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MEDICINE

Immune Checkpoint Inhibitors and Immune-Related Adverse Events

Laura Cappelli, MD MHS

May 11, 2018

Objectives

- Understand the mechanism of action of immune checkpoint inhibitors.
- Identify rheumatic immune related adverse events (irAEs) that occur from immune checkpoint inhibitors and describe their treatment.
- Discuss the use of immune checkpoint inhibitors in those with preexisting autoimmune disease.

Disclosures

- Research funding from Bristol-Myers Squibb (nivolumab, ipilimumab)

- I will discuss off label use of immunosuppression to treat IRAEs, specifically TNF-inhibitors, methotrexate, tocilizumab

Activating the immune system to treat cancer

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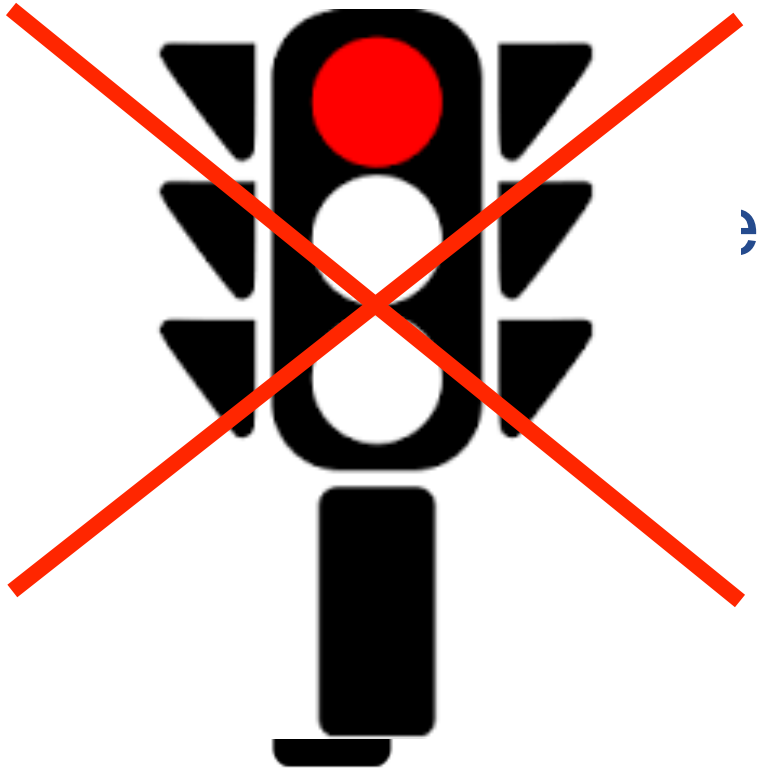
- Early 1900s: **Coley toxin**. Bacterial vaccine to treat a previously inoperable sarcoma.
- Next, melanoma with **IL-2 therapy**
- November 1984, a 33-year-old woman with metastatic melanoma was treated with rIL-2
- A few months later, all evidence of cancer was gone.
- Demonstration that a purely immunologic approach could lead to tumor regression.

Wiemann. Pharm. Ther. 1994. Rosenberg. J Immuno. 2014.

Activating the immune system to treat cancer, cont.

- High dose
- Cancer va ed and generic)
- CAR T ce



- Immune c

Immune Checkpoint Inhibitors

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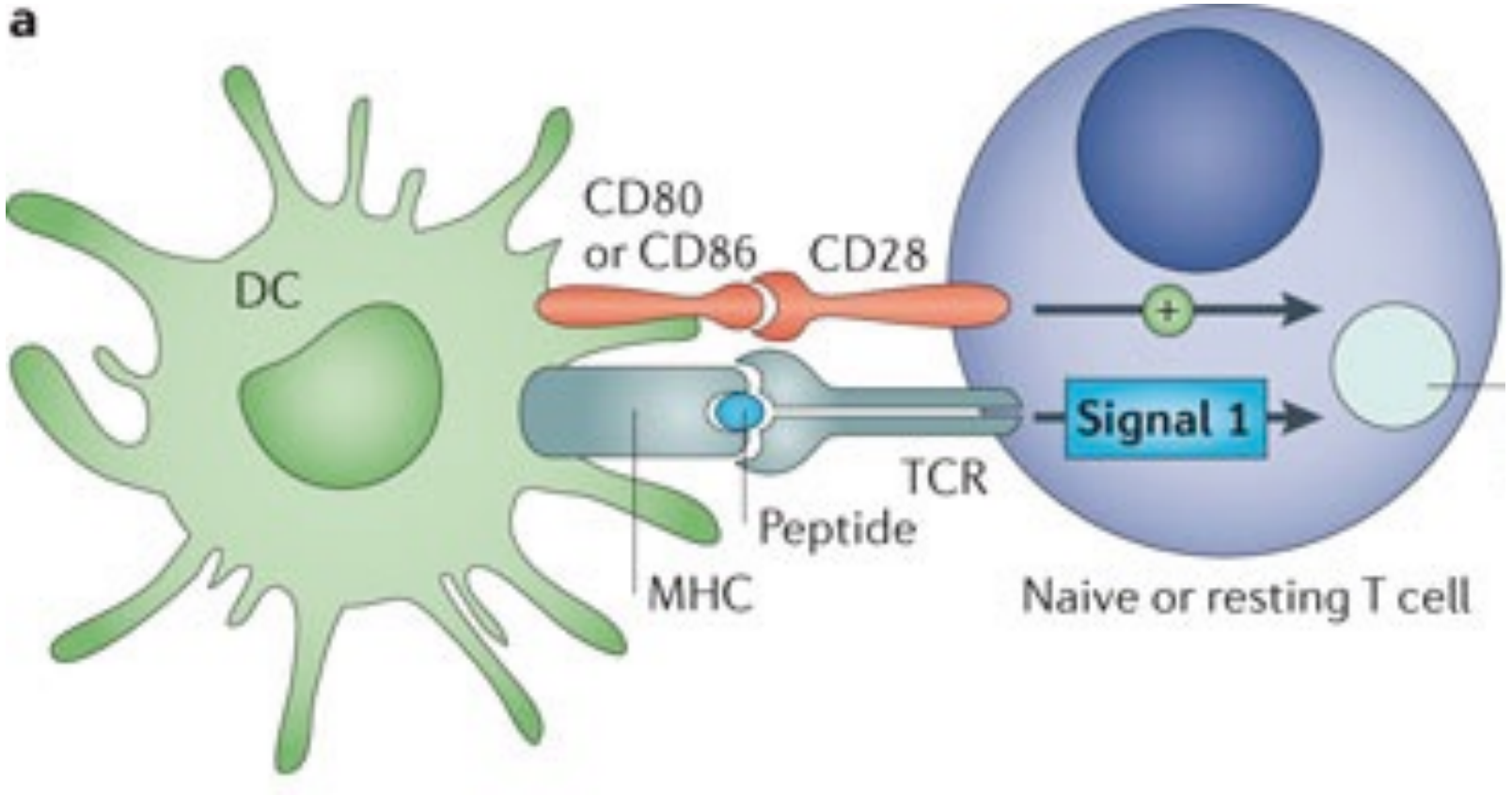
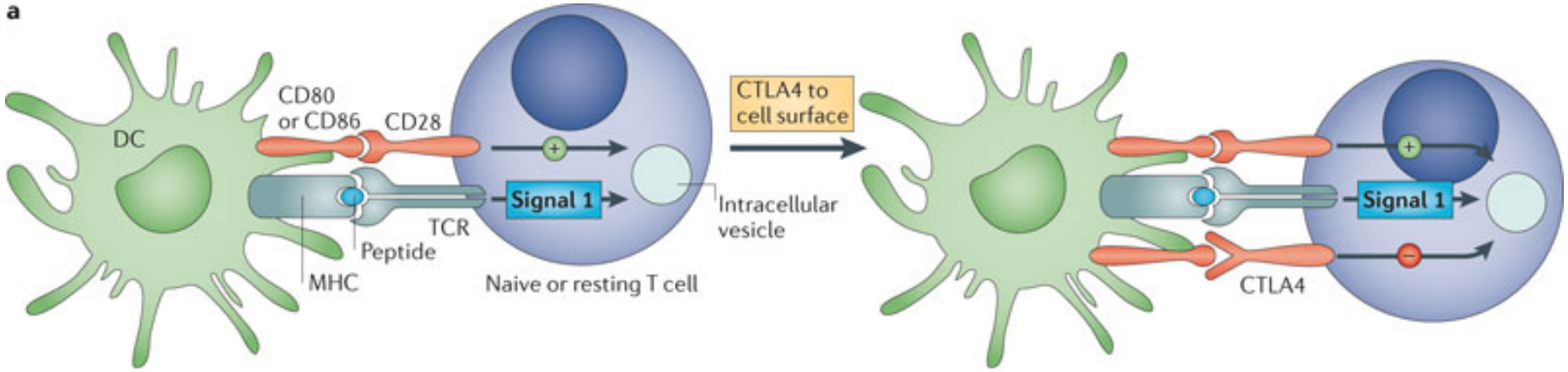
- One class of cancer immunotherapy
- Work by blocking negative costimulatory molecules, thus increasing activation of T cells
- Increase survival in a variety of advanced malignancies
- 6 FDA approved drugs currently
  - Ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab

