Update in Internal Medicine
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UT Southwestern Medical Center

Rheumatologic adverse events of immune checkpoint inhibitors.

Luigino Bernabela, M.D., RhMSUS.
Assistant Professor
Division of Rheumatic Diseases

Overview

- How do immune checkpoint inhibitors work?
- Review rheumatologic immune related adverse events (Rh-irAEs)
- Management of Rh-irAEs

Case

Immune checkpoint inhibitors (ICIs) opened a new chapter in cancer therapeutics

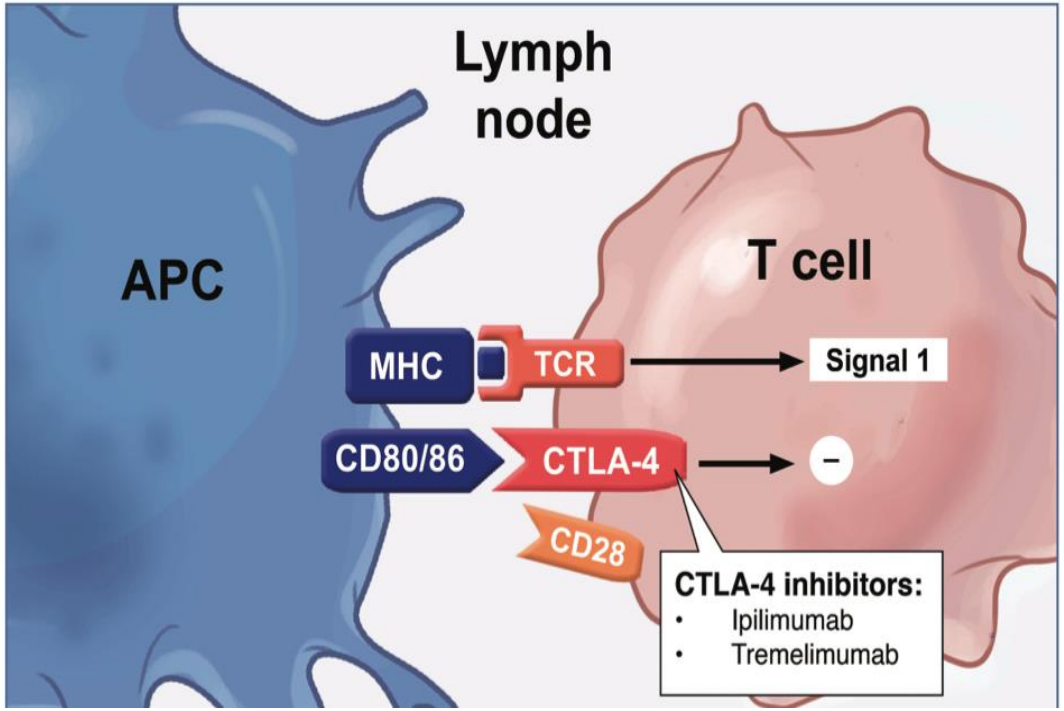
James Allison PhD and Tasuku Honjo MD, PhD 2018 Nobel Prize in Medicine and Physiology

Mechanisms of Immune checkpoint inhibitors

CTLA-4 mediates inhibition in the central lymphoid compartment.
CTLA-4 modulates the immune response by:

- Preferentially binding CD80/86 proteins on APCs,
- Preventing the binding of CD28 (2nd signal needed for T cell activation), and
- Inhibiting T cell activation.

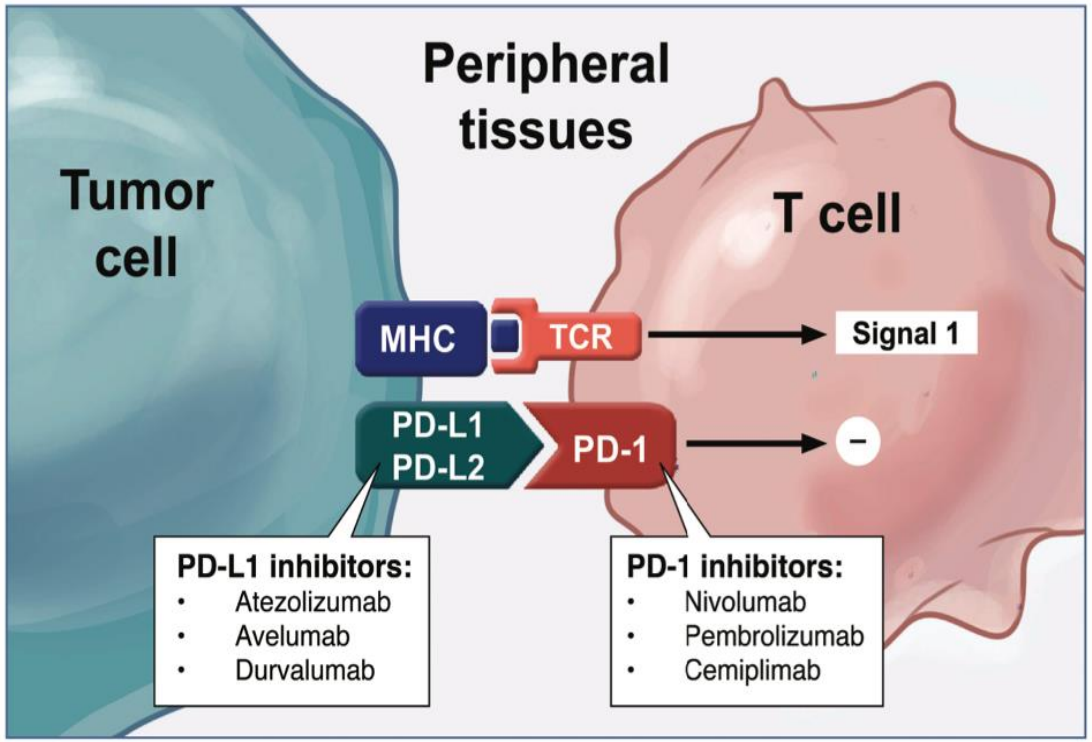
Antibodies that block CTLA-4 can lead to ongoing T cell activation. These T cells can then migrate to the peripheral tissues and attack tumor cells.



