Rheumatic Immune-Related Adverse Events

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I have no disclosures

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Overview

1. Inflammatory arthritis
2. Sjogren's
3. Myositis
4. Patients with underlying rheumatic diseases

CI-associated inflammatory arthritis - incidence

- Prospective observational single-center study
  - 524 CI-treated patients
- **3.8%** referred to rheumatologists
  - for inflammatory arthritis

Kostine M Ann Rheum Dis 2017

Inflammatory arthritis
PD-1/L1 vs. CTLA-4 blockade

- Clinical trials: odds ratio 3.5 with PD-1/L1

  Khoja. Ann Oncol 2017

- Head to head trials
  - [PD-1 vs. CTLA-4 vs. combo] = [7.7% vs. 6.1% vs. 10.1%]

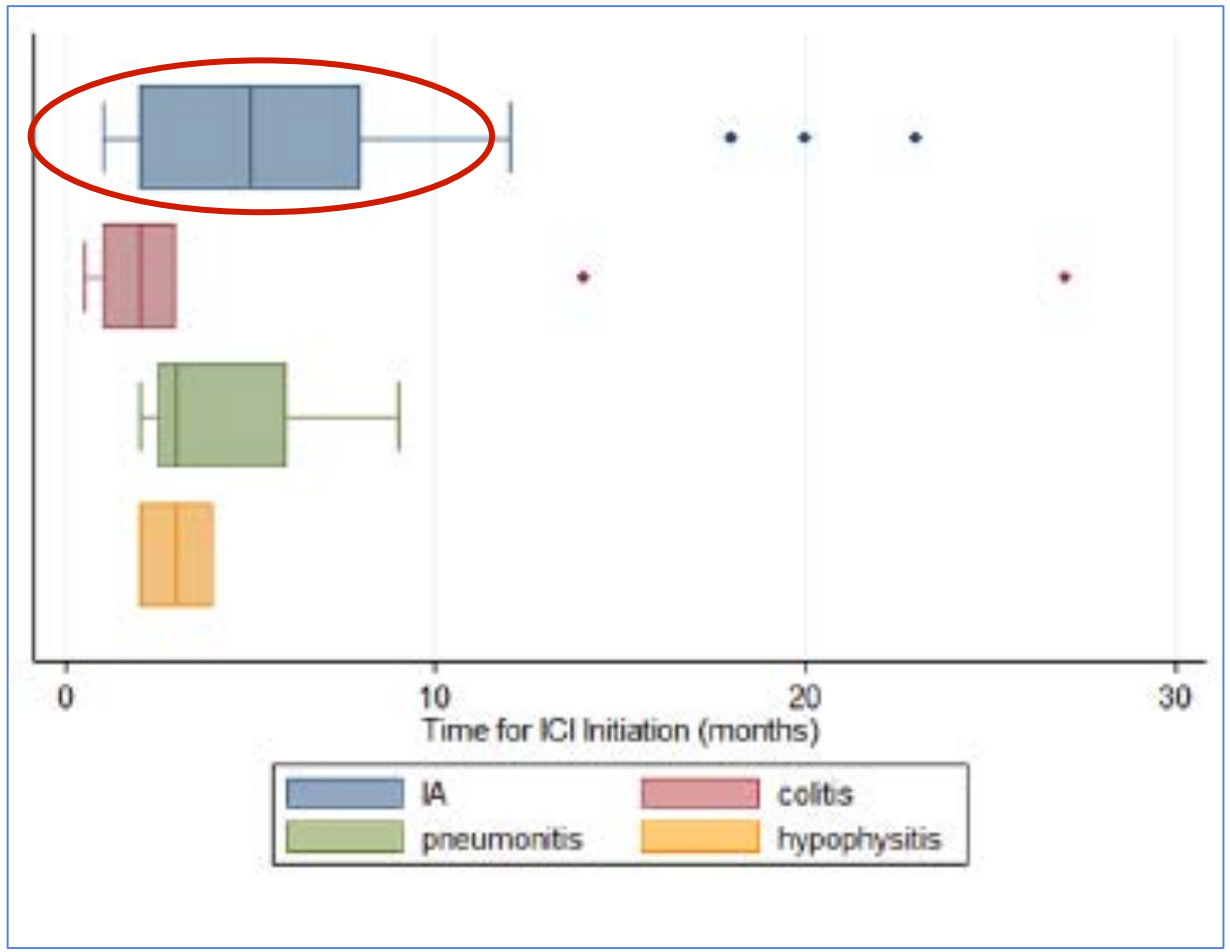
    Larkin NEJM 2015

PD1/PDL1 introduced later, used longer in individual patients

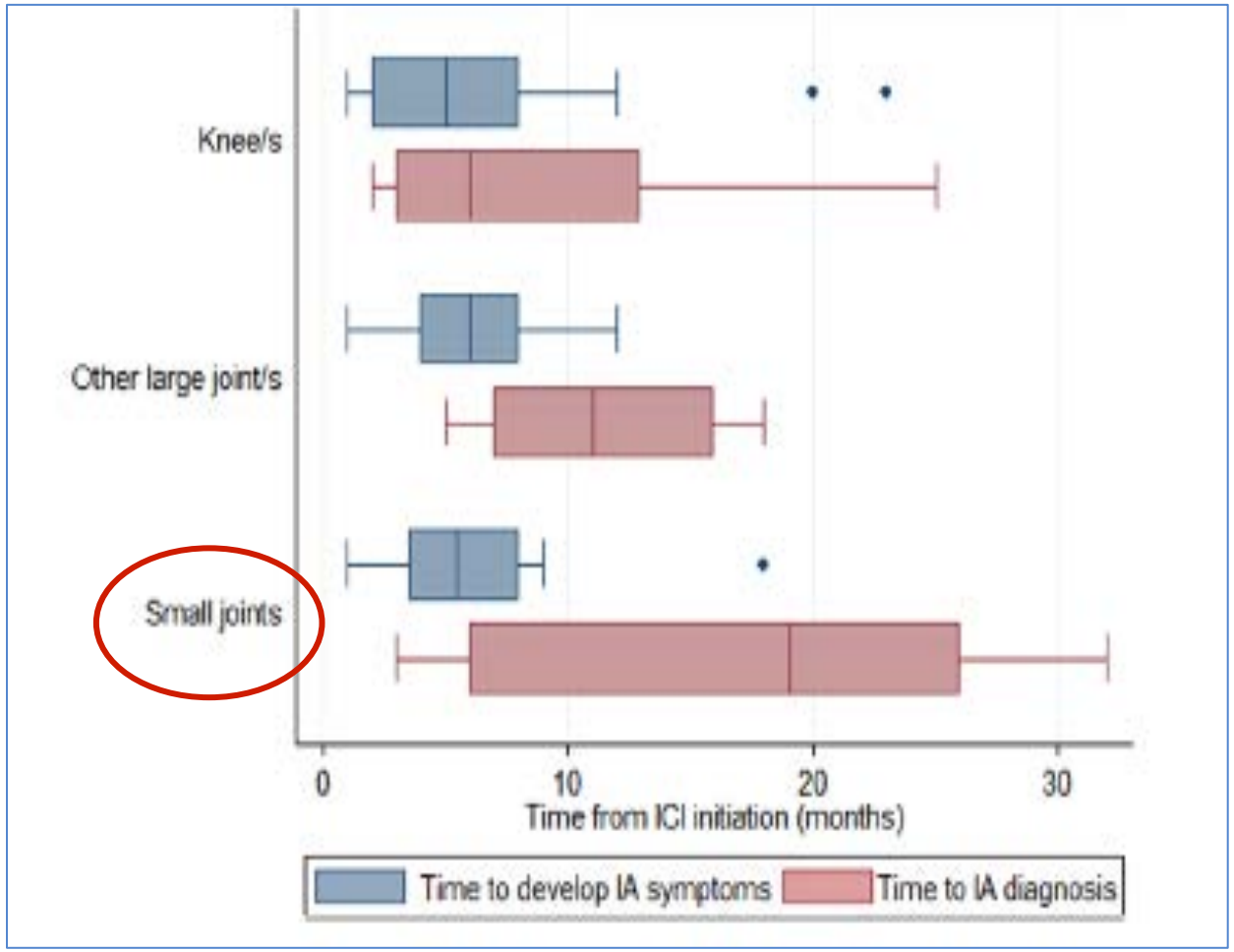
CI-arthritis: onset

- 1- 93 weeks after CI initiation

Calabrese 2016, Belkhir 2017, Kostine 2017, Smith 2017



- Delay in referrals



Cappelli L. Semin Arthritis Rheum 2018 (N=30)

Hospital for Special Surgery (HSS) CI-Arthritis Registry – (N=37)

