UT Southwestern
Medical Center

Rheumatologic immune related adverse events with immune checkpoint inhibitors
" My cancer therapy is a pain in the neck"

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Disclosures

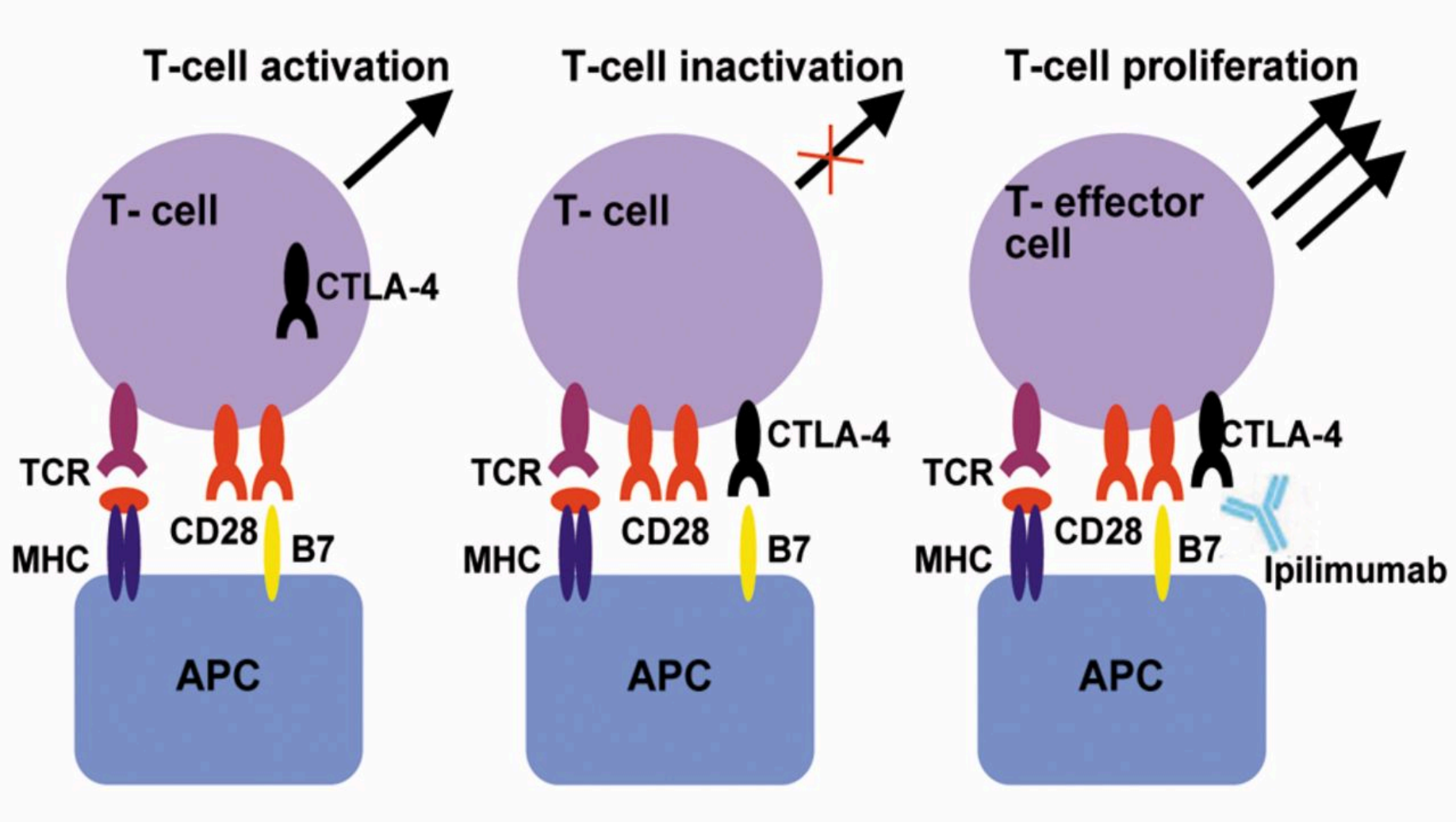
- No financial disclosures
- I am not an oncologist
- I am not an immunologist

Overview

- Why would check point inhibitors cause rheumatologic adverse events?
- Review rheumatologic immune related adverse events (irAEs)
- Management
- The future

Why would immune checkpoint inhibitor therapy cause rheumatologic adverse events?