PD-1 mainly exerts its inhibitory effect on T cells in peripheral tissues.
The binding of PD-1 on T cells to PD-L1/PD-L2 on tumor cells can lead to:

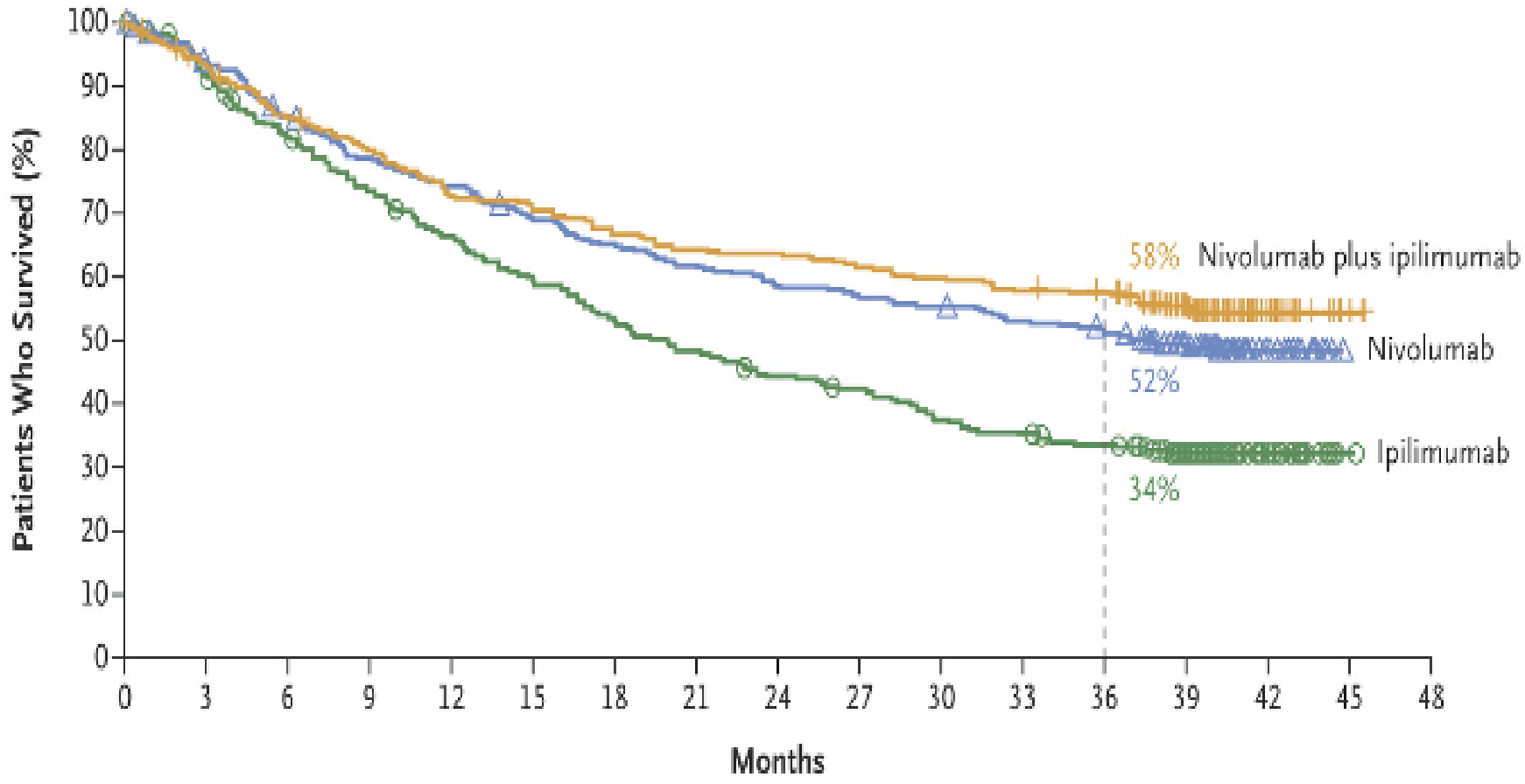
- Inhibition of downstream signalling,
- Suppression of T cell function, and
- T cell exhaustion.

Antibodies that block PD-1, PD-L1, and PD-L2 can restore T cell effector function for reactivated anti-tumor response.



Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018 Jan 11;378(2):158-168.

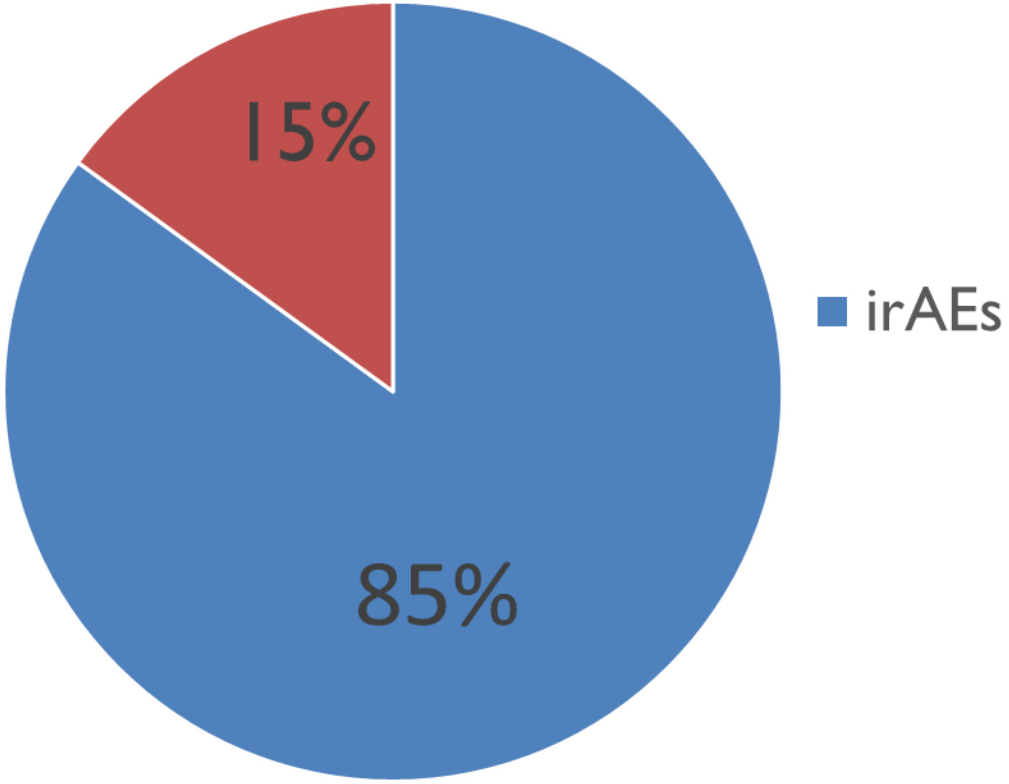
Overall survival with PD-1 blockade in advanced melanoma