T cell Activation Requires 2 Signals



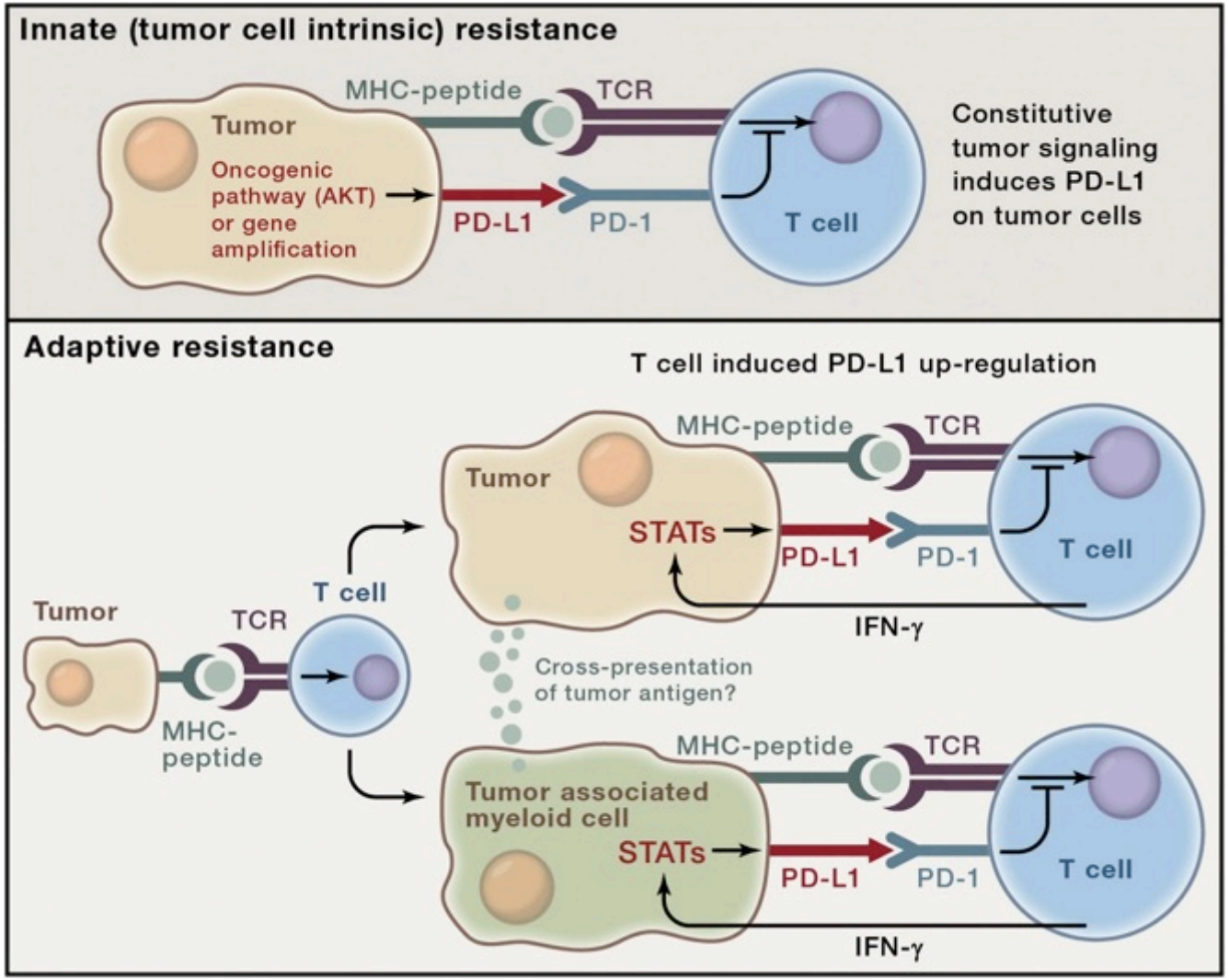
Pardoll DM, *Nature Reviews Cancer* 2012; 22: 252-64

Immune Checkpoints Control Immune Deactivation and Regulation



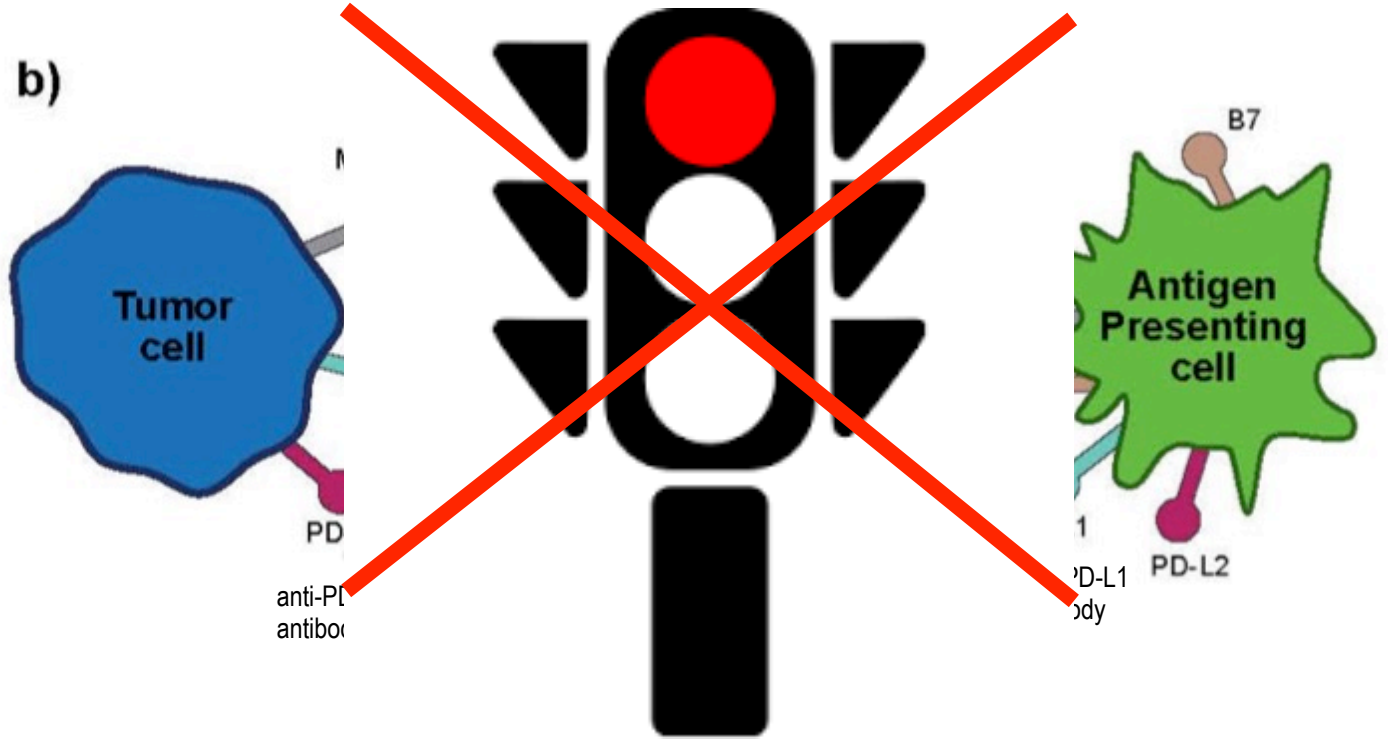
Pardoll DM, *Nature Reviews Cancer* 2012; 22: 252-64