Age (years)	67 [59, 77]
Female	60%
Smoker	49%
Months to onset	2.8 [0.9, 12]
Months to presentation	5.0 [1.0, 10]
Checkpoint discontinued	61%

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HSS CI-Arthritis Registry – Cancers

Melanoma	**14 (38%)**
NSCLC	4 (11%)
Renal cell	5 (14%)
Urothelial	2 (5.4%)
Other	12 (32%)

Combination CTLA-4/PD1	12 (32%)
PD-1 or PD-L1 alone	**25 (68%)**

Complete Remission	9 (26%)
Stable	11 (31%)
Partial Remission	7 (20%)
Progression	**8 (23%)**

median follow up 5.4 [2.5,15] months

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HSS CI-Arthritis Registry – Serologies

ANA +	22 (67%)
RF +	4 (12%)
CCP +	8 (23%)
RF or CCP	**10 (29%)**

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HSS CI-Arthritis Registry – Phenotypes

	Small joint 22 (59%)	**Large joint only** 5 (14%)	**Arthralgia** 8 (22%)	**PMR** 2 (5%)
Prednisone >20 mg	9 (41%)	**3 (60%)**	4 (50%)	1 (50%)
Biologic	5 (23%)	1 (20%)	0 (0%)	0 (0%)
RF or CCP	6 (30%)	**0 (0%)**	3 (38%)	1 (50%)
Duration arthritis (mos)	18 [3.0,34]	13.0 [13,13]	8.8 [5.5,12]	3.0 [3.0, 3.0]
Tenosynovitis/enthesitis*	1 (5%)	**3 (60%)**	5 (63%)	0 (0%)