Wolchok JD, Rollin L, Larkin J. Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2013 Dec 21;377(25):2503-2504.

No such thing as free lunch….

298 patients treated with ipilimumab for Melanoma



Horvat TZ et al, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol. 2015 Oct 1;33(28):3193-8

Immune related Adverse events

Dermatologic

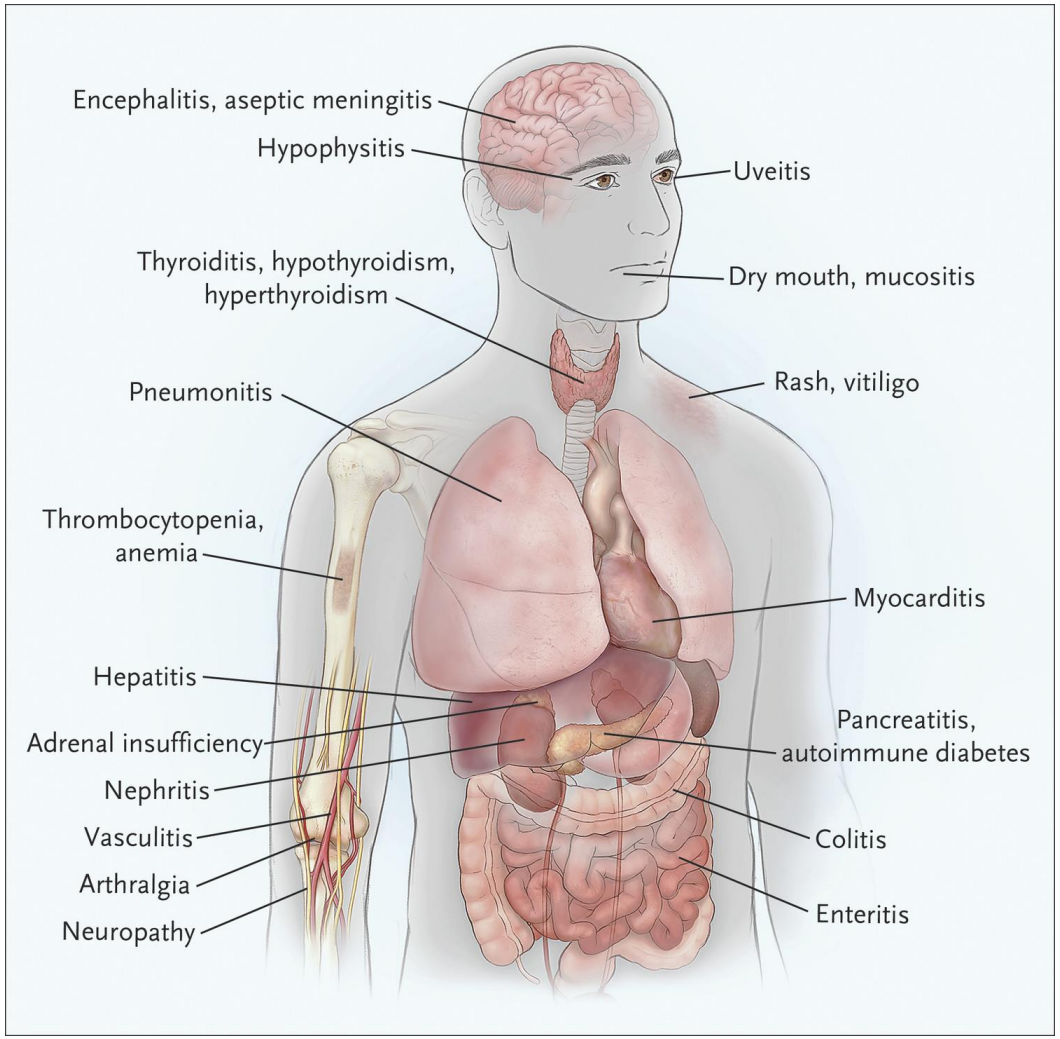
- Vitiligo
- DRESS
- Maculopapular rash

Gastrointestinal

- Colitis
- Hepatitis

Endocrine

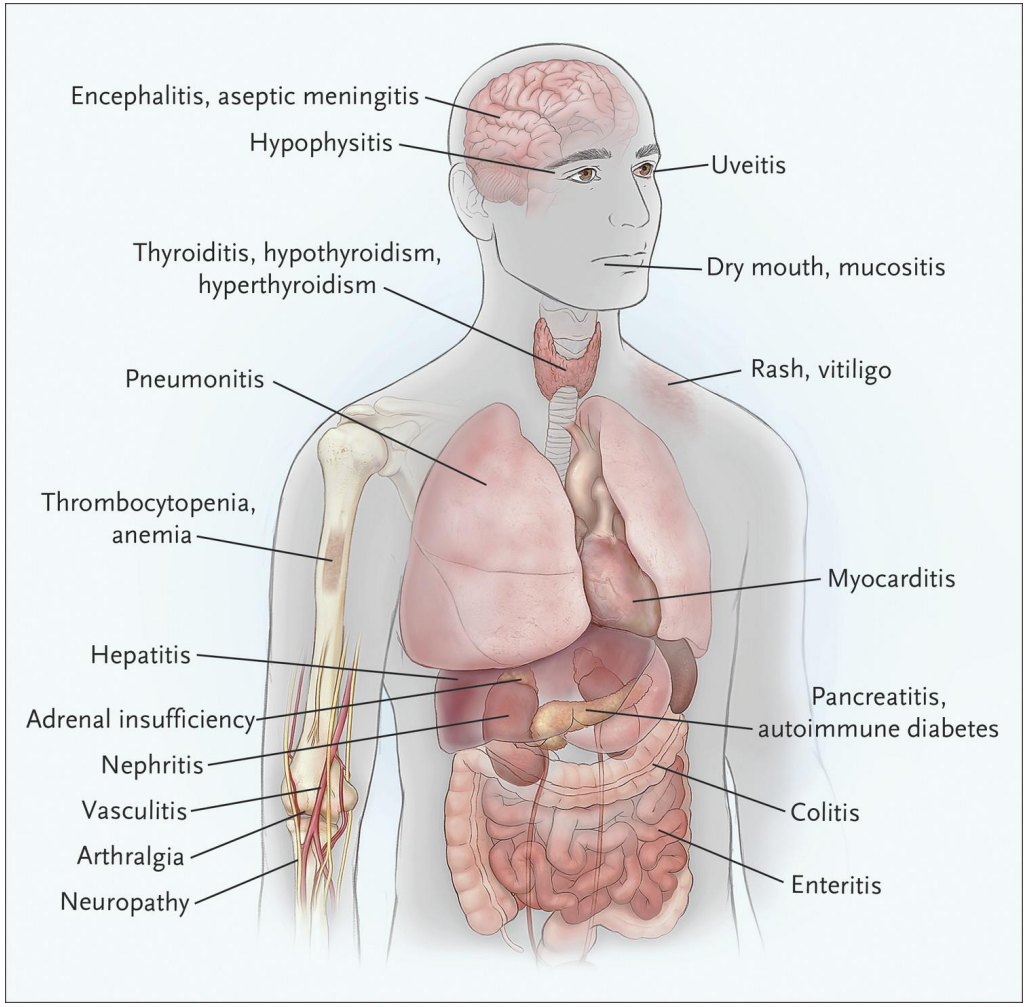