Tumors Express Checkpoint Ligands and Dampen T-Cell Responses



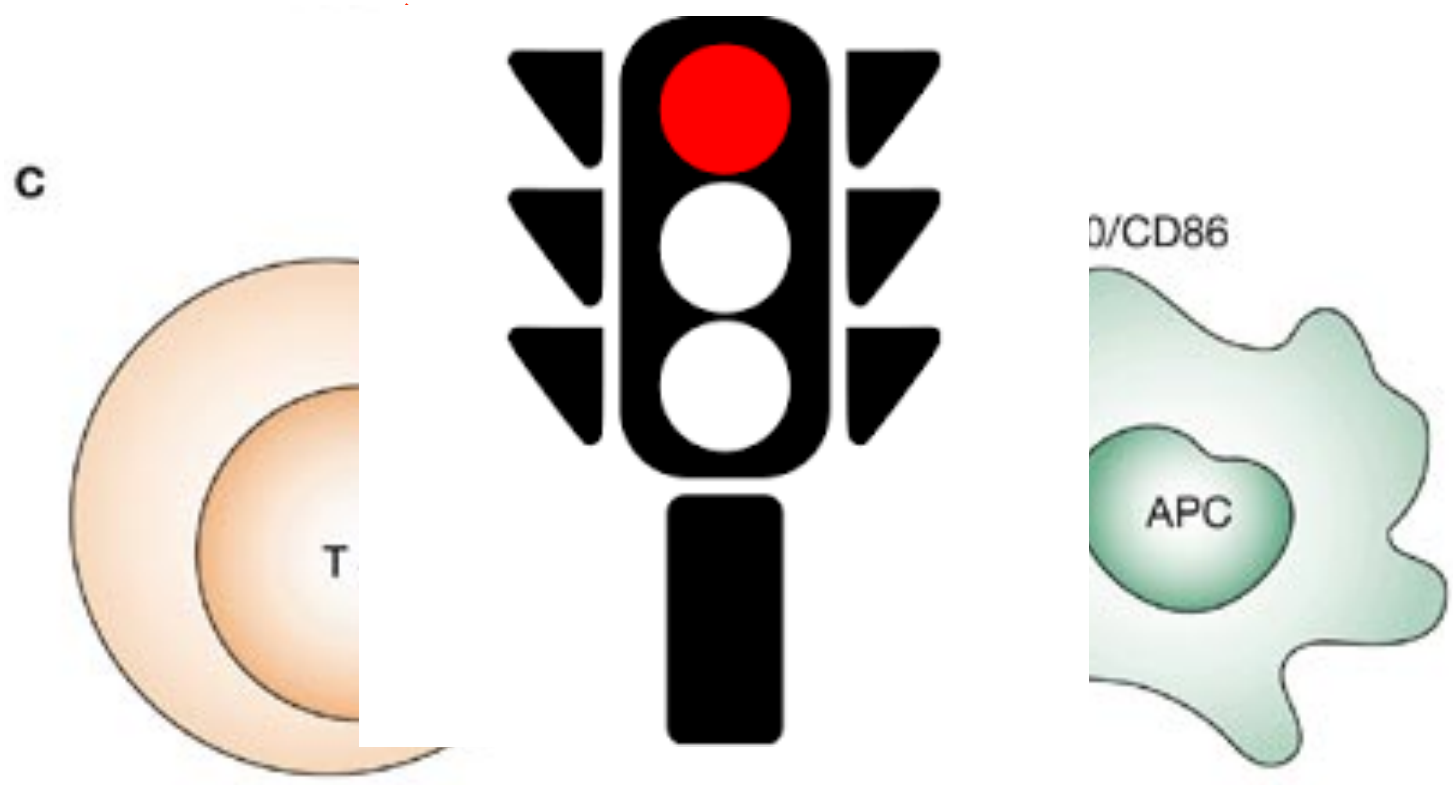
Topalian SL et al, *Cancer Cell* 2015.

Immune Checkpoint inhibitors block regulatory interactions



Modified figure from: Cappelli LC, et al. Rheum Dis Clin. 2016.

Contrast with abatacept mechanism

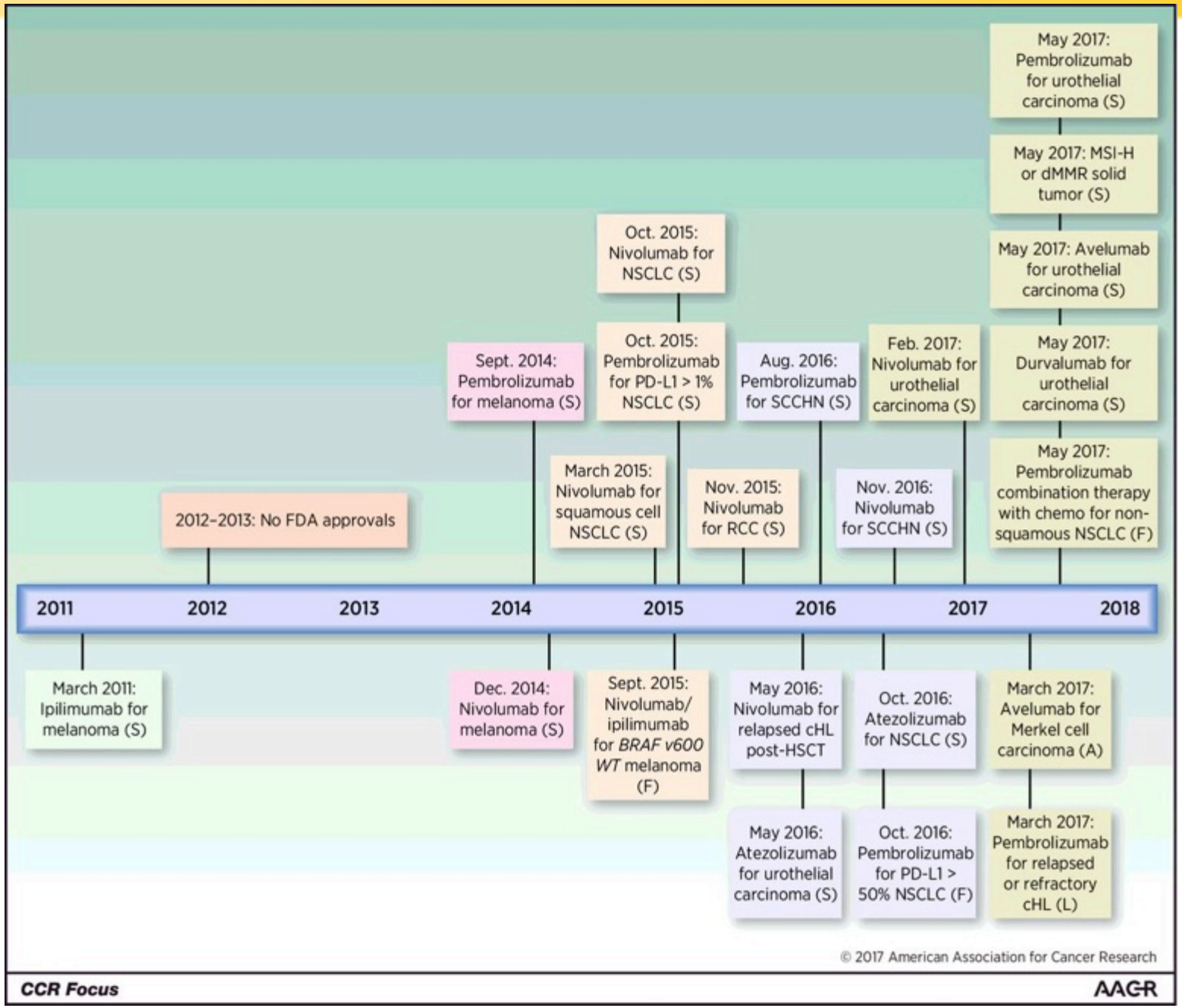


Ruderman and Pope. Nature Clinical Practice Rheum. 2006.