Ipilimumab prevents T cell inactivation

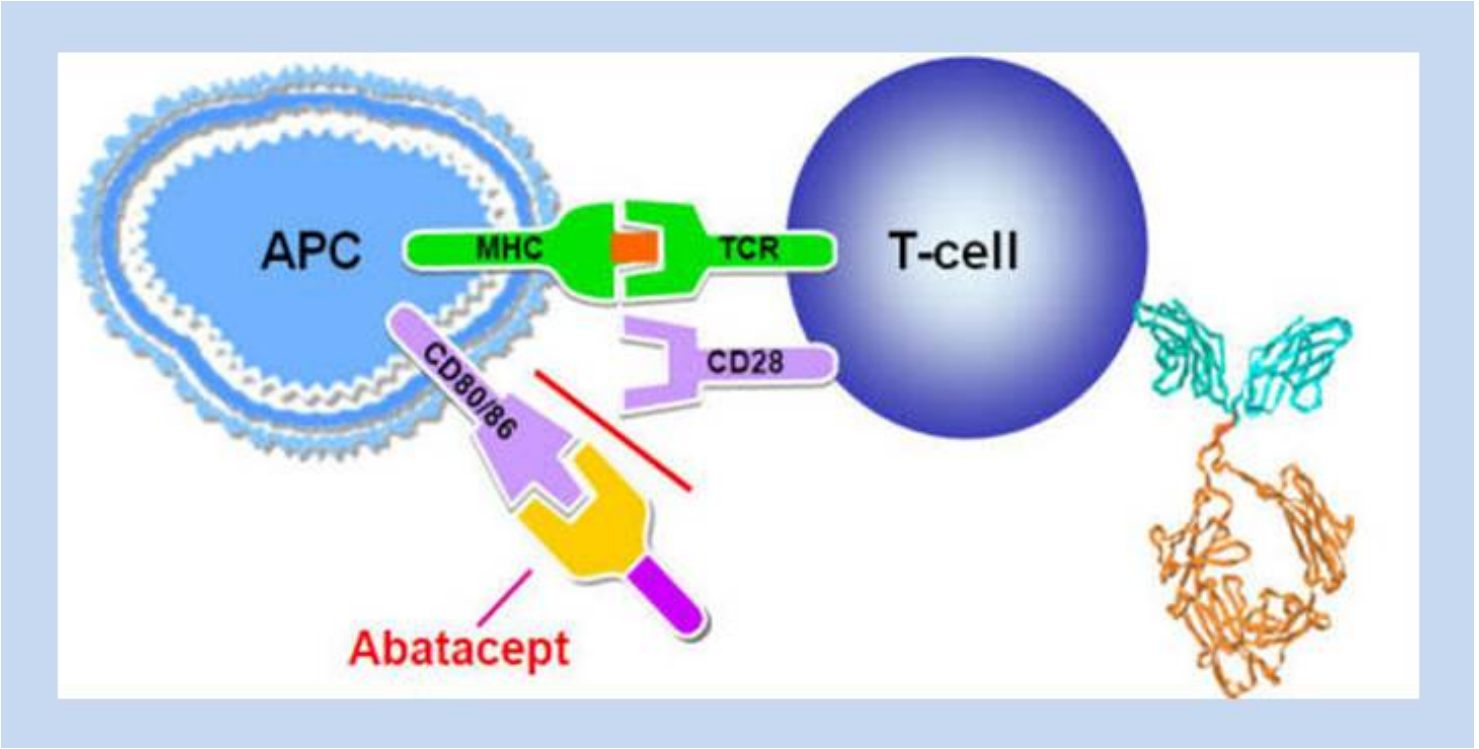


CTLA-4 pathway in rheumatologic disease

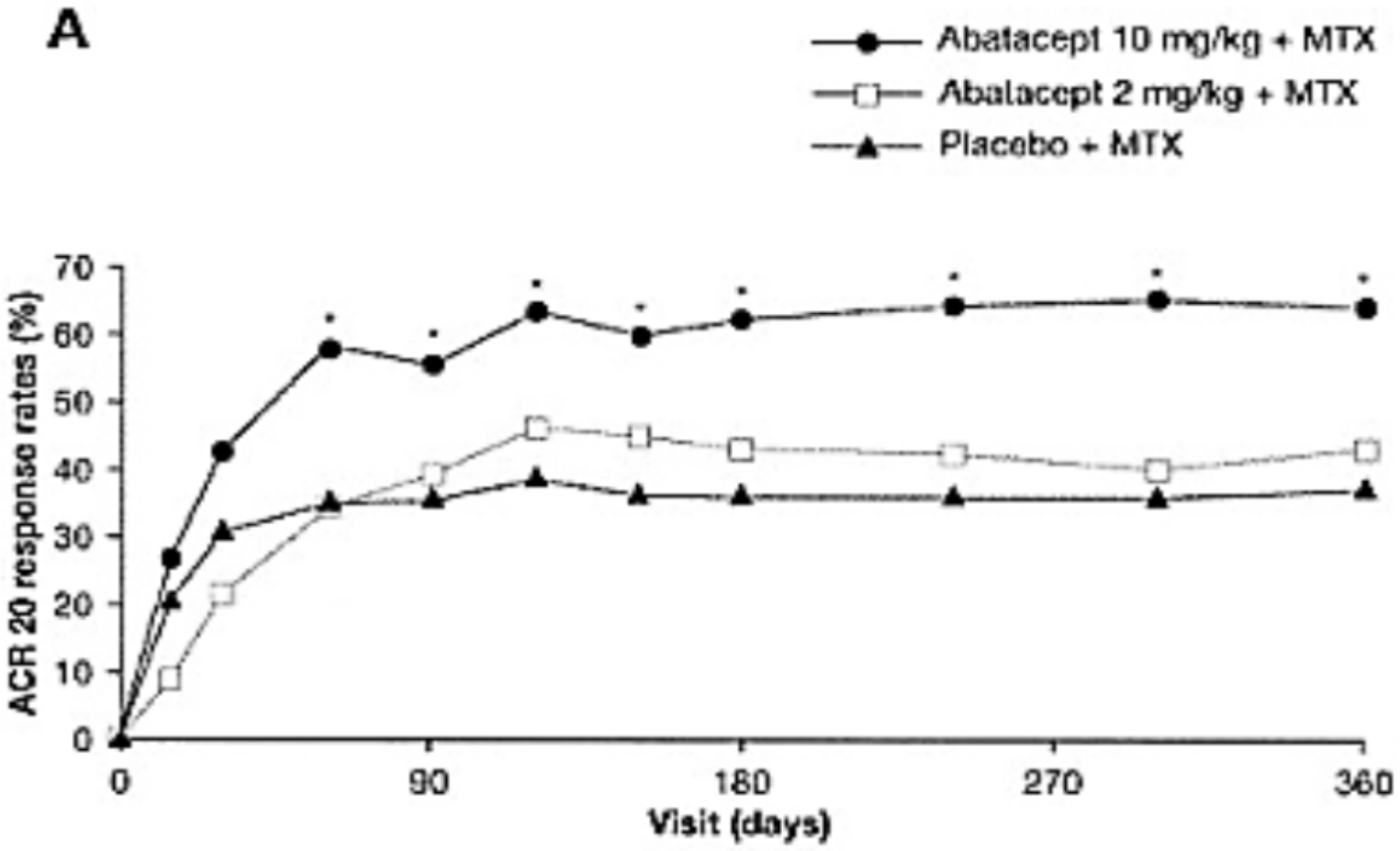
- CTLA-4 -/- mice develop auto-immune conditions
- CTLA-4 deletion results in autoimmunity
- Abatacept, a CTLA-4 agonist, is used to treat rheumatic disorders – the opposite mechanism to ipilimumab

Klocke PNAS, 2016

Abatacept: Mechanism of action



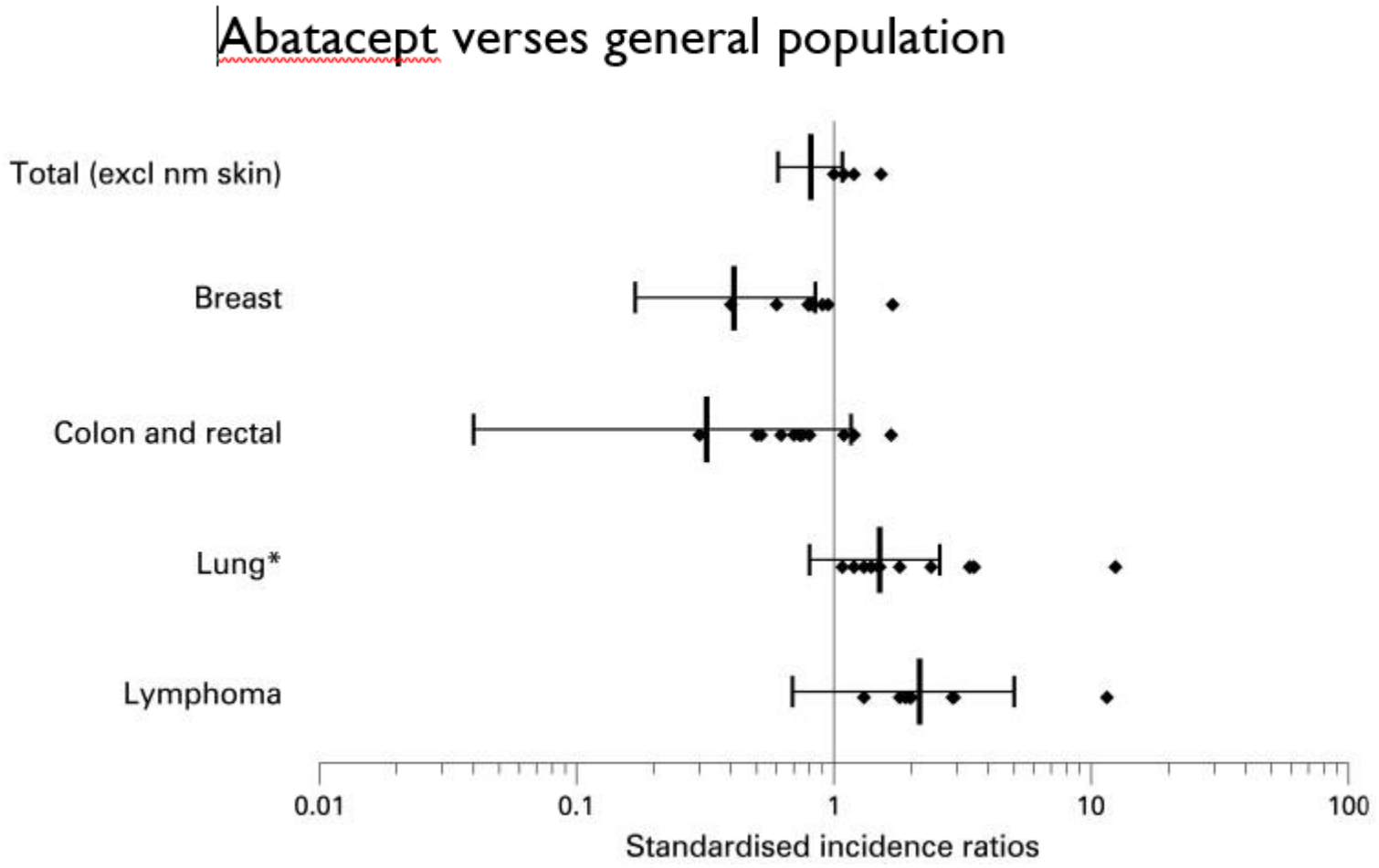
Abatacept for Rheumatoid Arthritis



 Kremer Arthritis Rheum 2005

What about the cancer risk of abatacept?