- Hypophysitis
- Hypothyroidism/Hyperthyroidism
- Type -1 Diabetes



Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018 Jan 11;378(2):158-168.

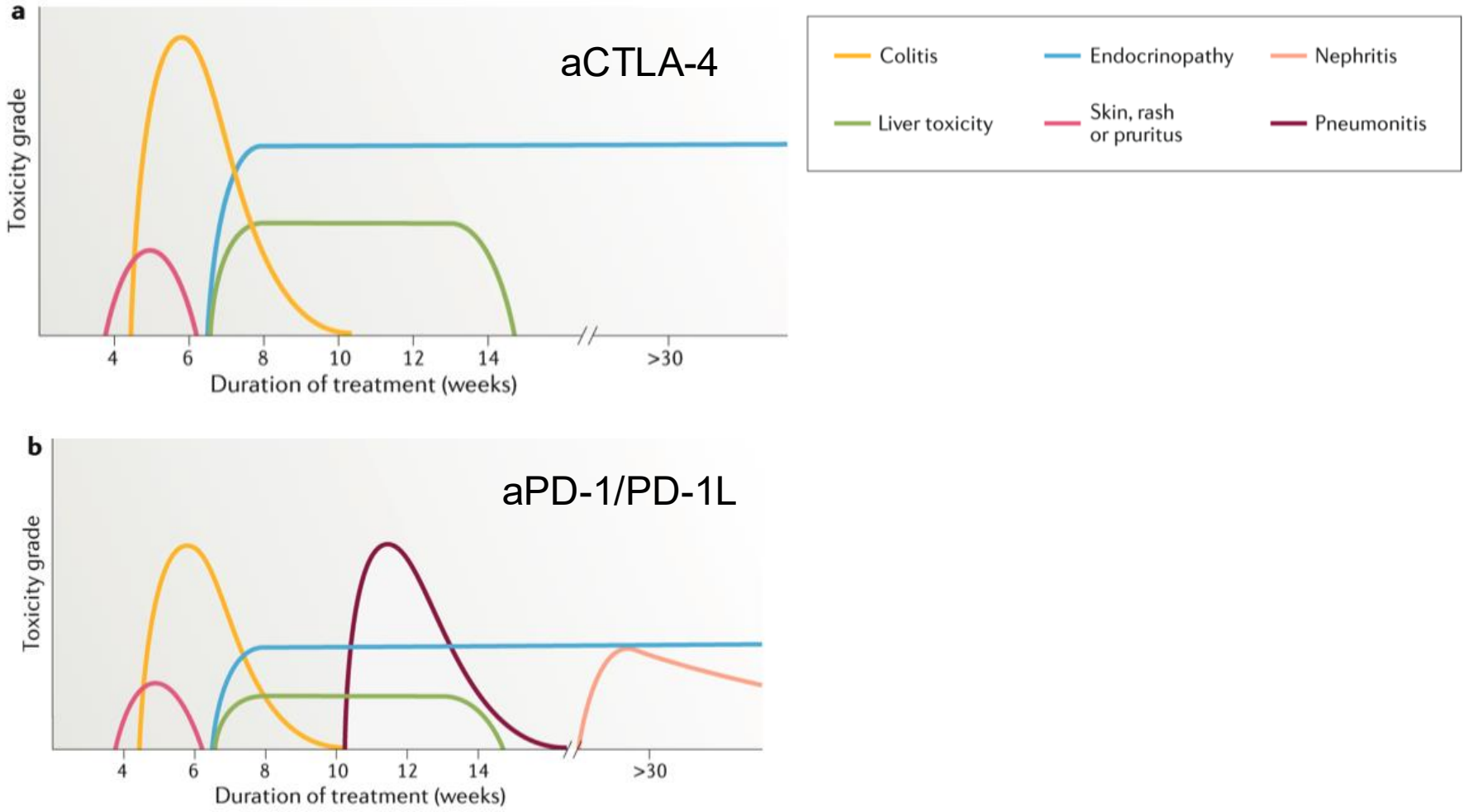
Immune related Adverse events

- Pulmonary
  - Pneumonitis
  - Sarcoid
- Other
  - Myocarditis
  - Myelitis
  - Guillain –Barre
  - Nephritis
- Rheumatologic ~5-6%
  - Inflammatory arthritis, PMR, Myositis, SLE, SICCA



Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018 Jan 11;378(2):158-168.