Wide variety of indications

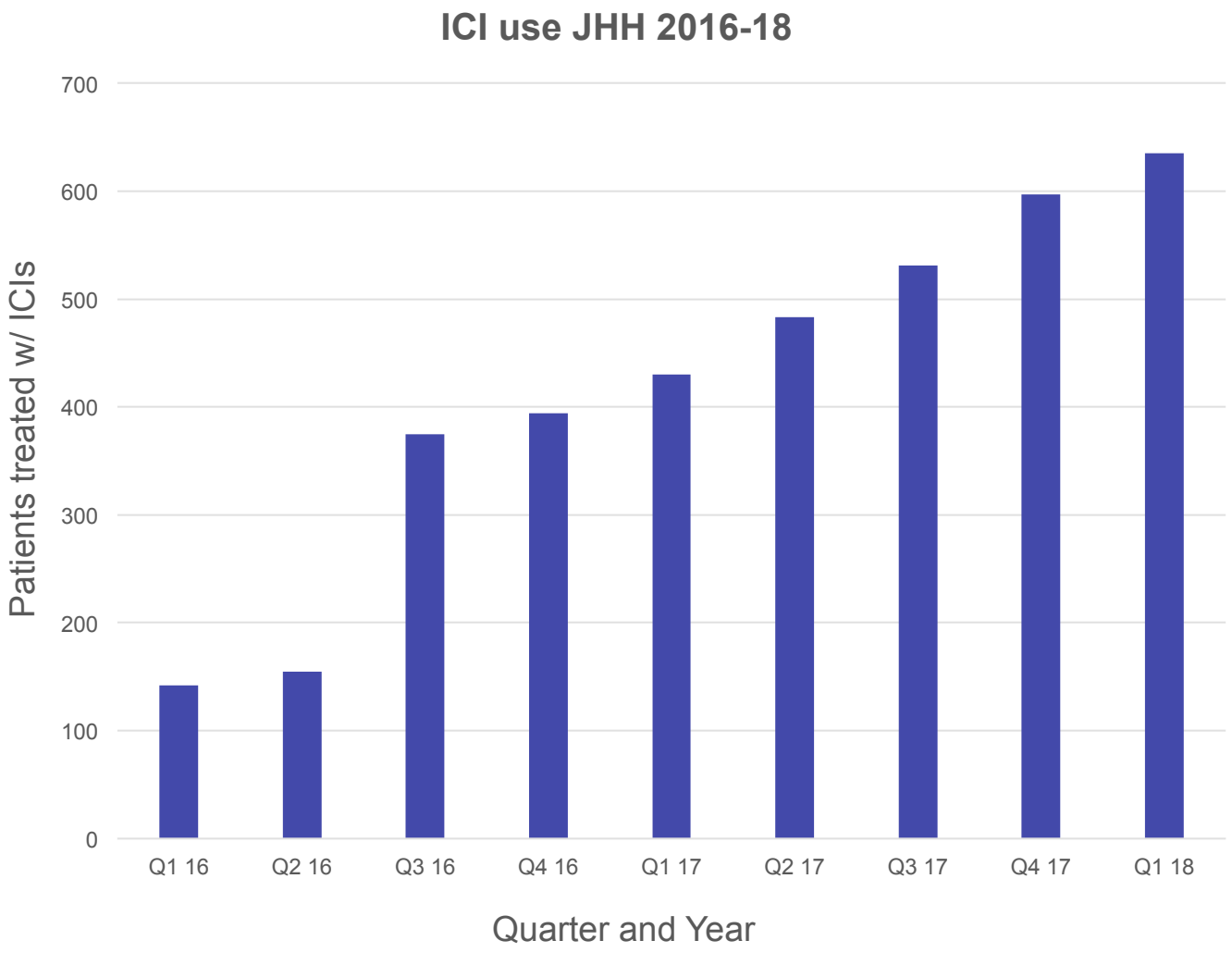
Approved ICIs	Target	Indications
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, NSCLC, RCC, Hodgkin lymphoma, Urothelial carcinoma, SCCHN
Pembrolizumab	PD-1	Melanoma, NSCLC, Urothelial carcinoma, MSI-H solid tumors, SCCHN
Atezolizumab	PD-L1	Urothelial carcinoma, NSCLC
Avelumab	PD-L1	Merkel cell carcinoma
Durvalumab	PD-L1	Urothelial carcinoma
Ipilimumab/Nivolumab	CTLA-4/PD-1	Melanoma, RCC

RCC: renal cell carcinoma; NSCLC: non small cell lung cancer; MSI-H: microsatellite instability high; SCCHN: squamous cell carcinoma of head and neck



Baik et al. Clin Cancer Res. 2017.

JHH ICI Use by quarter



So these drugs work and are everywhere, but…

- Why should a rheumatologist care?

- For both conceptual and practical reasons!

Conceptual

- Associations of autoimmune diseases and their treatment with malignancies
- Tumors can express disease-defining autoantigens
  - E.g. RNA Pol III and scleroderma; TIF1 and myositis
- Immune checkpoints like CTLA-4, PD-1 potentially important in SLE, RA, Sjogren's, etc.

Egiziano G et al. *Best Pract Res Clin Rheumatol* 2016; Shah AA et al. Arthritis Rheum 2015. Pinal-Fernandez et al. Rheum (Ox) 2018. van der Vlist et al. Nat Rev Rheumatol. 2016.

What happens when…

The forces of activation outweigh those of inhibition

WPClipart.com

A double edged sword

Dec. 3, 2016

Immune System, Unleashed by Cancer Therapies, Can Attack Organs

Immunotherapy drugs have been hailed as a breakthrough in cancer treatment, but doctors are finding that what makes them effective is also what poses serious risks.

By MATT RICHTEL

PERSPECTIVE

nature medicine

Is autoimmunity the Achilles' heel of cancer immunotherapy?

Carl H June[1,2], Jeremy T Warshauer[3] & Jeffrey A Bluestone[1,4]

Nytimes.com, Nature Medicine 2017.

ICIs cause Immune-related Adverse Events (irAEs)

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- Unopposed general T-cell activation induces robust immune response
- Off-target (non-tumor) tissue damage = **irAEs**
- Seen in all agents and across all indications
- Diverse phenotypes (multiple organs and systems)
- Severity from mild to life-threatening
- Temporality to ICI exposure is variable
- Risk factors mostly unclear, more common in combo ICI Tx

Spectrum of irAEs

IRAE	Clinical Characteristics
Colitis	Diarrhea (30%), severe colitis (5-10%), perforation and death possible
Rash	Vitiligo, neutrophilic dermatoses, Psoriasis, TEN/SJS
Thyroiditis	Usually hypothyroidism, often later, up to 20%
Pneumonitis	Mild dyspnea/cough to respiratory failure, 1-5%
Hypophysitis	Can affect all hormonal axes or can be selective, 0.5-10%
Hepatitis	Transaminitis, with or without ↑ bilirubin, 5-10%
CNS	Encephalopathy, 1%; aseptic meningitis, transverse myelitis
Peripheral NS	Peripheral neuropathy, Guillain-Barre syndrome
Myocarditis	Rare, can be severe, leading to heart failure, death

Rheumatic irAEs in 2018

- Inflammatory arthritis
  - (5-7% in a retrospective cohort of anti-PD1 treated patients)
- Sicca syndrome
- Polymyalgia rheumatica/Giant Cell Arteritis
- Myositis (dermatomyositis, polymyositis)
- Single Organ Vasculitis
- Lupus nephritis (n=1)
- Psoriasis, Psoriatic arthritis
- Scleroderma, others

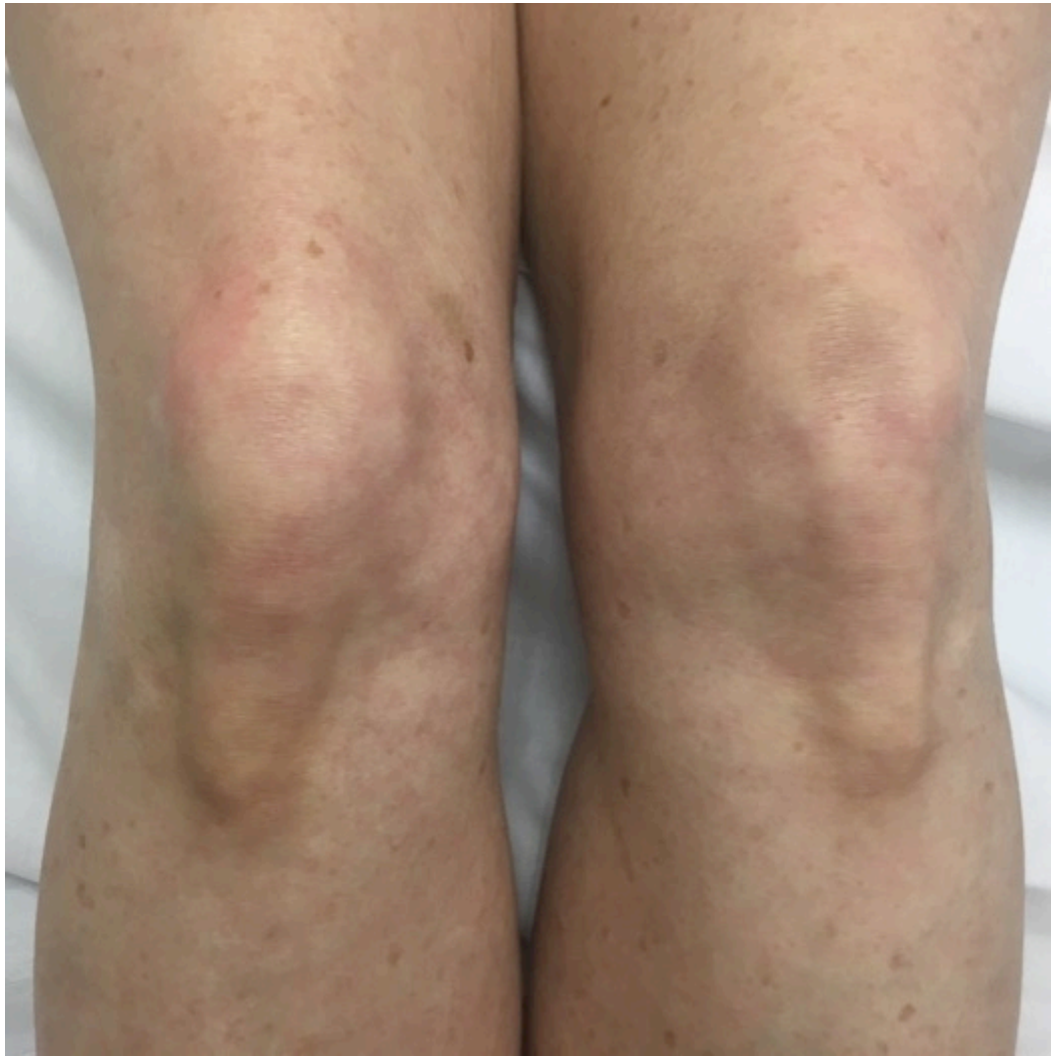
Buder-Bakhaya et al. Cancer Immuno Immunother. 2017. Cappelli et al. Ann Rheum Dis. 2017. Chan et al. J Immunotherapy. 2015 Goldstein et al. Arthritis Rheum 2014. Minor et al. J Clin Onc 2013. Sheikh Ali et al. JAMA Derm. 2014. Yoshioka et al. J Derm. 2015. Fadel et al. NEJM 2009. Bonigen et al. J Eur Academ Dermatol Venerol. 2016. Law-Ping-Man et al. Rheum (Ox). 2016. Barbosa et a. Mayo Clin Proc. 2017.