*Wrists, patellar, quadriceps, triceps tendon

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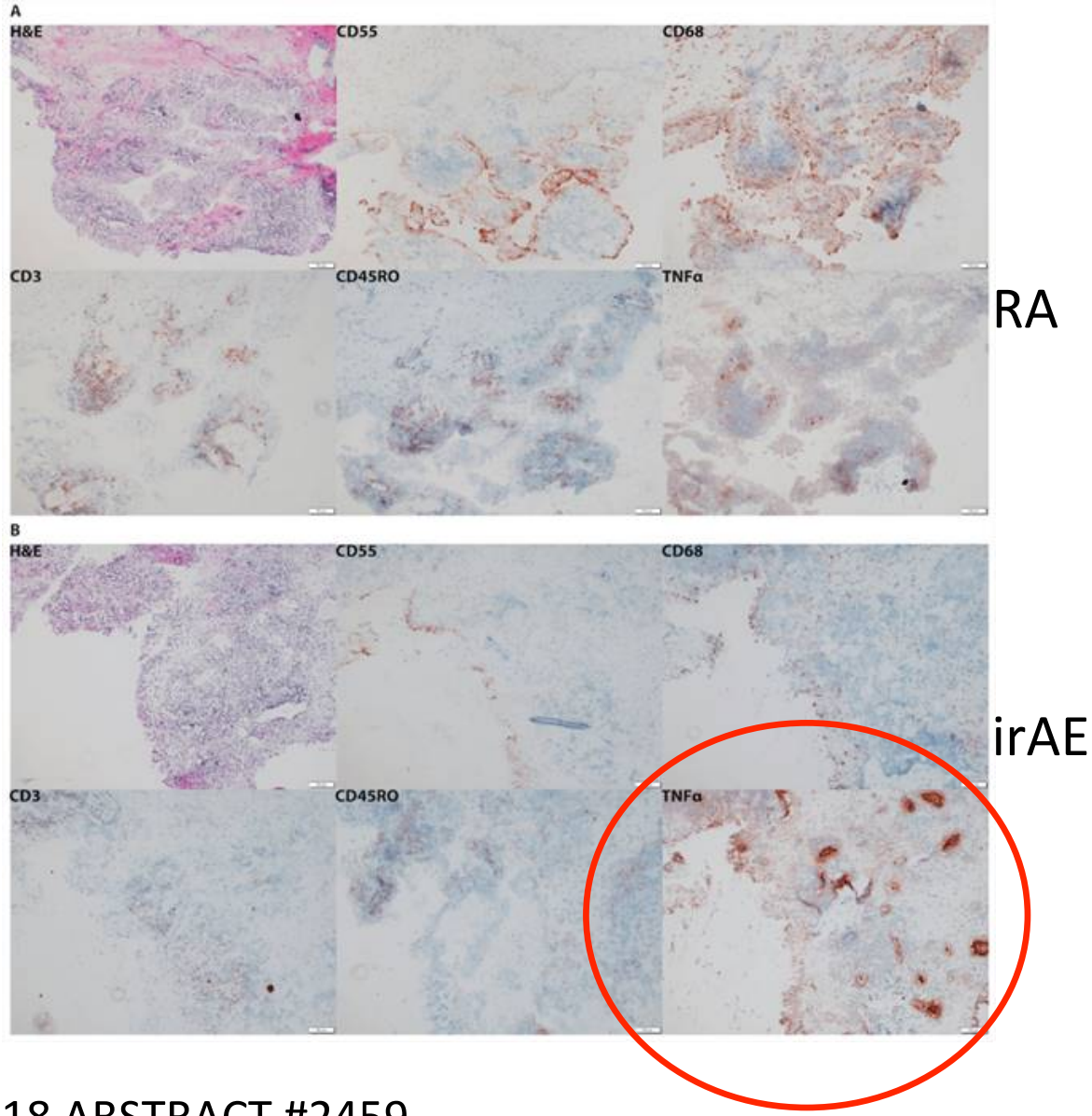
Pathology

- Similar to RA:
  - Macrophages (CD68+)
  - B cells (CD20+)
  - Memory T cells
    - (CD3+ CD45RO+)

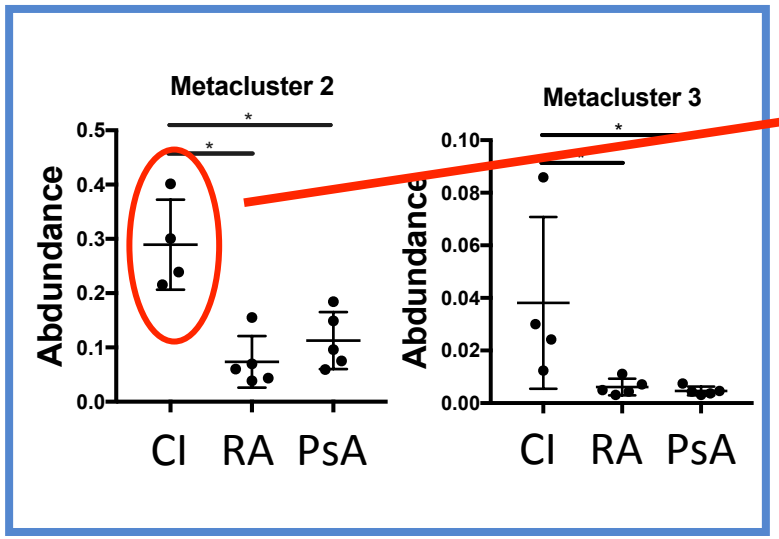
- Difference from RA:
  - Markedly elevated TNFα