Kinetics Immune related Adverse events



Martins, F. *et al.* Adverse effects of immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 16, 563–580 (2019)

Rh-Immune related Adverse events

1) Inflammatory arthritis (RA), arthralgia/myalgia

2) Polymyalgia Rheumatica

-Myositis

-SICCA

-Vasculitis

<u>Distinct characteristics of Rh-irAEs</u>

- Most associated with aPD-1/PD-1L inhibitors or aPD-1 +aCTLA-4 combination therapy
- Typically, autoantibodies absent
- Late onset (>10 weeks), but chronic
- Can develop after cessation of ICIs
- Often need longer period of prednisone and/or steroid sparing agents

Presentation Title

- Polyarthritis similar to **Rheumatoid arthritis**
- **Polymyalgia Rheumatica-** Hip and shoulder stiffness
- **Seronegative spondylarthritis** with inflammatory back pain and larger joint involvement
- **Reactive arthritis**, large joints with and urinary symptoms.

Cappelli LC, et al Inflammatory arthritis differs by immunotherapy regimen. Semin Arthritis Rheum. 2018 Dec;48(3):553-557.

Inflammatory arthritis

Incidence ~ 2-4%

Rheumatoid arthritis phenotype like

ANA, RF, anti-CCP negative

>6 wks of ICI treatment, as late as 2 yrs after ICIs

Persistence of symptoms >3 months ICI cessation

Table 2
Treatment requirements for IA and outcomes

Variable	All patients (n = 32)	PD-1/PD-L1 monotherapy (n = 18)	Combination CTLA-4/ PD-1 therapy (n = 14)	p Value[a]
Required systemic corticosteroids: N (%)	24 (80%)	11 (68.9%)	13 (92.9%)	0.18
Maximum dose of steroids for IA[b]: median (IQR) N = 23	40 (20–60)	40 (20–40)	40 (20–60)	0.32
Required additional immunosuppression: N (%)	10 (33.3%)	2 (12.5%)	8 (57.1%)	**0.02**
Type of additional immunosuppression[c]: N (%) Total, N = 10	TNF-inhibitor: 7 MTX: 3	TNF-inhibitor: 0 MTX: 2	TNF-inhibitor: 7 MTX: 1	0.07
Persistence of symptoms > 3 months after ICI cessation Total, N = 21	18 (85.7%)	8 (72.7%)	10 (100%)	0.21

Cappelli LC, et al Inflammatory arthritis differs by immunotherapy regimen. Semin Arthritis Rheum. 2018 Dec;48(3):553-557.

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Inflammatory arthritis

	Traditional Rheumatoid arthritis	ICI-associated Rheumatoid arthritis
Epidemiology	0.5-1% of general patient population Female-to-Male ratio of 3:1	2-4% of cancer patient population receiving checkpoint inhibitors Even Female-to-Male ratio of distribution
Onset of arthritis	Incidence 30-50yrs	Time from ICI exposure to development from IA ranges from days to years.
Genetics	Presence of HLA-DRB1 shared epitope	No strong association with HLA-DRB1 shared epitope
Risk factors	Periodontal disease Smoking	Combination anti-CTLA4/anti-PD1 or PD-L1 > anti-PD1 monotherapy. Duration of ICI therapy Presence of other IrAEs
Articular disease	Small symmetrical arthritis (MCPs, PIPs, wrist). Large joint involvement Tenosynovitis	Small symmetrical arthritis (MCPs, PIPs, wrist). Large joint involvement Tenosynovitis
Extra-articular disease	Nodules Interstitial Lung disease Scleritis/Episcleritis.	Other organ manifestation are likely irAEs in setting of checkpoint inhibitor use
Radiographs	Erosions are common	Erosions are not so common.
Prognosis	Chronic disease requiring immunosuppression. Poor outcomes in untreated disease	Self-limiting but persistent arthritis is common. Can be disabling if left untreated.

Bernabela L, Bermas B. Immune Checkpoint Inhibitor Associated Rheumatoid Arthritis. Curr Rheumatol Rep. 2024 Nov 26;27(1):3.

Inflammatory arthritis

60 year-old man with RCC treated with a PD-1 inhibitor

de Velasco G, Bermas B, Choueiri TK. Autoimmune Arthropathy and Uveitis as Complications of Programmed Death 1 Inhibitor Treatment. Arthritis Rheumatol. 2016 Feb;68(2):556-7.

Polymyalgia Rheumatica

Typical phenotype, hip and shoulder girdle pain and stiffness. ~1%

Elevated CRP and ESR

ANA, RF, anti-CCP negative, normal CPK.

Persistence of symptoms >3 months ICI cessation

More associated with anti-PD-1/PD-L1 antibodies

Prednisone 10-20mg a day for 4 weeks, DMARDs, IL-6 antagonist

Table 2 Characteristics of patients with PMR after ICI treatment for cancer

Patients	Sex/age, years	Type of cancer	ICI	Date of first ICI exposure	Date of IrAE	Type of rheumatic IrAE	IrAE response to treatment	Autoantibody results	Tumour response
7	F 76	Mesothelioma	Anti-PDL1	June 2014	March 2015	PMR	Resolution with prednisone 20 mg/day then tapered	ANA, RF, CCP negative	Progression switch for pemetrexed
8	M 69	Gastric adenocarcinoma	Pembrolizumab	September 2016	October 2016	PMR	Resolution with prednisone 20 mg/day then tapered	ANA, RF, CCP negative	Progression
9	M 62	Colon adenocarcinoma	Nivolumab+ipilimumab (four cycles) then nivolumab alone	June 2015	October 2015	PMR	Resolution with prednisone 60 mg/day then tapered	ANA 1:320 with anti-ENA negative, RF, CCP negative	Stable disease
10	M 68	Metastatic melanoma	Nivolumab	August 2016	August 2016	PMR	Resolution with prednisone 40 mg/day then tapered	RF, CCP negative	Stable disease

Belkhir R, Burel SL, et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. Ann Rheum Dis. 2017 Oct;76(10):1747-1750

Giant Cell Arteritis

Incidence <1%

Organ threatening disease

Cases > 6 weeks of ICIs

Typical features: headache, scalp tenderness, and jaw claudication.