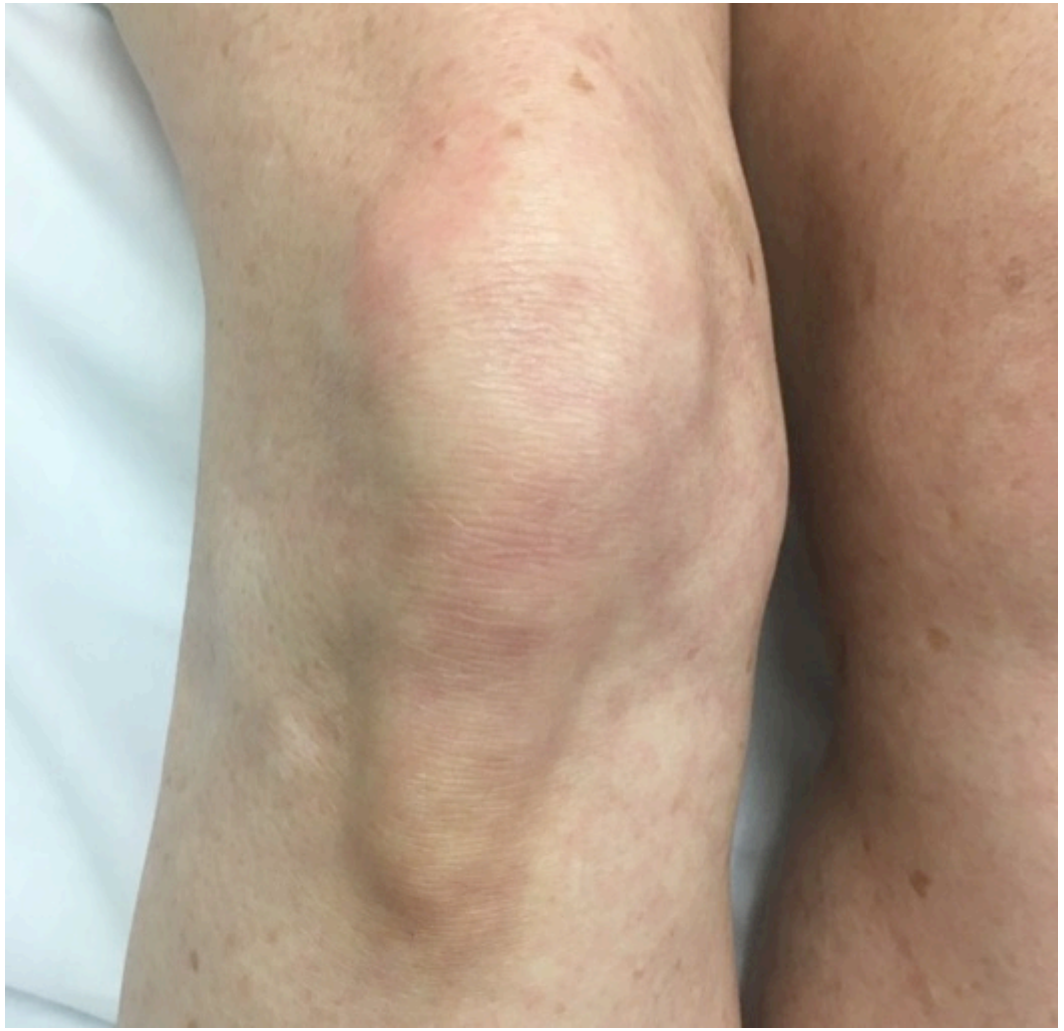
Inflammatory Arthritis: Presentation

- Our cohort > 60 patients + other series
- For most, medium to large joints first
  - Knees, ankles, shoulders
  - Small joints can be affected first
- Many evolve to small joints
  - MCPs, PIPs, wrists
- Reactive arthritis can be seen
  - Conjunctivitis, urethritis, arthritis
- Tenosynovitis, other tendon involvement noted

Cappelli LC et al, Ann Rheum Dis. 2017. Chan et al. J Immonther 2015. Cappelli LC et al, Seminars Arthritis Rheum, 2018. Calabrese C et al. RMD Open. 2017.

Tendon involvement





Inflammatory Arthritis: Presentation, cont.

- Type of ICI/s may influence presentation
  - Combination therapy (anti-PD-1/CTLA-4) with higher inflammatory markers, more likely to have knee involved first
  - Reactive arthritis seen only in combination therapy (all with preceding colitis)
  - PD-1/PD-L1 inhibitor monotherapy: more likely to have small joints involved first, more likely to have IA as only irAE

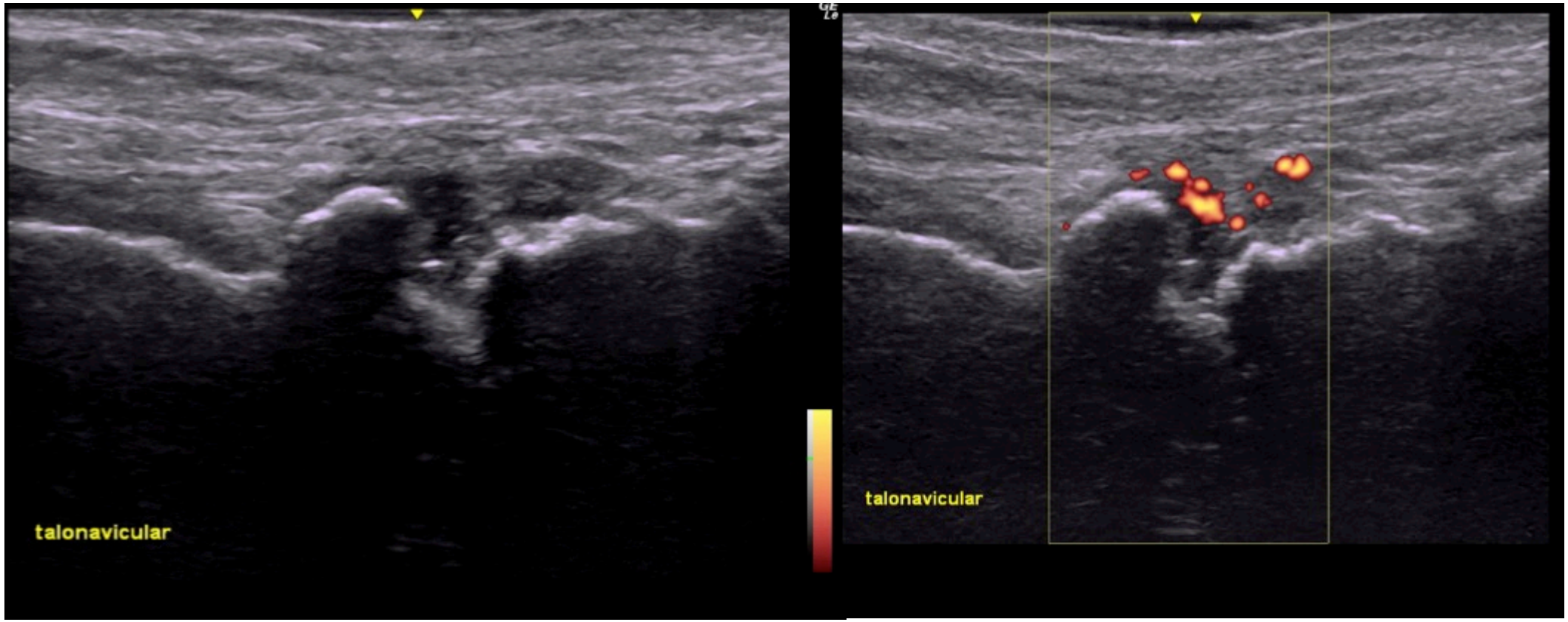
Cappelli LC et al, Seminars Arthritis Rheum, 2018.