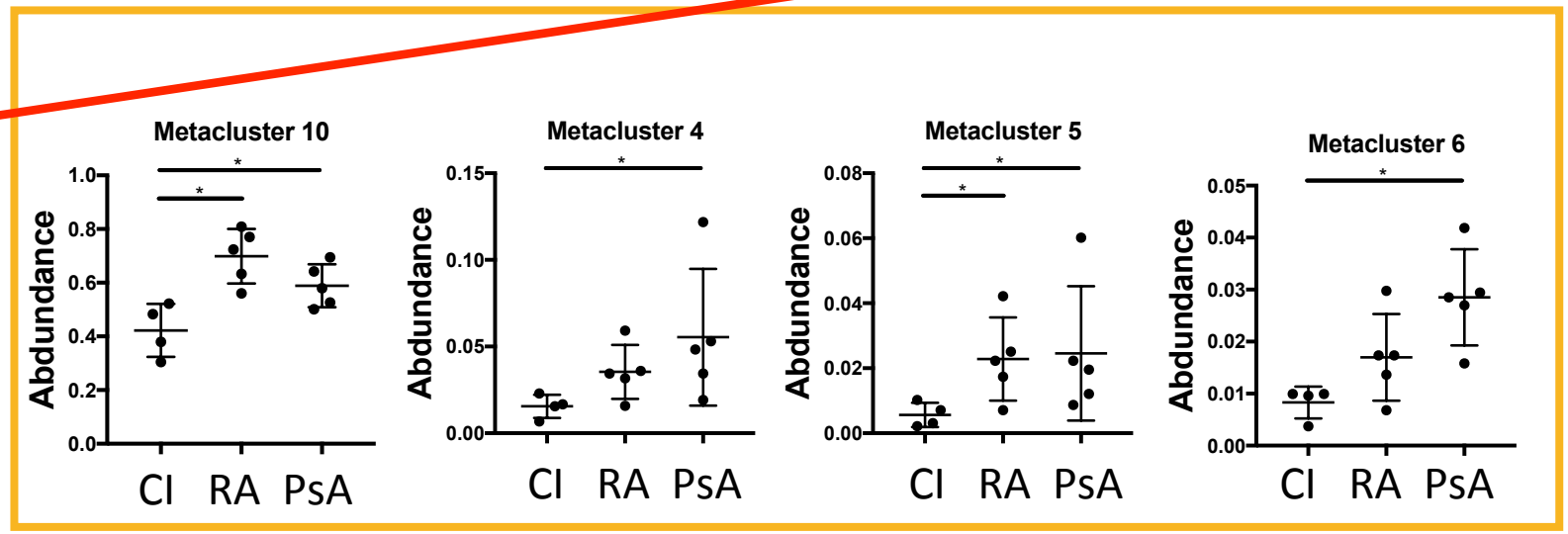


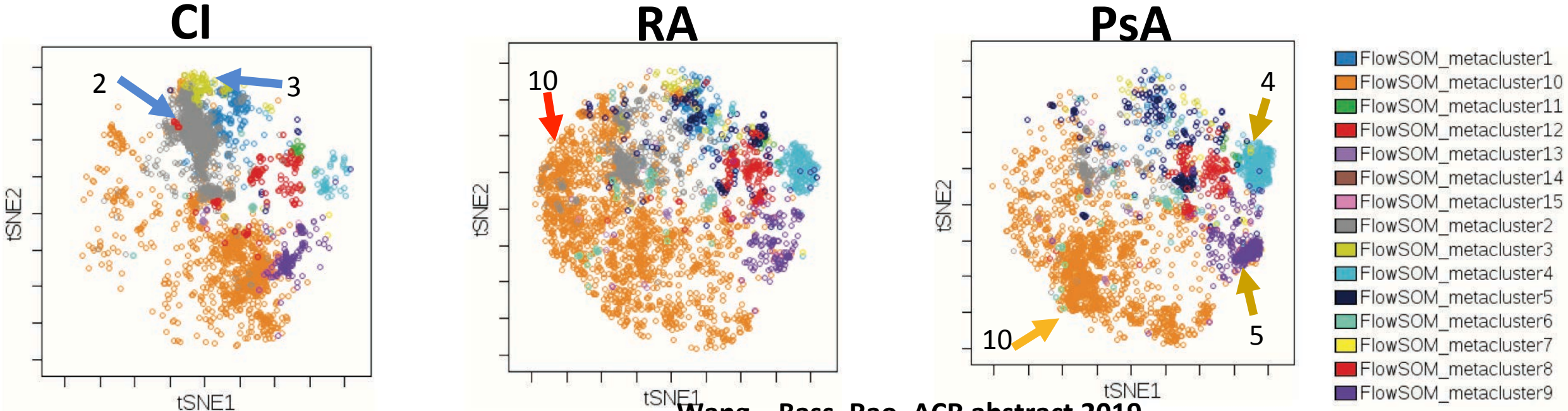
William Murray-Brown. ACR 2018 ABSTRACT #2459

FlowSOM on CD8 ViSNE- synovial fluid

CD8+CD28+CD127-PD1+







Wang …Bass, Rao. ACR abstract 2019

General approach to treatment

- Grade 1: NSAIDS, intraarticular injections, consider prednisone 5-20mg, try to taper over the month.
  - see back in 3-4 weeks
  - If unable to taper, add hydroxychloroquine (Plaquenil) or sulfasalazine

- Grade 2-3: Prednisone 20-120 mg
  - see back in 1-2 weeks
  - If not dramatically better at follow up, strongly consider TNFi
  - MTX can also be used but slow onset

