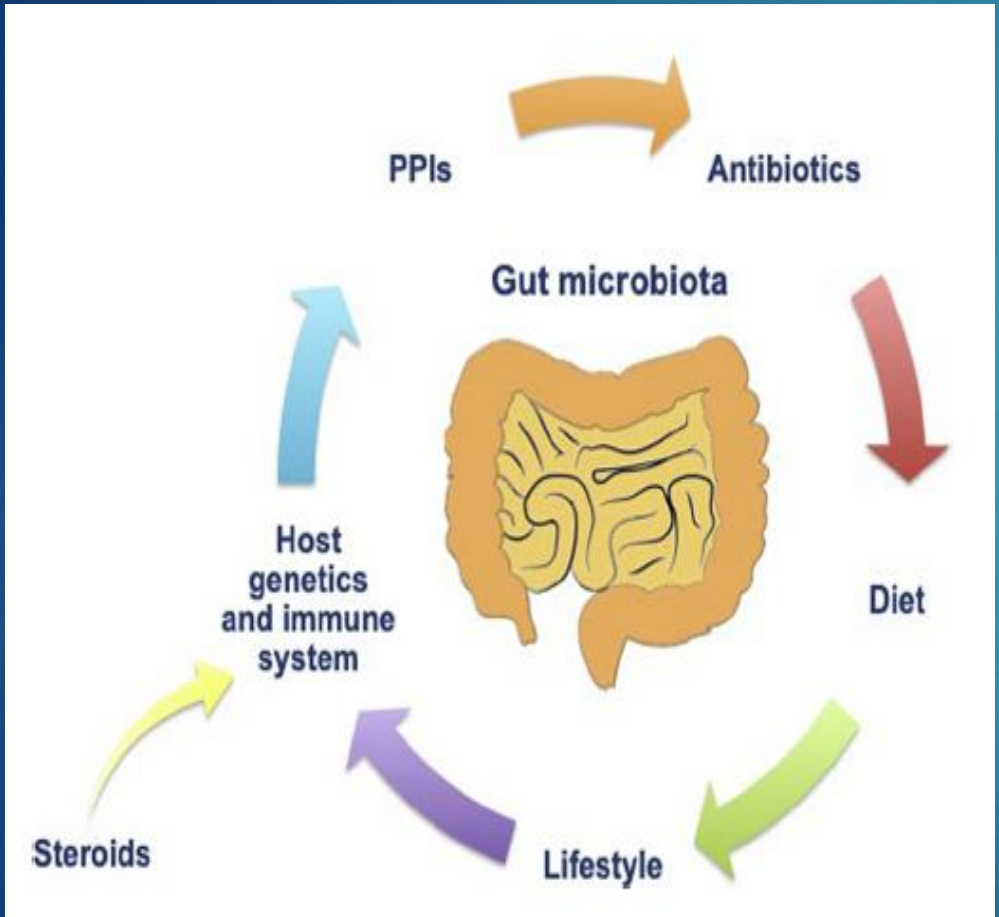


Figure 2. Impact of ATB use on the response rate of therapy. *CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.*

Oncoimmunology 2019;vol,8,e1568812
ImmunoTherpy of Cancer(2019) 7:787

ICIs –Concurrent Medications



- Prospective studies needed to define:
  - Optimal window for antibiotics, antibiotic class, route, duration
  - Potential impact of other concomitant medications and conditions that may alter the microbiome
    - PPI's
    - Corticosteroids
    - Diet

Critical Reviews in Onco/Hema 2019; 142:26-34

ICIs – irAEs
Conclusions

Immune checkpoint inhibitors have revolutionized the treatment of cancers, especially advanced malignancies, and may provide further clues about the underlying pathophysiology of autoimmune diseases

Prospective studies are needed to examine the impact of **specific interventions** and their optimal timing

The evaluation of patients with irAEs will benefit from **collaborative** management provided by different medical subspecialies

Future studies should also provide information about **specific markers that may predict** the development of irAEs in order to provide timely interventions and about the impact of **concurrent medications**

Retrospective studies thus far, suggest that patients with **pre-existing autoimmune** diseases can also benefit from immune checkpoint inhibitor therapy

Questions?