Inflammatory Arthritis: Diagnostic Testing

- Inflammatory markers elevated in many (70% in our cohort)
- HLA B27 seems to be mostly negative (1 or 2 +)
- Serologies
  - JH (n=60): positive ANA in 3, only 1 at significant titer, 2 with RF (3.3%), 2 with anti-CCP Abs (3.3%). Cleveland: 1/9 patients + for RF, none for CCP
  - Seropositive RA has been reported, some with Abs before ICI
- Joint Fluid
  - Elevated WBC (3-30K), PMN predominant (>70%)
- Imaging
  - Effusions, synovitis, erosions, tenosynovitis

Cappelli LC et al, Ann Rheum Dis. 2017. Calabrese C et al. RMD Open. 2017. Belkhir et al. Ann Rheum Dis. 2017.

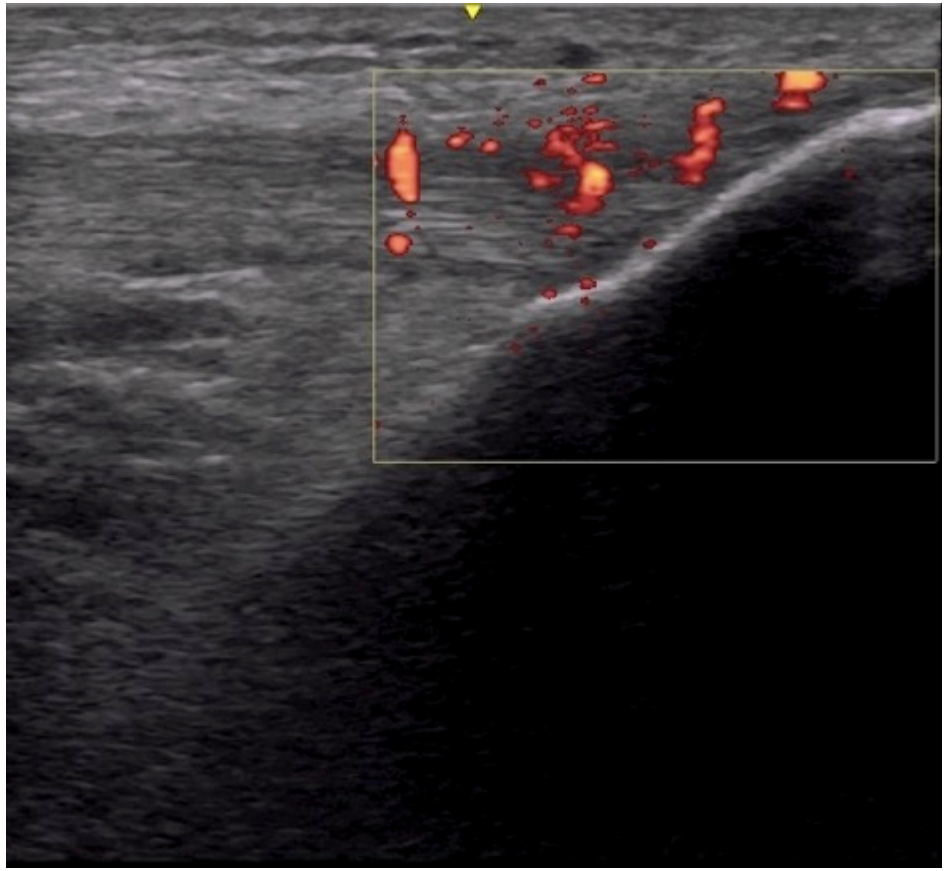
Imaging example (US)



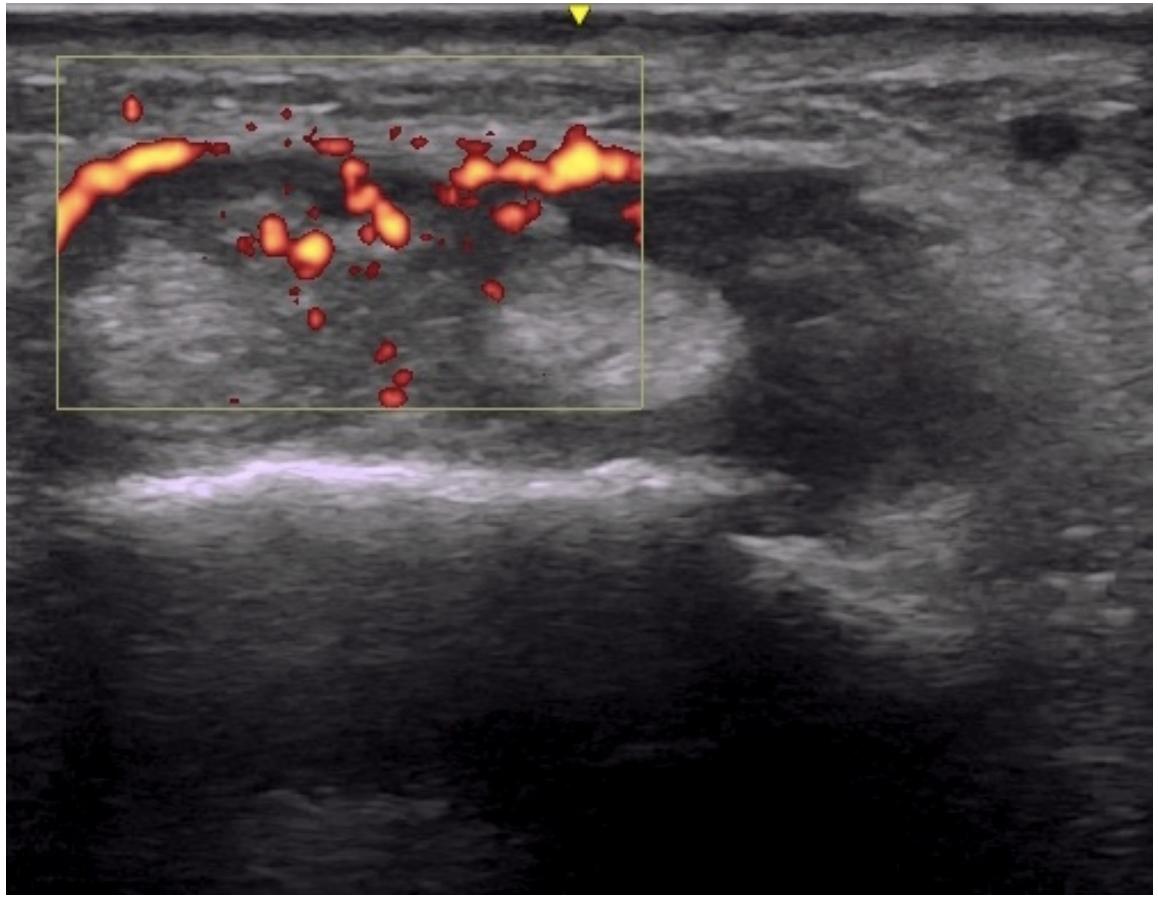
Talonavicular synovitis and erosion

Cappelli LC et al, Ann Rheum Dis. 2017.