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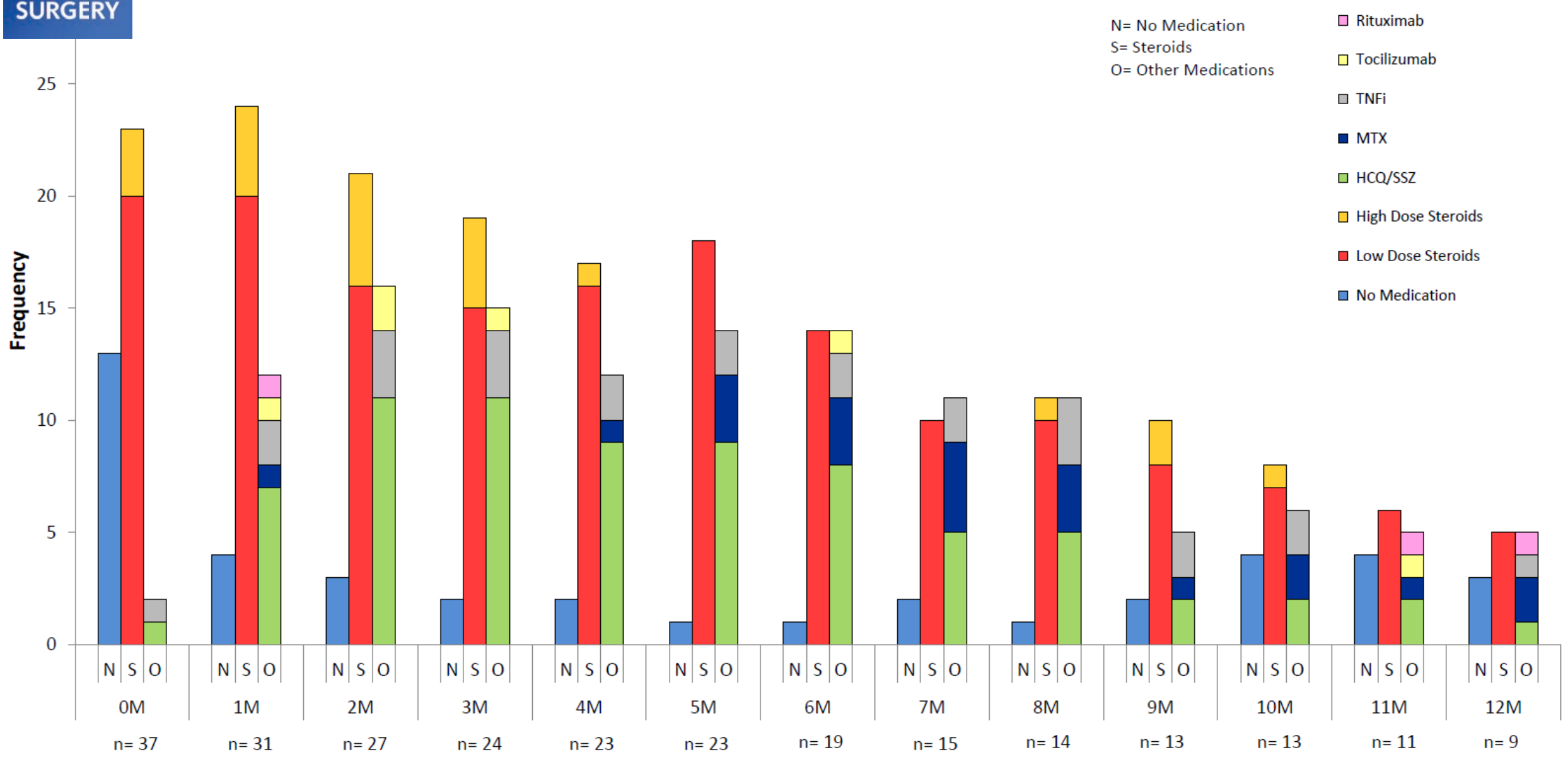
Arthritis treatment - HSS CI Registry



CI-associated Sjogren's

- 20 patients, 14M/6F
  - 10 melanoma, 3 thymic, 4 respiratory papillomatosis
  - 17 monotherapy, 3 combination CI
  - 3/20 cancer progression