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

Goldstein, B.L.; Gedmintas, L.; Todd, D.J. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. Arthritis Rheumatol. 2014, 66, 768–769

Myositis

Incidence < 1%

Elevated CPK >1000, Elevated troponins (myocarditis)

High mortality risk (up to 22%)

Early in ICI treatment course, ~ 4 wks. Contrast to Inflammatory arthritis (late)

aCTLA and aPD-1/aPD-1L

Older patients (Average age ~ 70s)

Unlike PM/DM, ICI-induced myositis often presents with ptosis and ocular motility disorders as initial symptoms.

Myasthenia gravis Overlap

Autoantibodies, myositis panel negative

Treatment

Prednisone 1 mg/kg and consider methylprednisolone 1–2 mg/kg or a high-dose bolus. Plasma exchange therapy and/or intravenous immunoglobulin therapy. ICIs avoided with cardiac involvement. DMARDs

Hamada, N.Incidence and Distinct Features of Immune Checkpoint Inhibitor-Related Myositis From Idiopathic Inflammatory Myositis: A Single-Center Experience With Systematic Literature Review and Meta-Analysis. Front. Immunol. 2021, 12, 803410.

Sjogren-like Sicca Syndrome

Incidence ~ 1%

Typically, abrupt in onset ~ 10 wks.

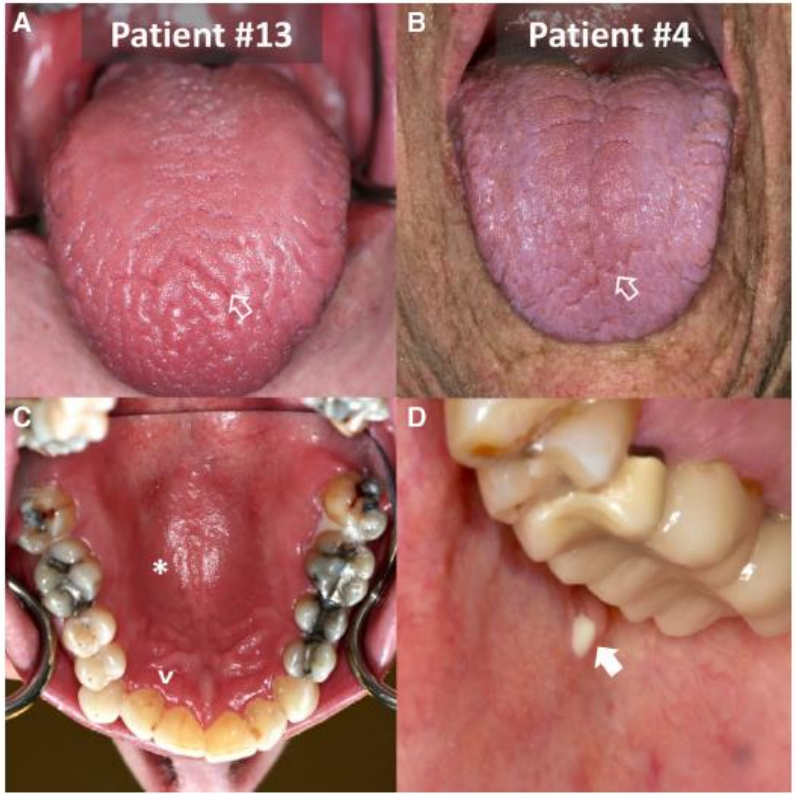
Dry mouth. Patients drink water to chew and swallow dry foods

Dry Eyes

Salivary gland biopsy

SSA, SSB antibodies absent

Symptoms often persist



<u>Treatment</u>

Corticosteroids help symptom only

Warner BM, Cappelli L, Alevizos I. Sicca Syndrome Associated with Immune Checkpoint Inhibitor Therapy. Oncologist. 2019 Sep;24(9):1259-1269

Uncommon Rheumatologic irAEs

Dermatomyositis

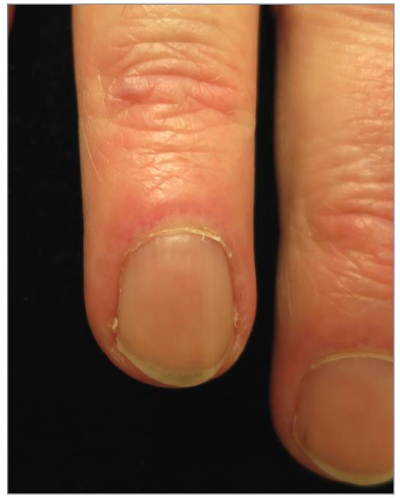
Psoriasis like rash

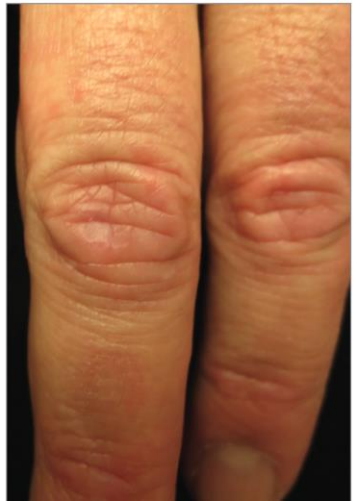
Scleroderma-like skin thickening.