Imaging cont. (US)

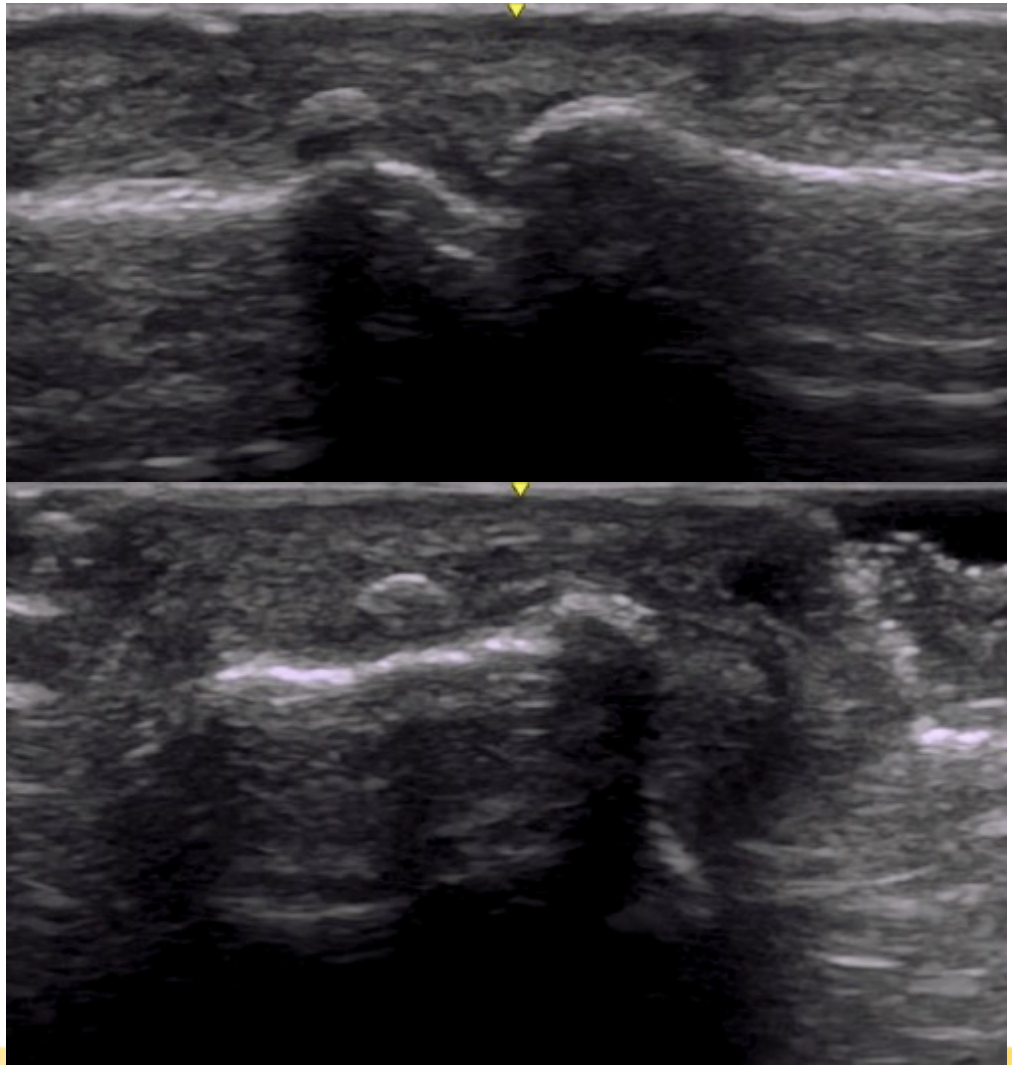


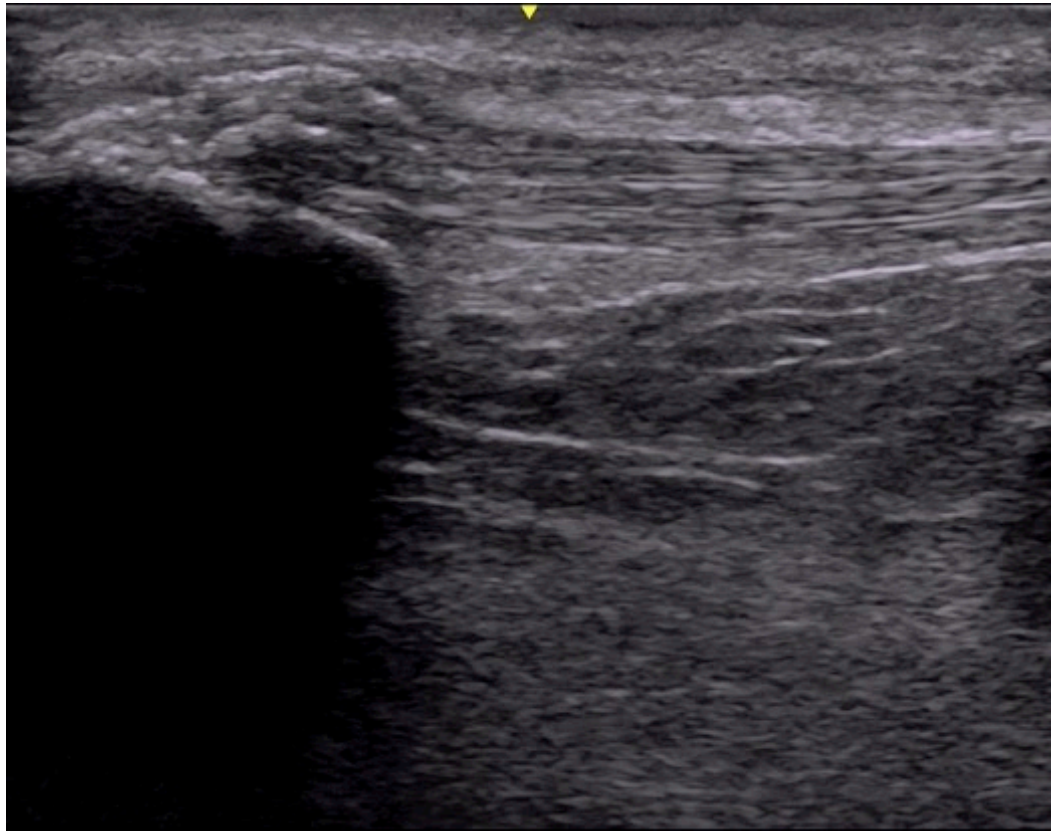
Patellar tendinitis



Wrist tenosynovitis

Imaging cont. (US)





Enthesophytes at PIP (left), patellar tendon proximal insertion (above)

IA treatment and outcomes

- NSAIDs, IA steroids for mild cases
- Corticosteroids needed in most (~75%) referred to rheumatology
- DMARDs (e.g. MTX), biologics often required
  - TNF-I, Tocilizumab used
- Persistence in many after ICI stopped
  - ICI effects persist ~ 6 months after cessation, but IA can last longer

Cappelli LC et al, Seminars Arthritis Rheum 2018. Kim et al. Ann Rheum Dis 2017.

Inflammatory Arthritis: Treatment

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CTCAE Grade	Management	Follow-up
1 • Mild joint pain • Inflammatory symptoms* • Joint swelling	**Continue Immunotherapy** • NSAIDs** • Consider prednisone 10 - 20 mg daily x 4 weeks, if NSAIDs ineffective • Consider intra-articular steroids	• Serial rheumatologic examinations, at 2 weeks and 4 weekly • Functional assessment • If not improving in 2-4 weeks, **escalate to grade 2 management**
2 • Mild/moderate joint pain • Inflammatory symptoms • Limiting instrumental ADLs	**Continue immunotherapy** • Oral prednisone 20 mg daily, increase to 1mg/kg/day or equivalent if no response after 4+ weeks and **consider hold immunotherapy** • Consider intra-articular steroids	•If symptoms worsen/ persist >8 weeks, **hold immunotherapy, escalate to grade 3+ management** •If symptoms improve, taper steroids over 4-8 weeks/until grade 1
3+ • Severe joint pain • Inflammatory symptoms • Joint swelling • Limiting self-care ADLs • +/-Irreversible joint damage	**Hold immunotherapy** • Oral prednisone 1mg/kg/day or equivalent x 4 weeks or until improve to grade 1 • Consider **TNF-inhibitors** • Consider **methotrexate** ? Tocilizumab, others	• After symptoms improve, taper steroids over 4-8 weeks/until grade 1 • If symptoms do not improve in 4-6 weeks, **discontinue immunotherapy**