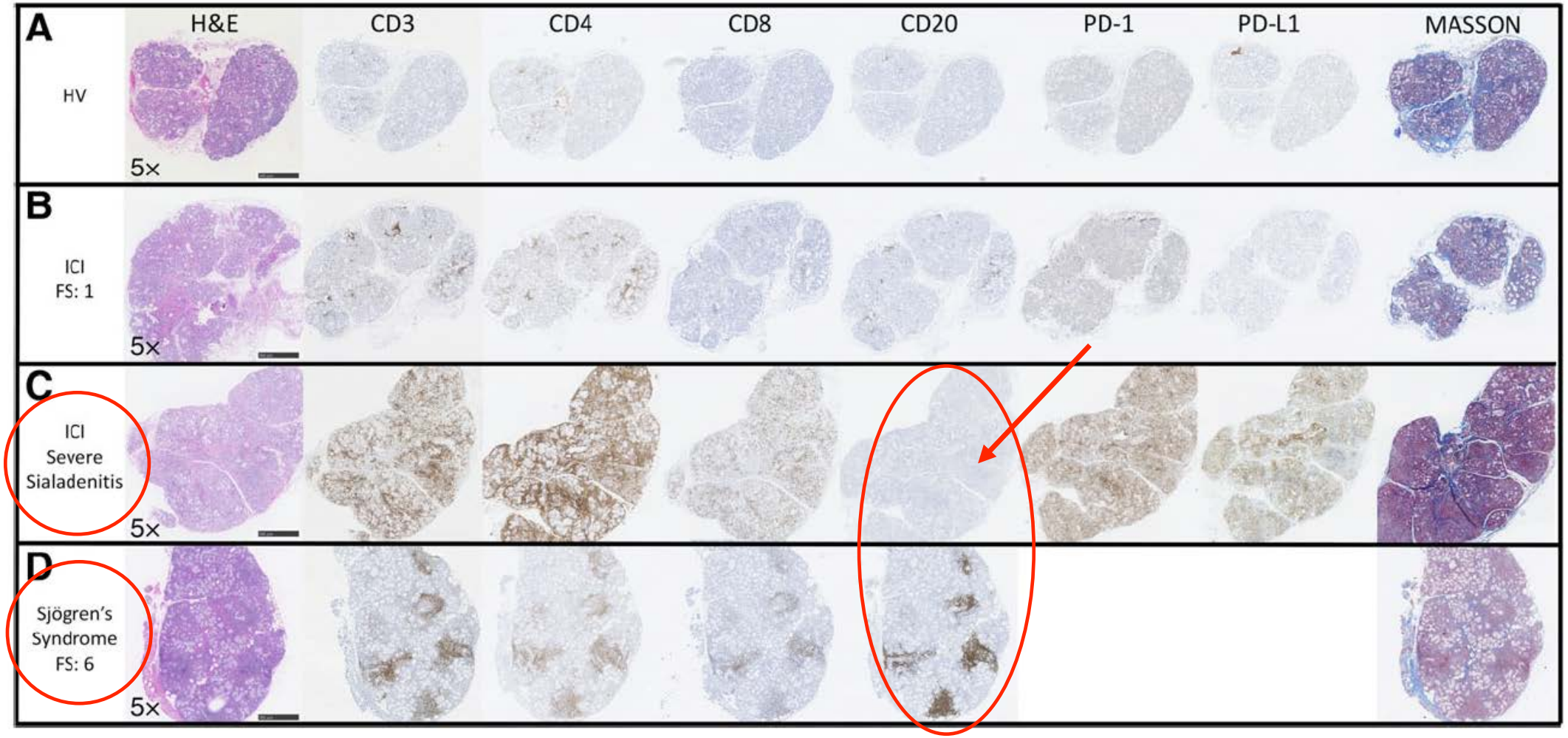
Warner Oncologist 2019;24:1–11

CI- associated Sjogren's

- Sicca: dry mouth predominant
  - Onset 70 days (30–206).
  - 5 grade 1, 15 grade 2
  - Some Candidiasis, some oral burning
- Serology:
  - 3 ANA, 2 RF/SSA, 1 Scl70

Warner Oncologist 2019;24:1–11

Salivary gland biopsy



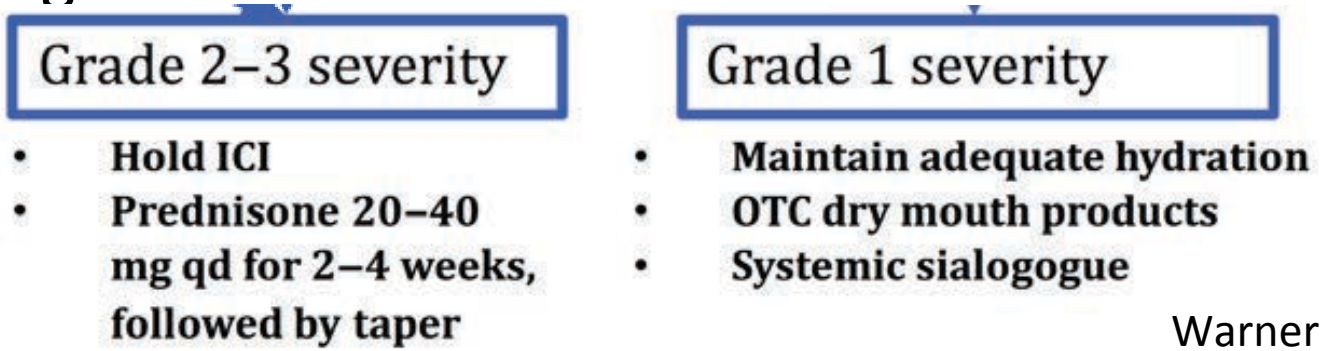
T cells

B cells

Warner Oncologist 2019;24:1–11

Sjogren's treatment

- Trial of corticosteroids - 20 mg or more
  - some symptomatic improvement but not resolution
  - salivary flow unchanged
- Consider hydroxychloroquine
- Pilocarpine (Salagen) and cevimeline (Evoxac)
  - can cause sweating, abdominal pain, flushing and increased urination
  - Can't use with asthma or small angle glaucoma
- Dental hygiene
- Anti-fungal agents if needed for thrush