Lupus-like disease

Vasculitis (eGPA, IgA vasculitis, LCV)

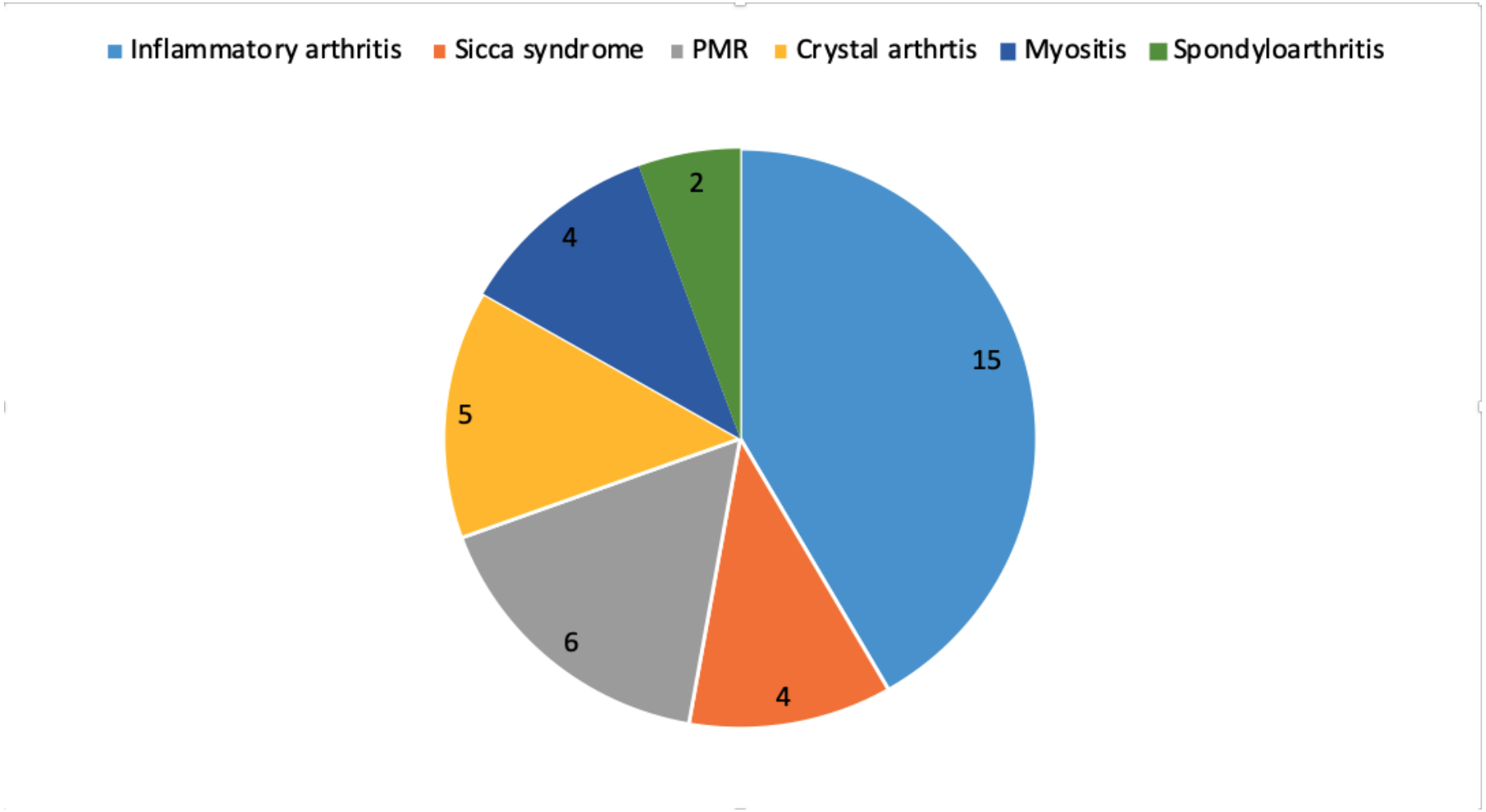
Recurrent Tenosynovitis (trigger finger)