Abatacept cancer risk



 Simon Ann Rheum Dis 2009

What about the programmed cell death 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) pathway?

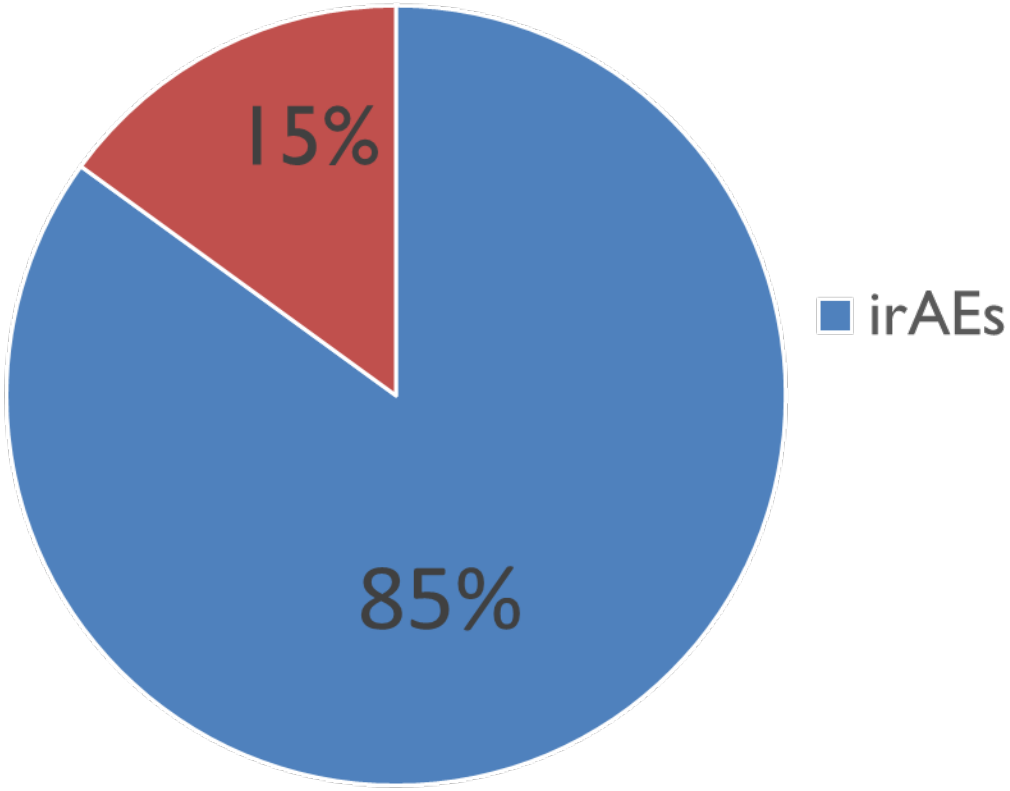
PD-1/PD-L1 in rheumatoid arthritis

- PD-1 -/- C57BL/6 mice have an increased incidence of collagen induced arthritis
- Patients with RA have increased levels of soluble PD-1 (sPD-1) their sera and synovial fluid
- sPD-1 functionally blocks the inhibitory effect of membrane bound PD-1 on T cell activation