Modified from Naidoo et al, *The Oncologist* 2017

Concerns with Immunosuppression

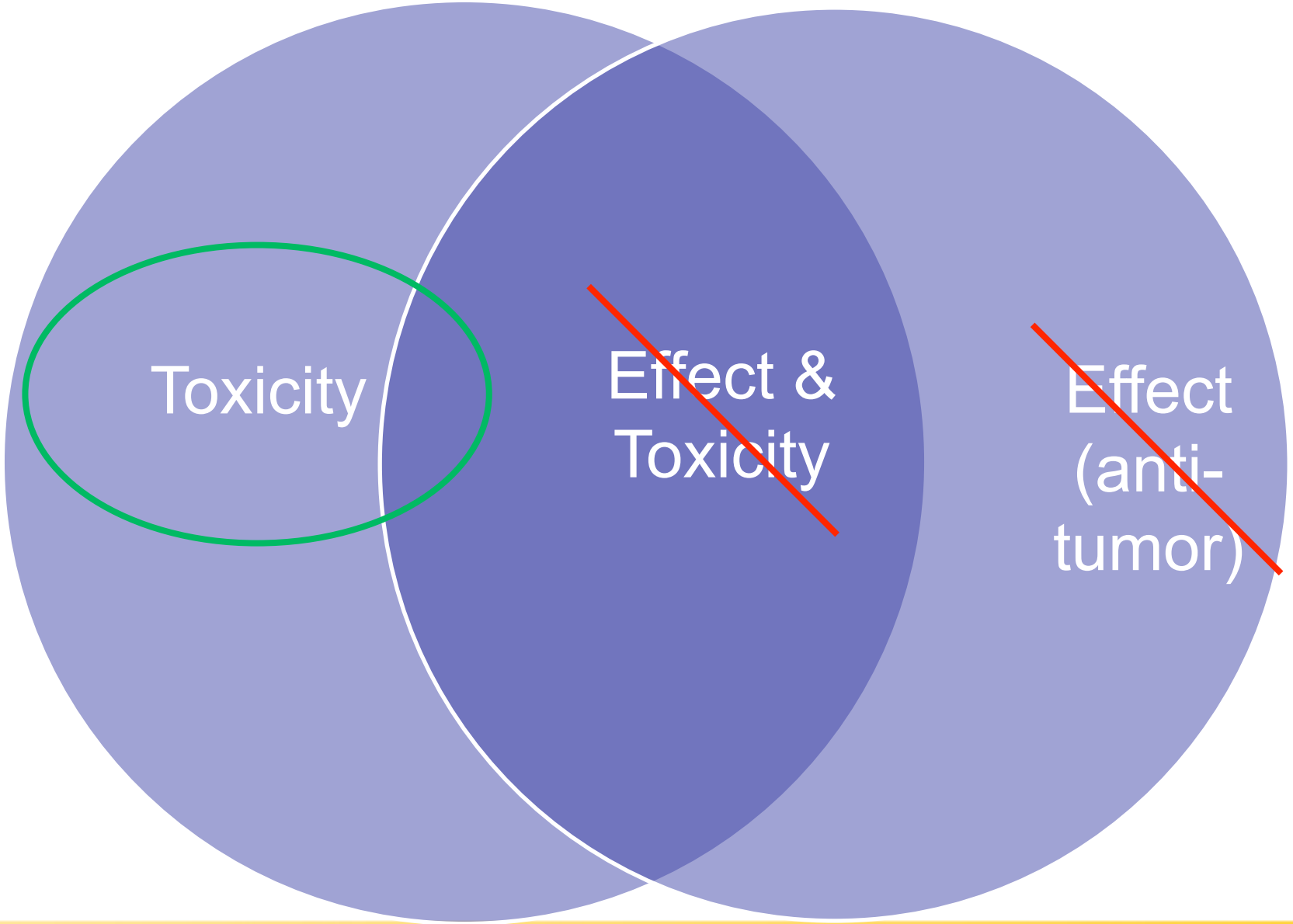
- Abrogating anti-tumor effect of ICIs
- Impairing natural tumor defenses
- Overlapping side effects?

Concerns with Immunosuppression

- Data mostly limited to **short term exposure**:
  - Corticosteroids, short term TNF-I did not affect melanoma response to ipilimumab
  - Better outcomes with lower doses of corticosteroids in hypophysitis [cite]
- Ultimately, multi-disciplinary discussion to decide on Tx

Horvat TZ, et al. *J Clin Oncol*. 2015;33(28):3193-8.

Selective toxicity treatment?



Is having an irAE a "good" thing?

- Nivolumab in melanoma; response lower in those with no iRAEs
  - Response rate higher in patients who had more severe irAE (80% response rate of tumor regression in those with 3+ irAE)
- Nivolumab in NSCLC: irAEs had better overall and progression free survival
- Anti-PD1 therapy for non-melanoma (pooled); those with low grade irAEs had better overall response rate
  - Those with higher grade events who needed corticosteroids had improved time to next treatment, but not significantly better overall survival

Hartani et all JAMA Oncol. 2018. Judd et al. Oncologist 2017.

irAE pathogenesis may give insight into anti-tumor mechanisms

- Parallel processes driven by increased immune reactivity
- Common antigen targeted (? Mutated or overexpressed in tumor)
- Not antigen driven, downstream effects of T cells in target tissue

Preexisting autoimmunity and ICIs

- What about “our patients” who develop cancer?
- Limited data on use of ICIs for cancer treatment in those with preexisting autoimmune disease
  - Were excluded from initial trials
- Data from retrospective series available, 1 systematic review

Preexisting autoimmunity and ICIs, cont.

- 30 patients with melanoma treated with ipilimumab (anti- CTLA-4)
- Prior RA, psoriasis, IBD, MS, SLE, and others
- 8/30 exacerbation (27%)
  - 6 resolved with steroids, 2 required infliximab.
- 10/30 grade 3 + “conventional” irAE (33%)
- 15/30 neither flare nor IRAE.

Johnson et al. JAMA Onc. 2015

Preexisting autoimmunity and ICIs, cont.

- 52 melanoma patients treated with anti-PD-1 agents
- Prior RA, PMR, Sjogrens, ITP, psoriasis, IBD, MS
- 20 (38%) flare requiring immunosuppression
  - 2 discontinued ICI due to flare
  - 14/27 (52%) patients with rheumatic disorders flared
- 15 (29%) developed other irAEs

Menzies et al. Annals of Onc. 2017

Systematic Literature Review: Preexisting autoimmunity

- Original case reports/series, observational studies included
- Ps/PsA, RA most common, then thyroid disease, IBD
- 123 patients; 92 (75%) had exacerbation of preexisting autoimmune disease
  - Equal exacerbations in active and inactive at start of ICI
- 31 (25%) had de novo irAE
- 21 (17.1%) discontinued therapy due to AE

Abdel-Wahab et al. Ann Intern Med. 2018.

Systematic Literature Review: Preexisting autoimmunity, cont.

- 27% receiving immunosuppressive therapy at start of ICI (steroids, csDMARDs mostly)
  - Equal exacerbations in those on and not; potentially lower rate of de novo irAEs in those on immunosuppression
- Anti-PD-1/PD-L1 higher rate of exacerbation; ipilimumab (anti-CTLA-4) higher rate of de novo irAE
- RA (N=20): 35% had arthritis flare only, 25% de novo irAE only, 15% had both

Abdel-Wahab et al. Ann Intern Med. 2018.

Strategies: Managing preexisting autoimmune disease

- Careful history is important, as is monitoring

- Better outcomes (potentially) if controlled at start
  - 2x as likely to flare if active symptoms in anti-PD-1 series
  - Endoscopy before ICI use in those with IBD to ensure controlled

Menzies et al. Ann Oncol. 2017. Cooper et al. J Neuromuscul Dis 2017. Lau et al. Muscle Nerve. 2016. Gieliesse, de Boer J Crohns Colitis. 2014.

Strategies: Managing preexisting autoimmune disease, cont.

- BUT, just because controlled doesn't mean they won't flare
  - Patients with isolated ocular or controlled myasthenia develop severe myasthenic crises on anti-PD-1 therapy
  - **30%** of those with inactive rheum disease flare on anti-PD-1
  - Equal exacerbations active vs. inactive in SLR
- DMARDs along with therapy?
  - 16% in SLR treated with DMARDs concurrently
  - Have used hydroxychloroquine, sulfasalazine, low dose corticosteroids, methotrexate in our practice

Menzies et al. Ann Oncol. 2017. Cooper et al. J Neuromuscul Dis 2017. Lau et al. Muscle Nerve. 2016. Gieliesse, de Boer J Crohns Colitis. 2014. Abdel Wahab et al all Ann Intern Med. 2018.

Question 1:

Which of these can be immune related adverse events due to immune checkpoint inhibitor therapy?

- a) hypophysitis
- b) myositis
- c) colitis
- d) all of the above

Question 1:

Which of these can be immune related adverse events due to immune checkpoint inhibitor therapy?

- a) hypophysitis
- b) myositis
- c) colitis
- **d) all of the above**

Question 2:

Many patients with inflammatory arthritis due to immunotherapy have:

- a) elevated rheumatoid factor (RF)
- b) high inflammatory markers (ESR or CRP)
- c) positive anti-nuclear antibodies (ANA)
- d) positive anti-CCP antibodies

Question 2:

Many patients with inflammatory arthritis due to immunotherapy have:

- a) elevated rheumatoid factor (RF)
- **b) high inflammatory markers (ESR or CRP)**
- c) positive anti-nuclear antibodies (ANA)
- d) positive anti-CCP antibodies

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