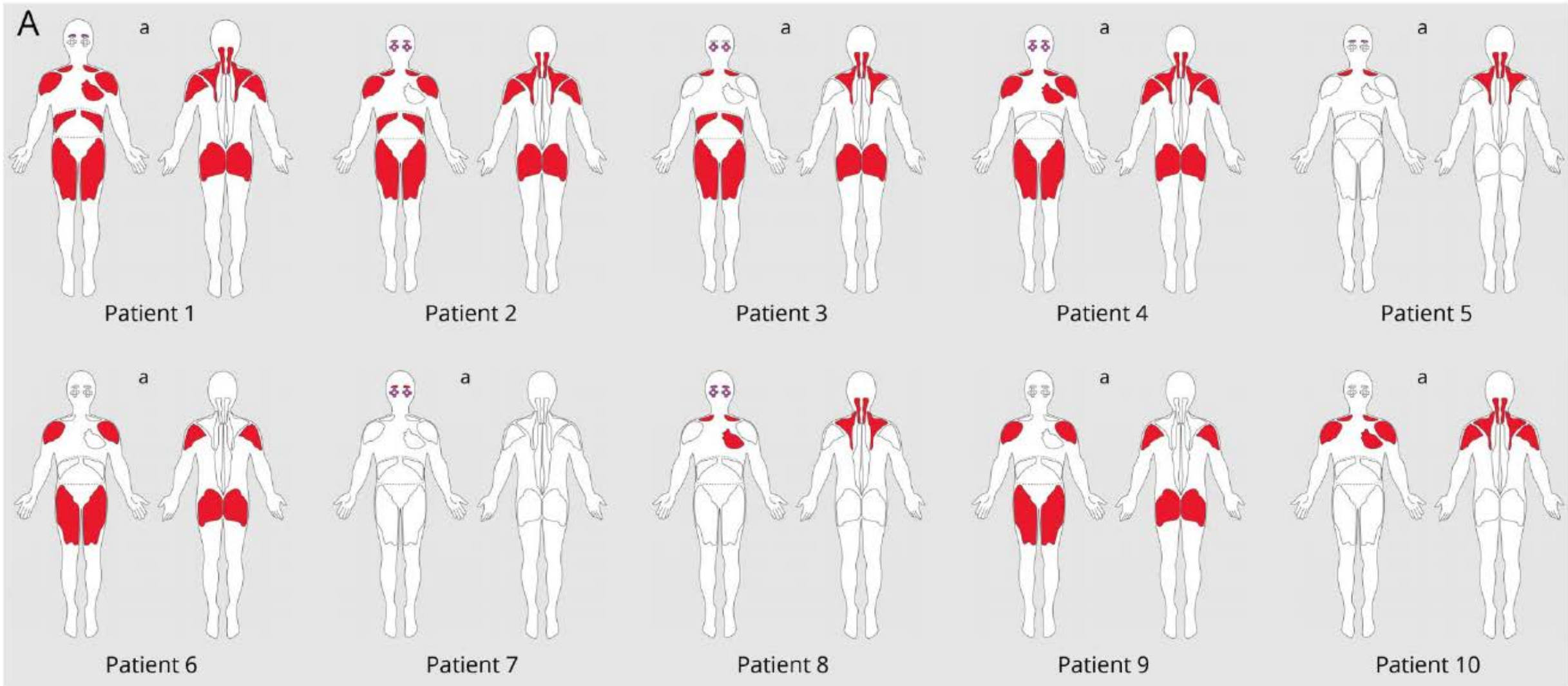
Warner Oncologist 2019;24:1–11

CI-associated myositis

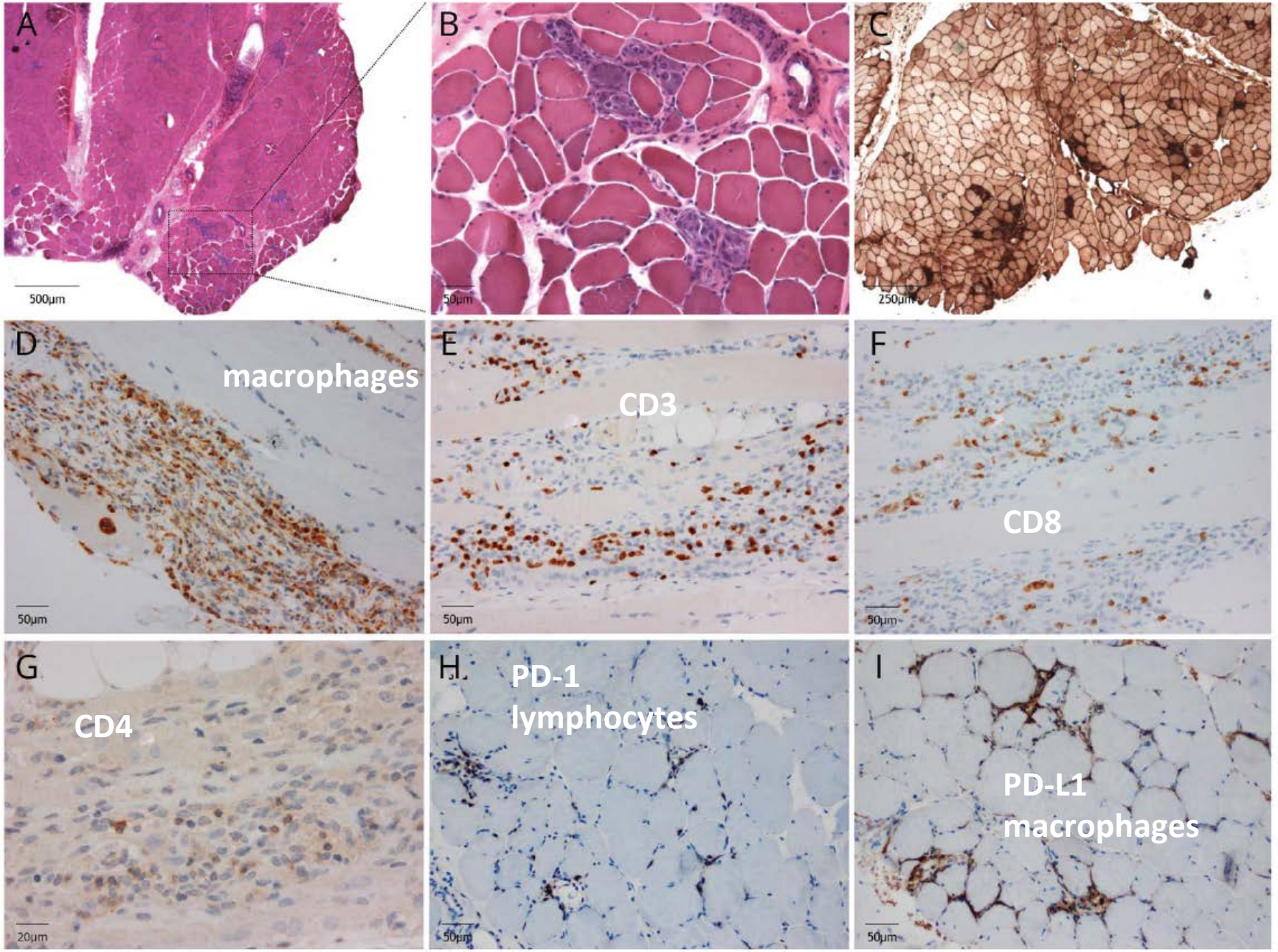
- Onset 2-7 weeks
- Proximal muscle weakness and elevated CPK
  - Occasional myalgia, dyspnea, dysphagia, hypophonia
- Myocarditis – can be concomitant
- Features of myasthenia gravis
  - Dysarthria, ptosis, opthalmoplegia, facial paresis, orbicularis oculi weakness
  - Anti-striated muscle antibodies