 Raptopoulou Arthritis Rheum, 2010; Liu, Arthritis Res Ther 2015

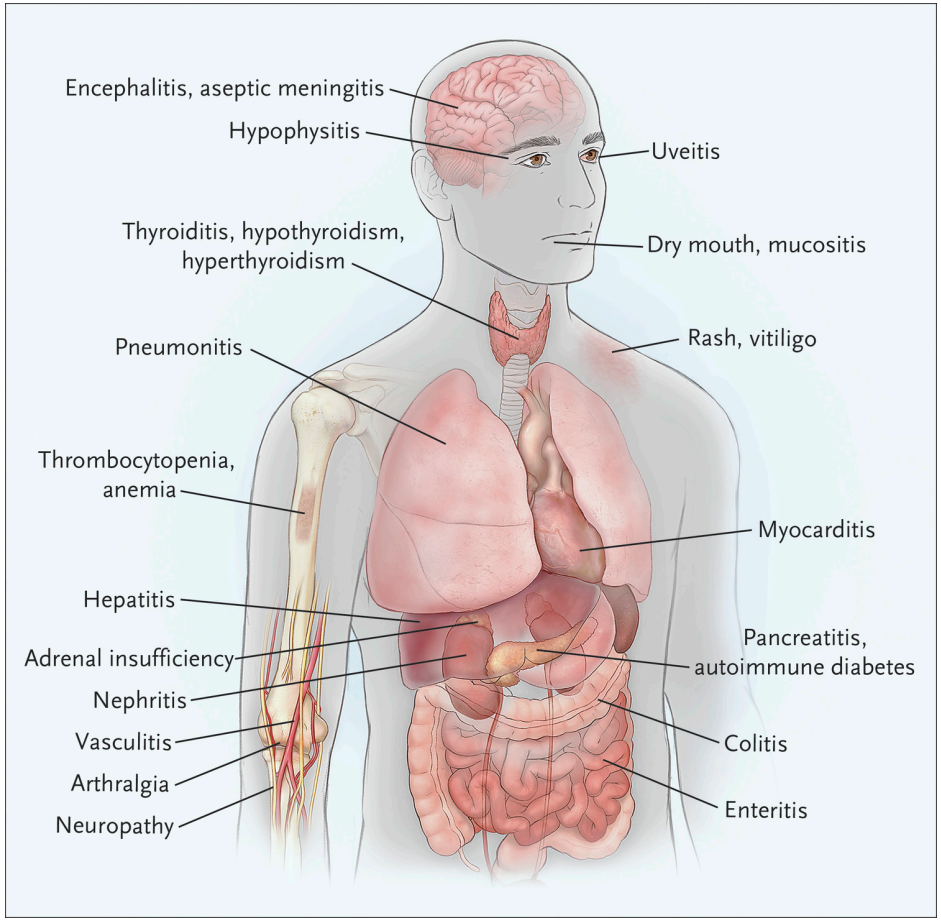
No such thing as a free lunch…

298 patients treated with ipilimumab for Melanoma



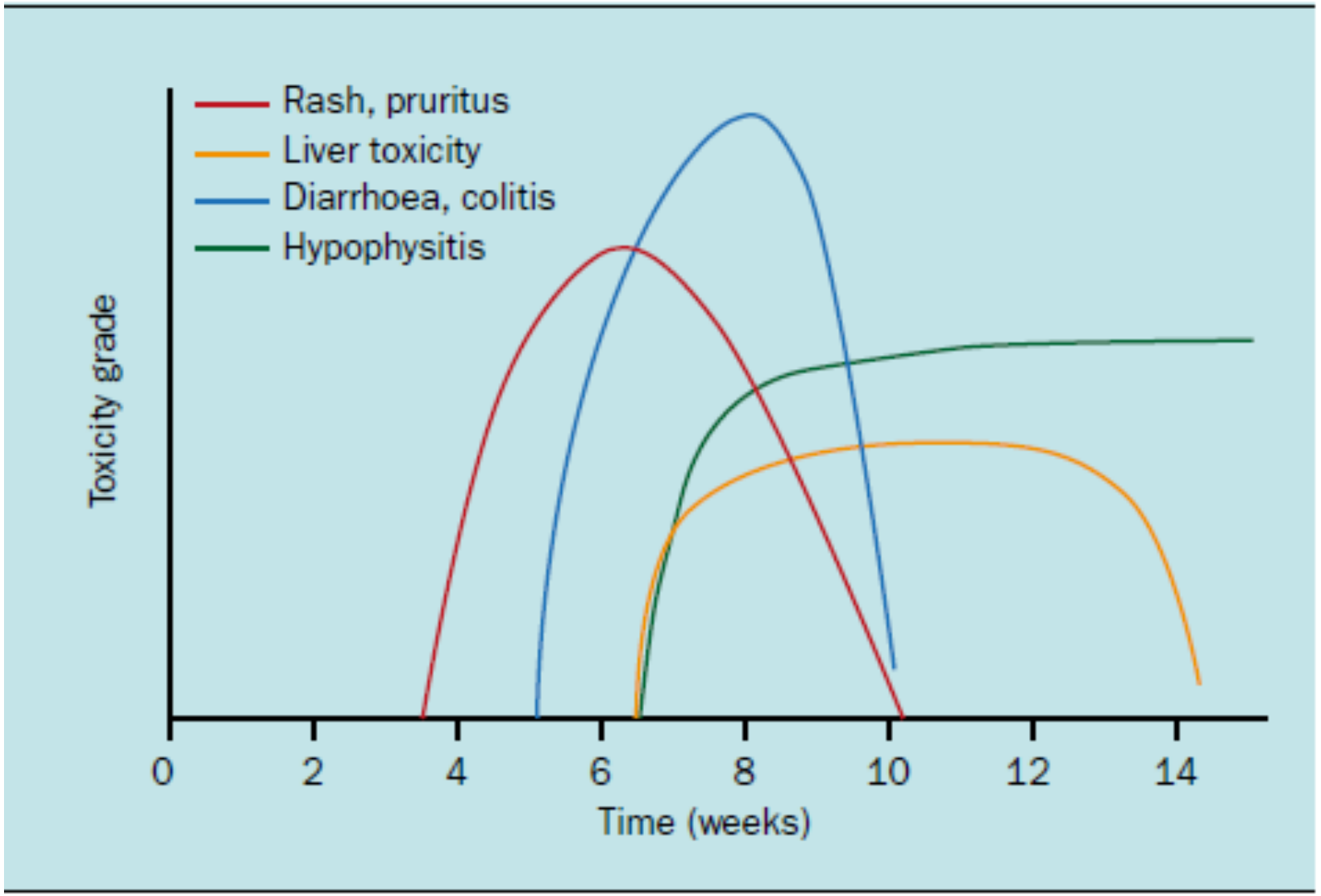
 Horvat J Clin Onc 2015

Organ involvement: irAEs



Postow NEJM, 2018

Kinetics of irAEs with ipilimumab



Weber J Clin Onc 2012

Rheumatologic immune related adverse events

Giant Cell Arteritis after Ipilimumab

A 62 year male received 5 cycles of ipilimumab. Presents with 6 weeks of headache, scalp tenderness, and jaw claudication.

- Temporal artery biopsy positive for giant cell arteritis
- Treated with high dose glucocorticoids

A 62 year old male presents with PMR like symptoms and facial swelling 10 weeks following ipilimumab treatment.

- Temporal artery biopsy positive for giant cell arteritis
- Treated with high dose glucocorticoids

17 Goldstein Arthritis Rheum 2014

PMR- like presentation after PD-1/PD-L1 blockade

- Patients treated with PD-1 and PD-L1 inhibitors
- Four cases of PMR-like presentation = pelvic girdle stiffness with elevated inflammatory markers
- Symptoms continued after discontinuation of immunotherapy
- Three patients responded well to glucocorticoids alone, one patient required methotrexate

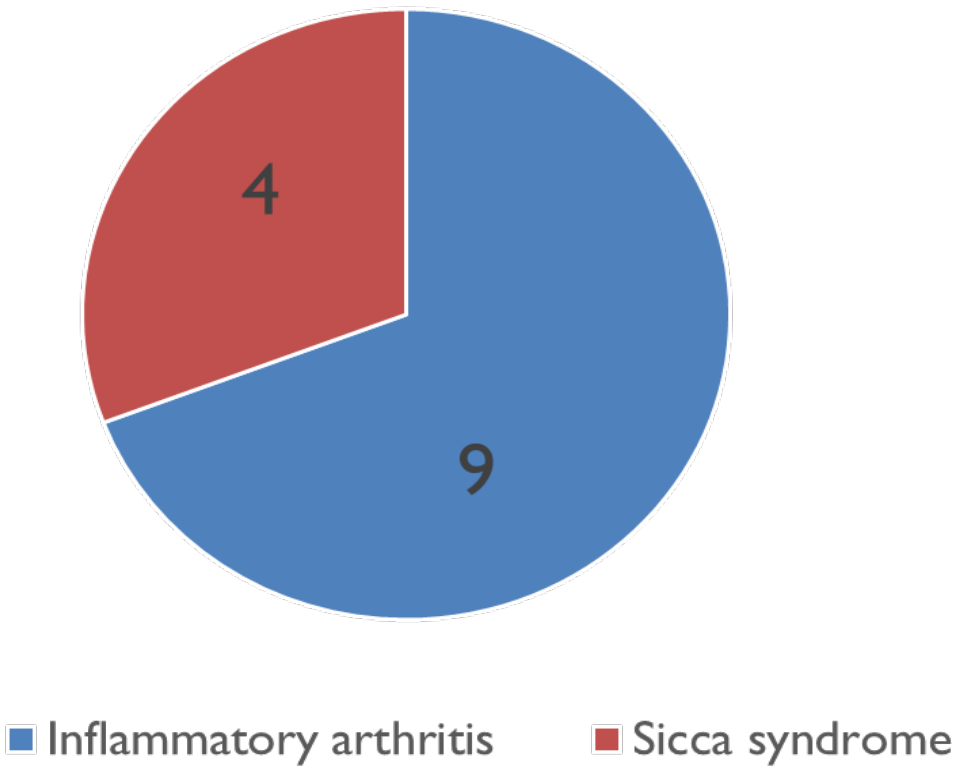
Kuswanto Sem Arthritis Rheum 2017

Johns Hopkins

- New rheumatologic symptoms in 13 patients undergoing treatment with ipilimumab (anti-CTLA-4) and/or nivolumab (anti-PD-1)
- Nivolumab and ipilimumab (N=8)
- Monotherapy (N=5)

Cappelli Ann Rheum Dis 2017

Johns Hopkins Experience



What types of arthritis ?