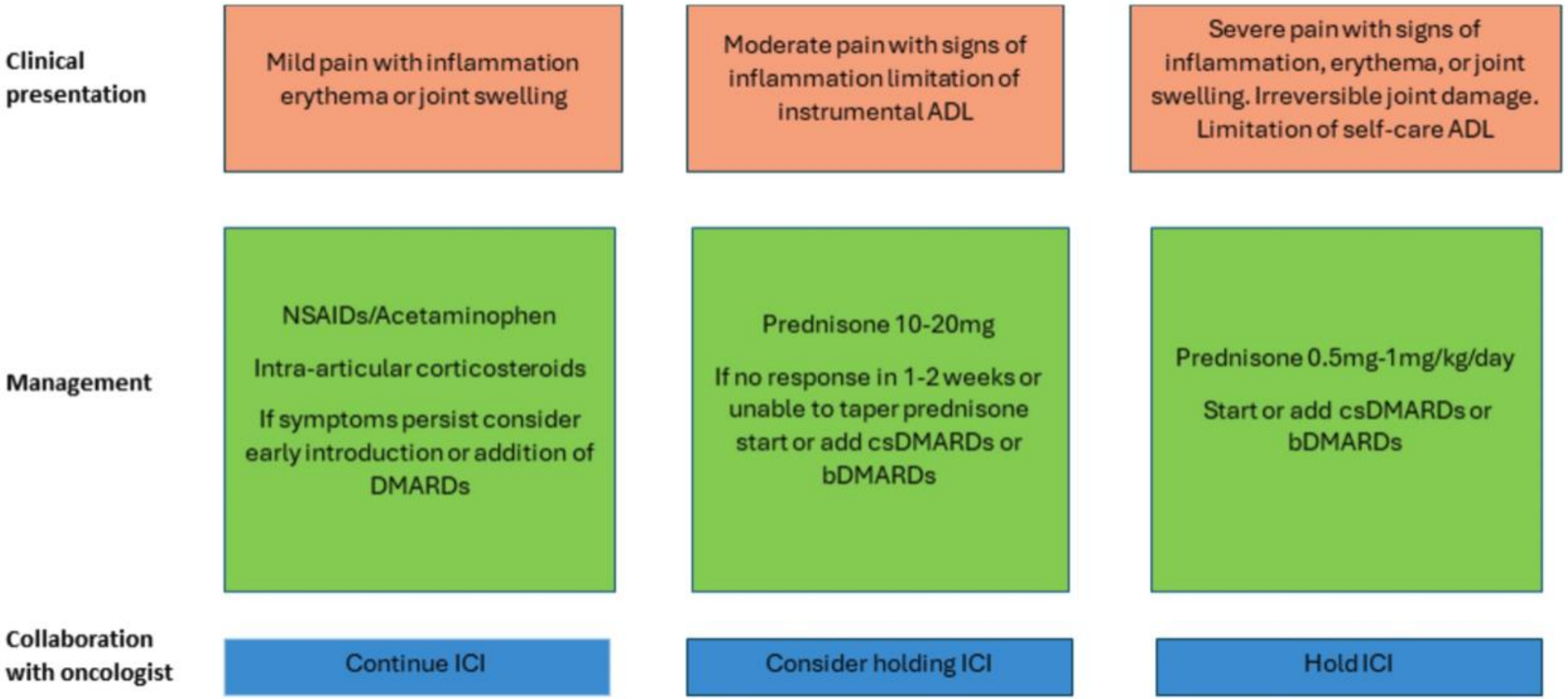


Sheik Ali S, Goddard AL, Luke JJ, et al. Drug-Associated Dermatomyositis Following Ipilimumab Therapy. *JAMA Dermatol.* 2015;151(2):195–199.

UTSW Experience



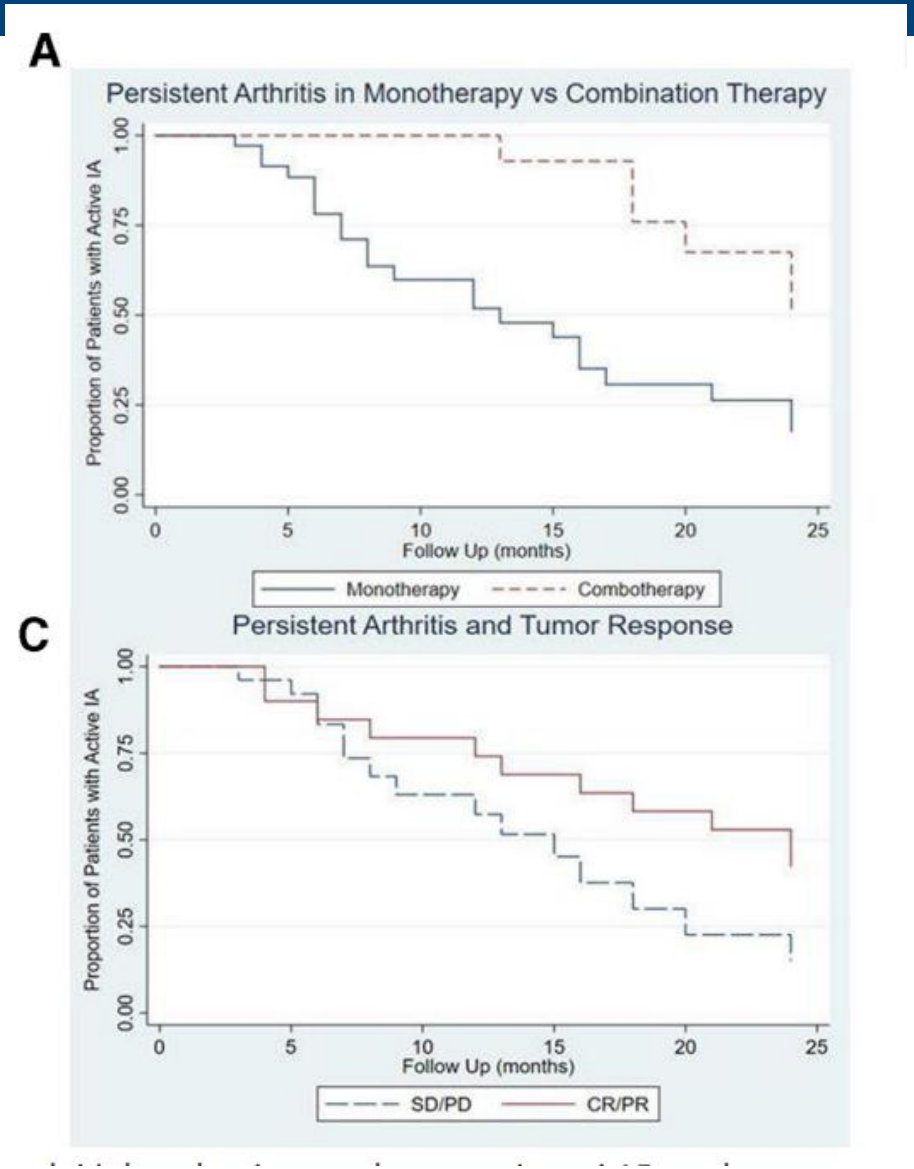
Management of Rh-irAEs



Bernabela L, Bermas B. Immune Checkpoint Inhibitor Associated Rheumatoid Arthritis. Curr Rheumatol Rep. 2024 Nov 26;27(1):3.

How do patients with Rheumatologic immune related adverse events (Rh-irAEs) do in the long run?

Prognosis Rheumatic irAEs



- Patients with a tumor response of complete response or partial response (CR/PR) had more persistent arthritis compared with those with stable disease or progressive disease (SD/PD) at follow-up

- IA was treated with CS, DMARDs, while still having good tumor response.

Braaten TJ, et al Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. Ann Rheum Dis. 2020 Mar;79(3):332-338

Take home messages for the internist

- Immune related adverse events (irAEs) are common
- Rheumatologic irAEs occur in about ~5-6% of patients
  - Inflammatory arthritis and PMR-like symptoms are most common
  - Sicca symptoms
  - Myositis
- Rh-irAEs portend better response to ICI therapy
- Rheumatic irAEs are debilitating and often become chronic.