- Polyarthritis similar to **rheumatoid arthritis**
- **Reactive arthritis** with conjunctivitis, urethritis and oligoarthritis
- Seronegative **spondyloarthritis** with inflammatory back pain and larger joint involvement

Cappelli Ann Rheum Dis 2017

Rheumatologis irAEs

Of 524 patients receiving immune checkpoint inhibitors, 35 referred to rheumatology (6.6%)

- Rheumatoid arthritis like n=7
- Polymyalgia rheumatica n=11
- Psoriatic arthritis n=2
- Other musculoskeletal conditions n=15

 Kostine Ann Rheum Dis 2018

All that glitters is not gold…

- 62 year old man with NSCL treated with nivolumab and ipilimumab.
- Nine months into treatment he presents with right knee and left elbow pain and swelling
- Doppler of the left elbow showed synovitis and erosive changes
- Taken off immunotherapy, given an elbow steroid injection, started on prednisone 60mg/day
- Still doing poorly and CT of his elbow showed a lytic mass compatible with a metastatic lesion

 Kostine Ann Rheum Dis 2018

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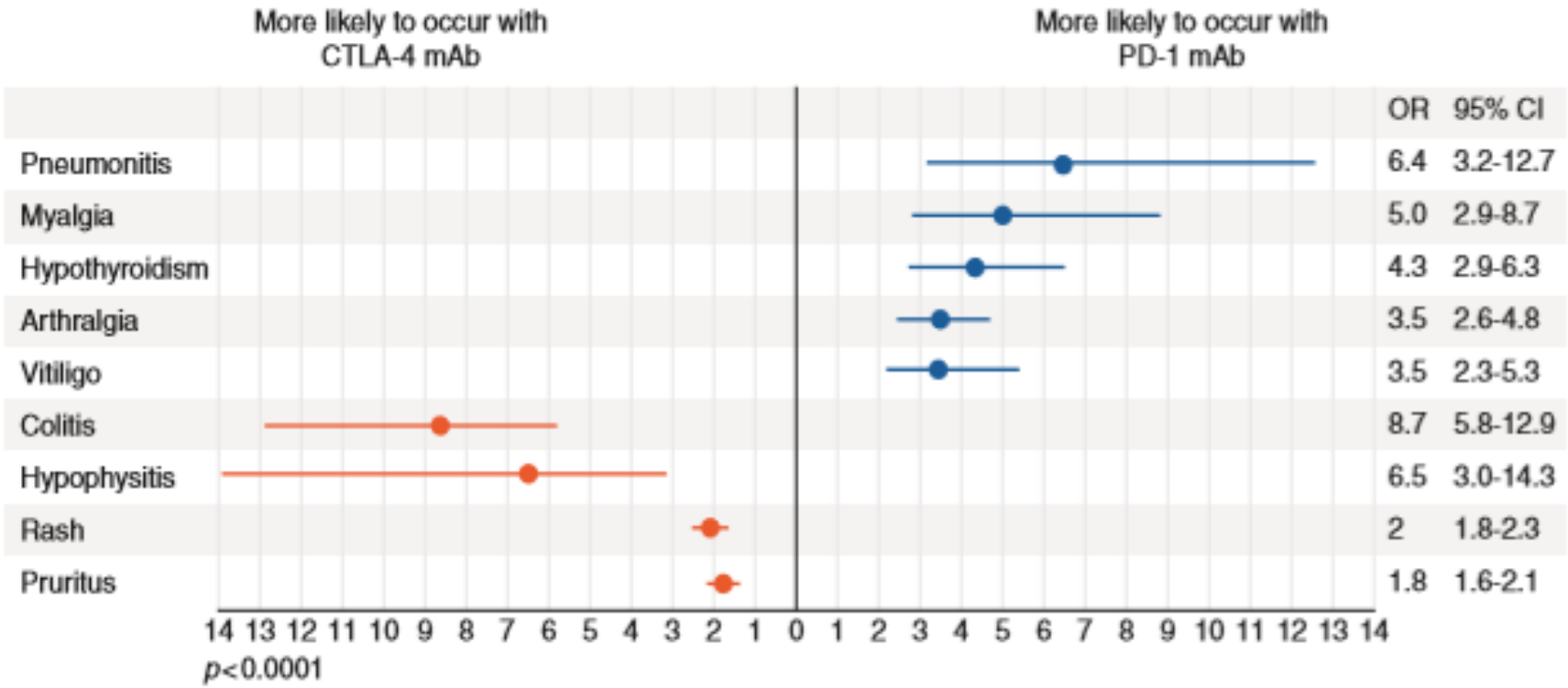
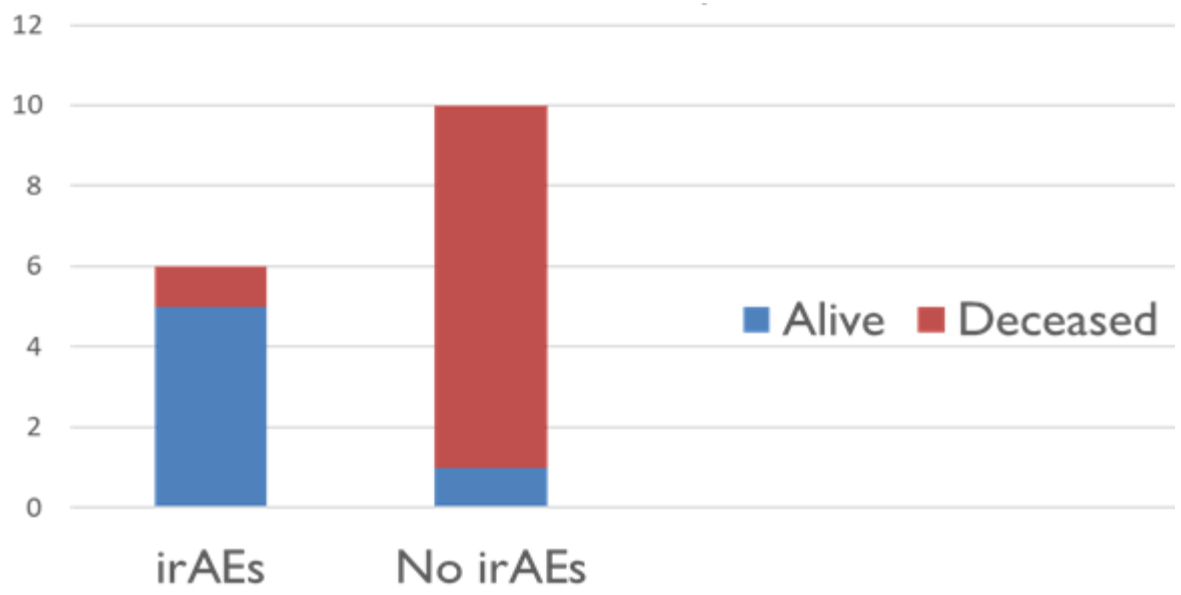
Does type of ICI determine phenotype of IRAEs?

PD-1 more likely to cause joint symptoms



 Khoja Ann Oncol 2017

Survival based on rheumatologic irAEs



26 Richter Arthritis Rheum 2018

Are rheumatologic irAEs more common in individuals with pre-existing rheumatic conditions?

16 patients with a pre-existing rheumatologic condition:

RA=5, PMR=5, Sjogren's=2, SLE=2, GCA =2

Six of these patients had an irAEs

- Colitis =3 (2 ipilimumb, 1 pembolizumab)
- One flare of the underlying GCA (Nivolumab)
- One flare of pneumonitis (Pembolizumab)
- One hypophysitis (Ipilimumab)

Richter Arthritis Rheum 2018

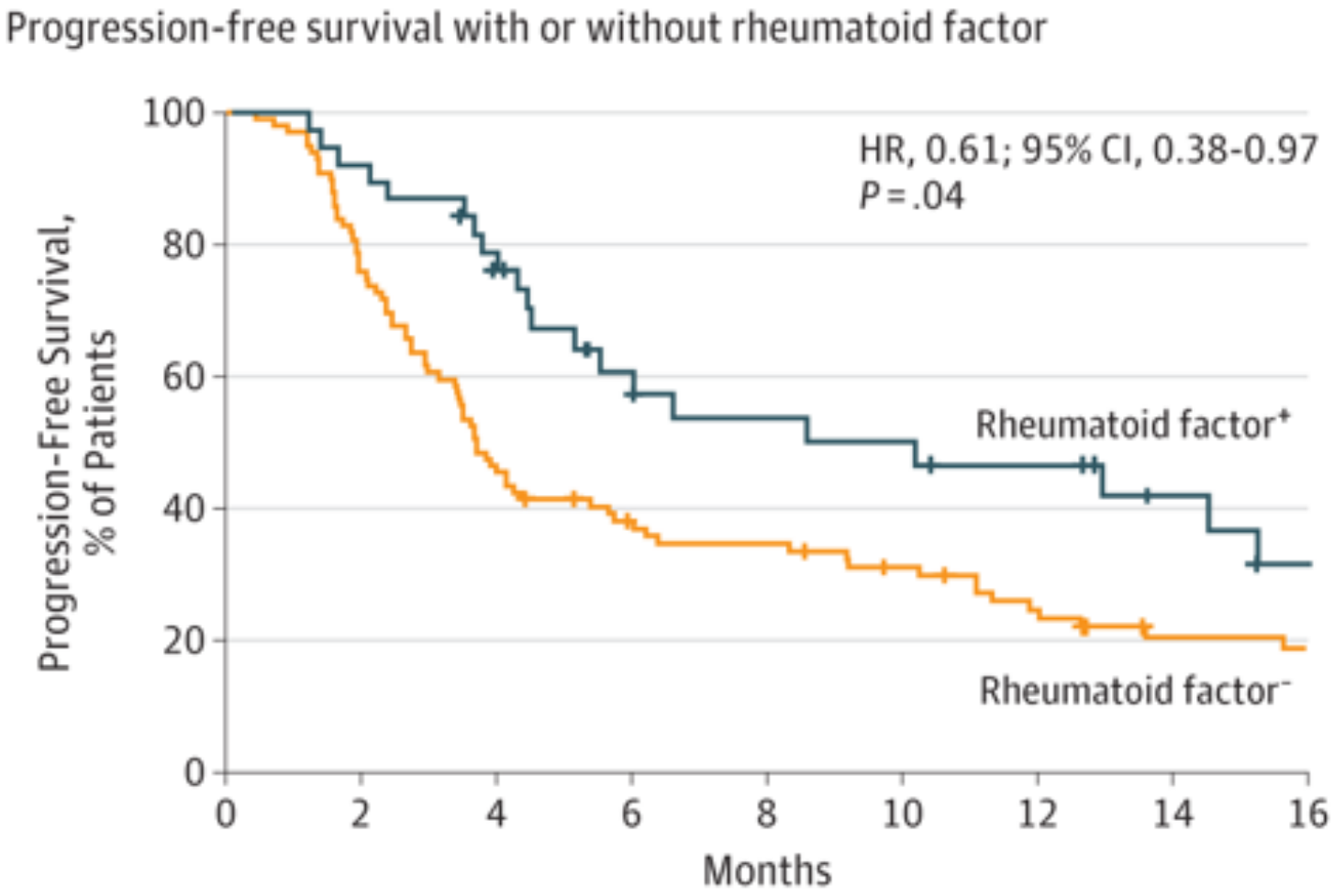
Rheumatologic irAEs in patients with pre-existing auto-immune diseases

123 patients with pre-existing autoimmune disease, 68 rheumatologic –mainly psoriatic arthritis (PsA) and RA

- 75% had exacerbation of pre-existing autoimmune disease, de novo irAEs or both
- 64% of PsA patients flared 35% of RA patients flared
- Flares more common in those receiving PD-1 or PD-L1 blockade
- De novo irAEs more common with anti-CTLA-4 therapy

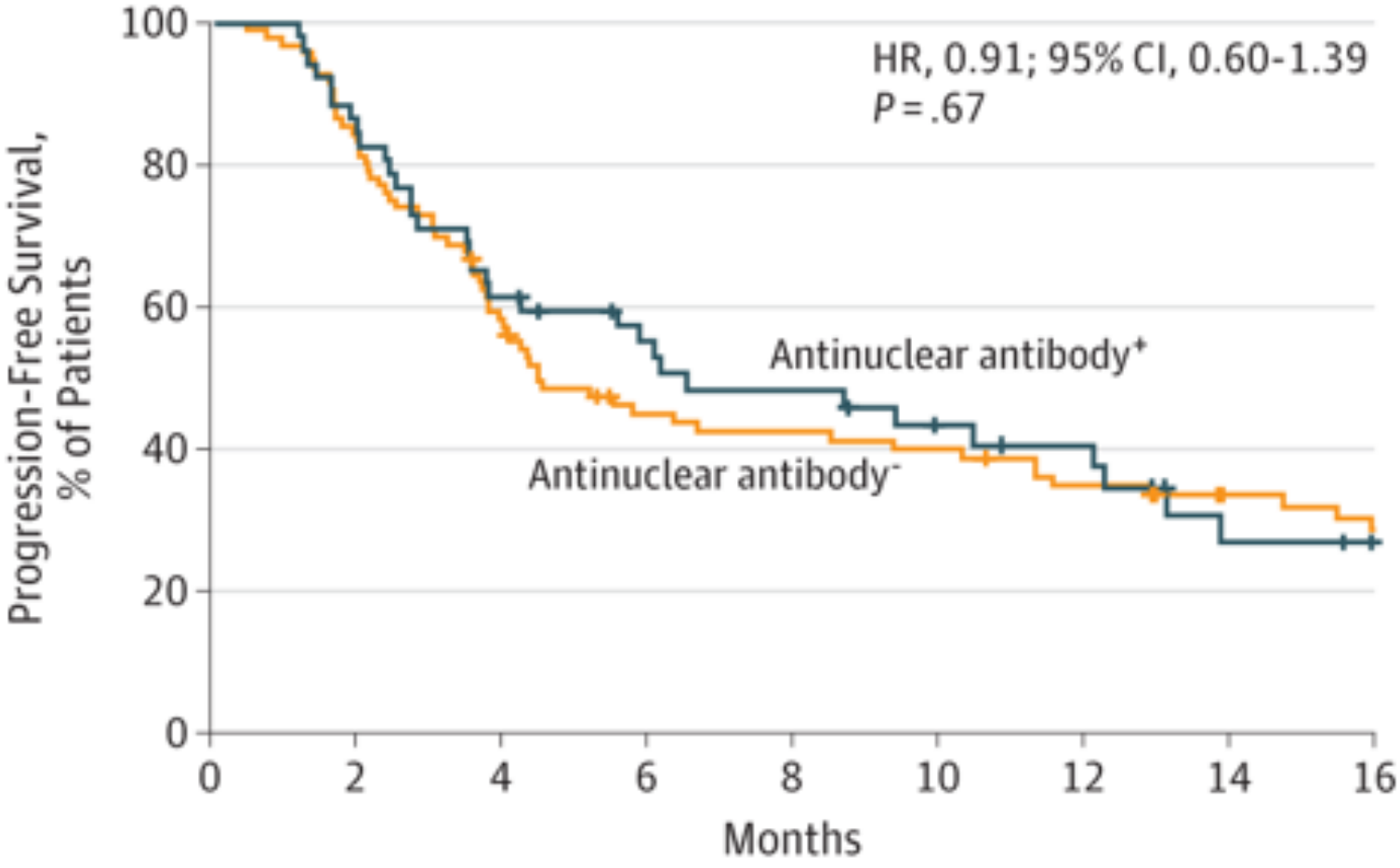
 Abdel -Wahab Ann Intern Med 2018

Survival according to baseline antibody status



29Toi JAMA Oncoloy 2018

Progression-free survival with or without antinuclear antibody



Grading of Rheumatologic irAEs

Grade 1: Mild pain with inflammatory symptoms, erythema, joint swelling

Grade 2: Moderate pain associated with signs of inflammation, joint swelling limiting instrumental ADL

Grade 3: Severe pain associated with signs of inflammation, erythema, joint swelling, irreversible joint damage (e.g. erosions) limitation in ADLs

Management of Rheumatic irAEs

Grade 1: Continue ICI, Analgesics 4-6 weeks- if ineffective prednisone 10-20mg daily -2-4 weeks, consider intra-articular corticosteroid injections

Grade 2: Consider holding IC, Rheumatology referral, assess for intra-articular steroid injection
Prednisone 20mg daily for 2-4 weeks, increase to 1mg/kg/day if no response

Grade 3: Hold ICI, Rheumatology referral, Prednisone 1mg/kg/day for 2-4 weeks, Consider additional immunosuppression if no response

Puzanov Journal ImmunoTherapy Cancer 2017

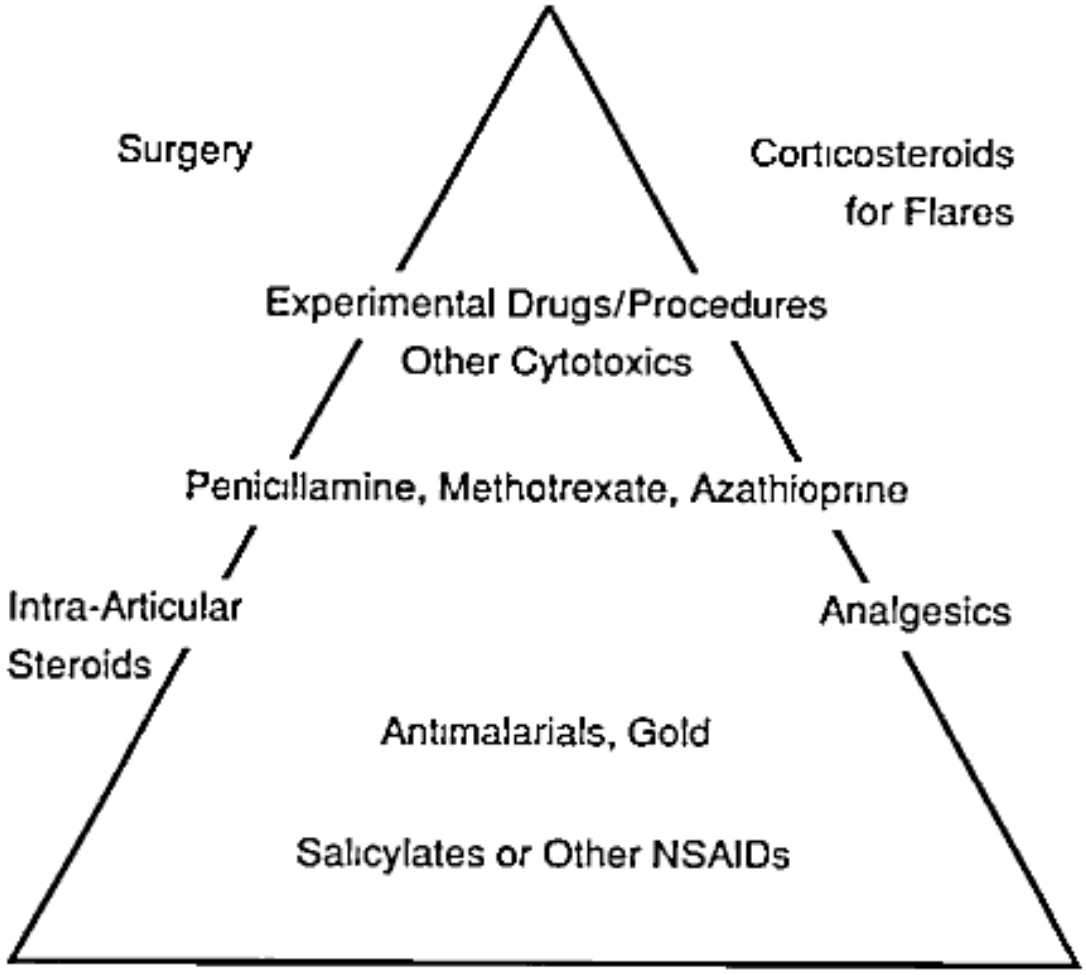
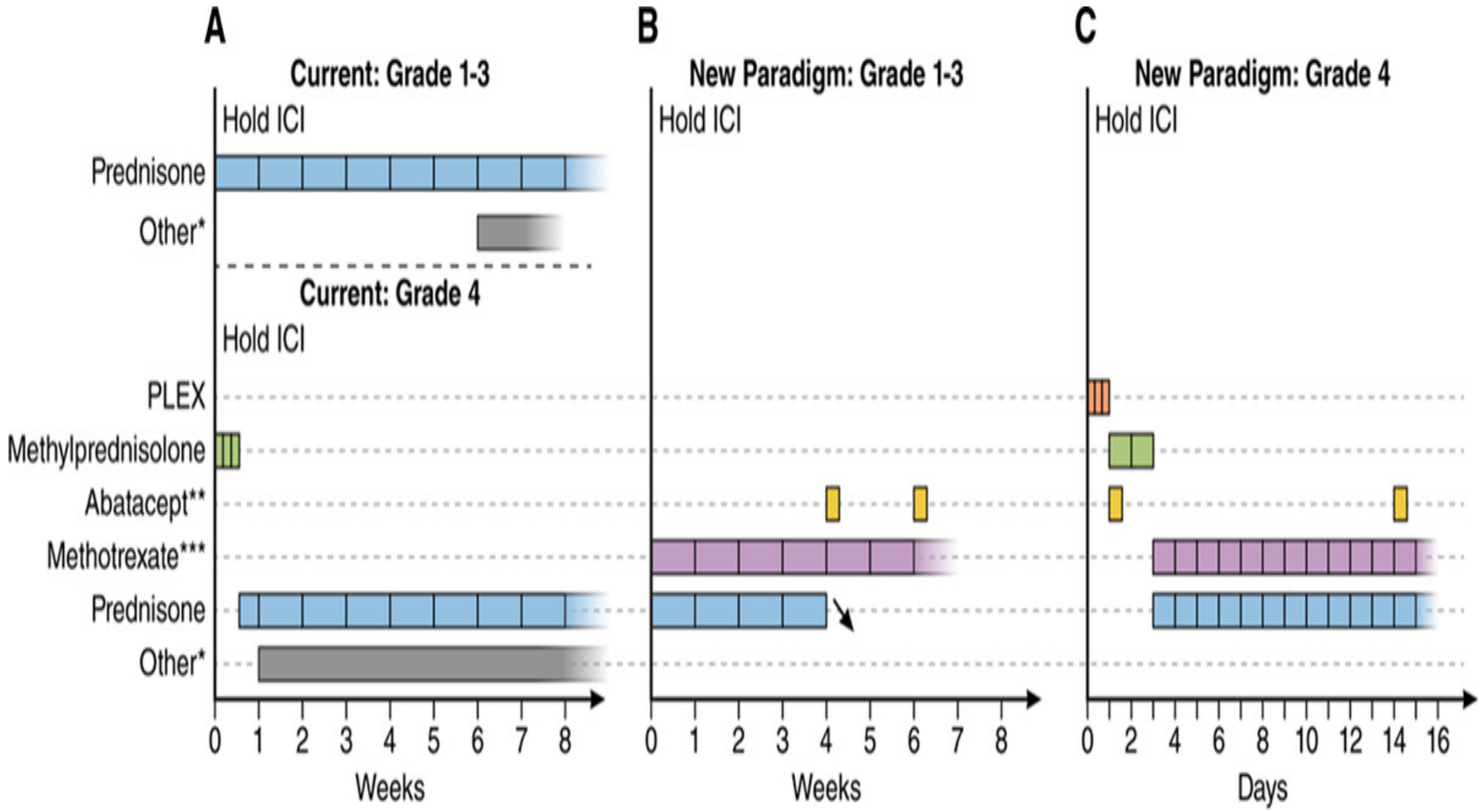


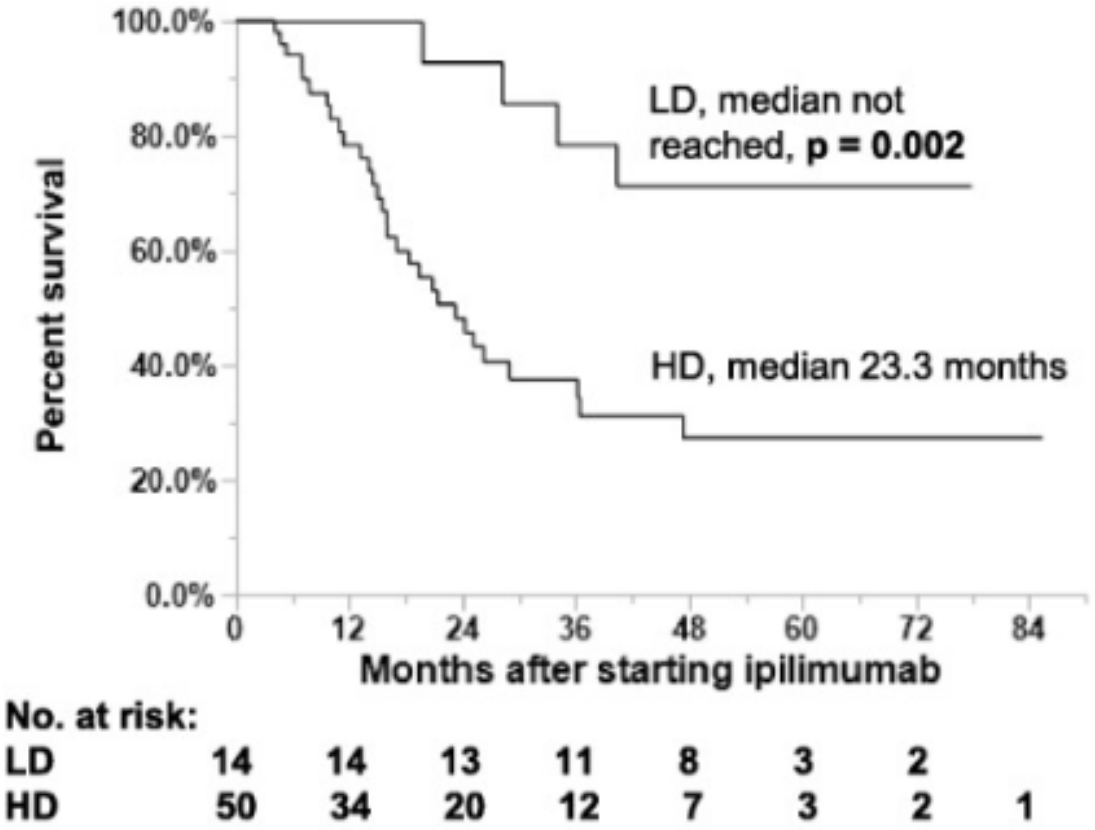
Fig 1: Treatment pyramid for rheumatoid arthritis.


A
Current: Grade 1-3
Hold ICI
Prednisone
Other*
Current: Grade 4
Hold ICI
PLEX
Methylprednisolone
Abatacept**
Methotrexate***
Prednisone
Other*
0 1 2 3 4 5 6 7 8
Weeks
B
New Paradigm: Grade 1-3
Hold ICI
0 1 2 3 4 5 6 7 8
Weeks
C
New Paradigm: Grade 4
Hold ICI
0 2 4 6 8 10 12 14 16
Days

Glucocorticoids
A rheumatologist's best friend (and foe)

- Oral and intra-articular glucocorticoids are often used to treat irAEs
- Rheumatic manifestations may require higher doses of systemic steroids than we typically use for these disorders not triggered by ICI
- Aim to get the dose of oral steroids under 10mg/day
- Remember bone health! PCP prevention!

How about glucocorticoids?



Second line therapy

- Hydroxychloroquine
- Sulfasalazine
- Leflunomide
- Methotrexate *

What about TNF-alpha blockade?

- Johns Hopkins group advocates using TNF-alpha inhibition for joint symptoms requiring higher doses or longer doses of glucocorticoids
- There are some studies in the IBD literature that advocate using TNF-alfpha blockade up front
- Others groups are concerned that TNF-alpha blockade will render the immune checkpoint inhibitor ineffective

How about tocilizumab?

- Three patients with severe polyarthritis during ICI therapy
- All successfully treated with tocilizumab
- Johns Hopkins group opposes to IL-6 blockade because of the increase risk of colonic perforation with these therapies

 Kim, Ann Rheum Dis 2017

Can we predict which patients will get which irAEs?

HLA-DRB1 shared epitope alleles and ICI-IA

HLA allele/s	Odds ratio ICI-induced inflammatory arthritis vs. controls	P-value
DRB1*04:05	8.6	0.04
1 or > SE allele	2.3	0.04

Cappelli Rheumatology 2019

Conclusions

- Immune checkpoint inhibitors have revolutionized cancer therapy
- ICI are associated with immune related adverse events (irAEs)
- Rheumatologic irAEs occur in about 6% of patients
  - PMR like symptoms
  - Inflammatory arthritis (oligo, reactive, symmetric)
  - Sicca symptoms
- irAEs portend better response to ICI therapy
- Before starting ICI- take a rheumatology [endocrine, gi, pulmonary, dermatology] history ? check auto-antibodies
- Check ESR and c-reactive protein

Conclusions

- Most patients can be treated for their rheumatologic symptoms and continue their ICI therapy.
- First line therapy consists of NSAIDs and glucocorticoids
- DMARDs (methotrexate, hydroxcyhloroquine, SSA, biologics-tnf alfa blockers and tocilizumab) can be used to manage irAEs.
- In the future we may be able to predict which patients will respond to which ICI, and which patients will get which irAEs.
- Great opportunity for multi-disciplinary collaboration and to care for patients

Thank you!

Case

- 68 year old woman w/ RCC
- Treated with PD-1 blocker
- Three months into therapy presents with swelling in the joints of her hands
- ESR and c-reactive protein are elevated

- ICI therapy discontinued
- Started on prednisone 60mg a day
- Rheumatology referral made
- Rheumatology reduced prednisone to 20mg a day
- Rheumatology attempt to taper the prednisone to <10mg a day over one month but the patient had increased hand pain and swelling
- Methotrexate 15mg a week added and the patient improved. Prednisone able to be tapered to off and ICI resumed