- Uncommon:
  - ILD not reported
  - Dermatomyositis very rare

Figure 1 Clinical features, treatment, and outcome of patients with irMyositis



Touat M. Neurology 2018; 91:e985-e994



myophagocytosis
necrotic myofibers

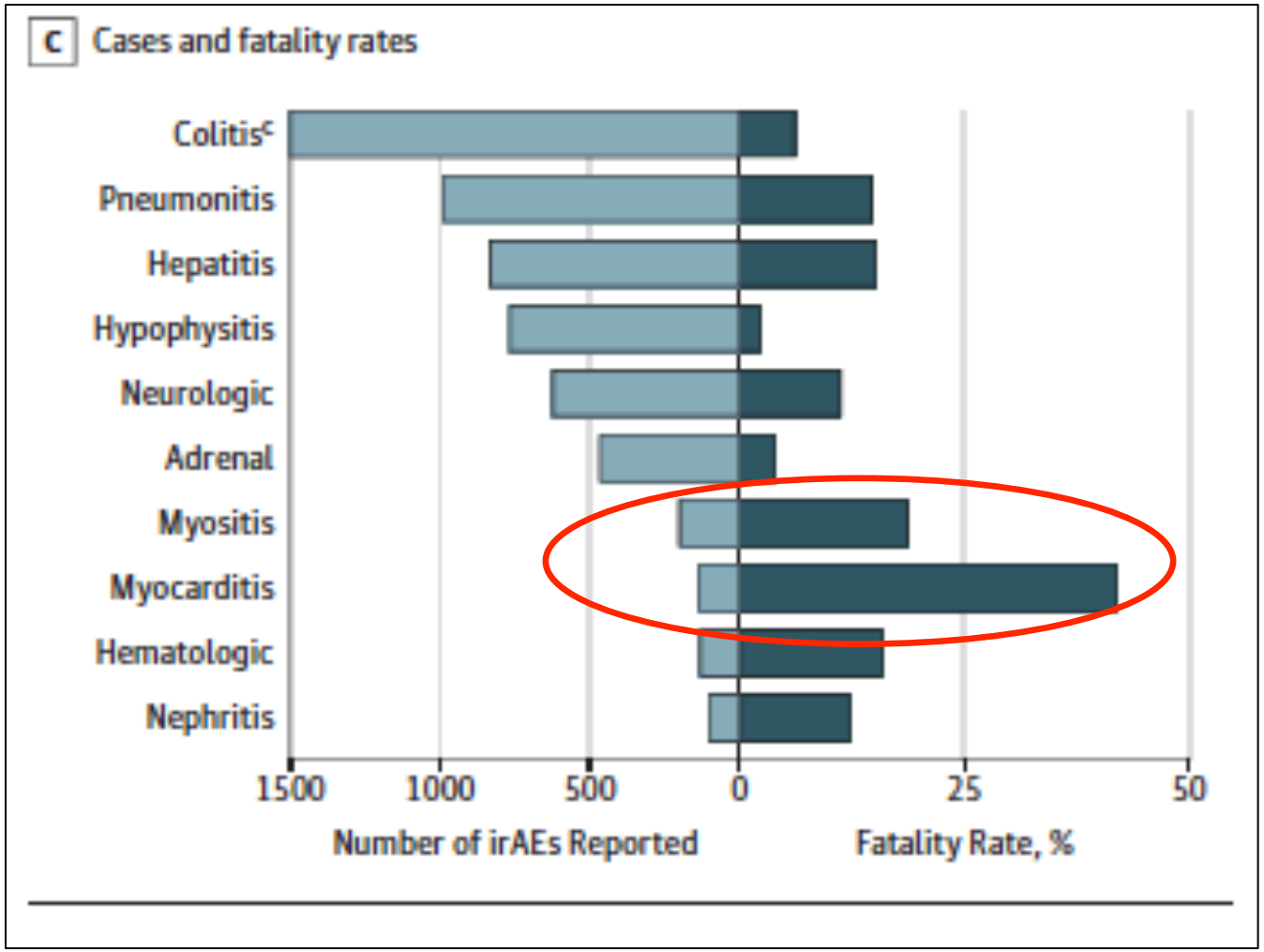
Touat M. Neurology 2018; 91:e985-e994

Treatment

- Grade 1: myalgia no weakness: NSAIDS, prednisone 10-20 mg
  - Advance to grade 2 if weakness or elevated CPK
- Grade 2: moderate pain or weakness: prednisone 20-60
  - Watch for bulbar weakness, myocarditis
  - Advance to grade 3 if no response 2-4 weeks
- Grade 3 -4: moderate to severe weakness and/or pain
  - Methylprednisolone 1 gm IV daily x 3 days
  - Consider IVIG, plasmapheresis (Plex)
  - Consider MMF, AZA, MTX
  - Consider TNFi or Rituximab

Ladak K, Bass AR, Best Practice & Research Clinical Rheumatology 2019

Cases and case fatality rates –
Global Pharmacovigilance – WHO Vigibase



Wang DY. JAMA Oncol 2018

Preexisting autoimmune disease

- Are they at greater risk for IRAE?
- Is it safe to treat them with CI?

Preexisting autoimmune disease – Systematic literature review (SLR)

- 123 cases
  - 49 publications
- 46% active autoimmune disease

- **23% PsA, psoriasis**
- **16% RA**
- **11% IBD**
- 9% Thyroid disease
- 5% Multiple sclerosis
- 4% Sarcoid
- 3% Myasthenia

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130

Preexisting autoimmune disease – Treatment changes at time of CI initiation

Treatment	Before CI (%)	At time of CI initiation (%)
Steroids	29	21 (< 10 mg)
DMARDS	24	14
Biologics	7	1
No treatment	**17**	**56**

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130

Preexisting autoimmune disease – IRAE

- Total irAE 75%
  - Disease exacerbation 50%
  - De Novo irAE 34%

- CTLA-4 more de novo
- PD-1/PD-L1 more autoimmune disease flares

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130

Preexisting autoimmune disease – IRAE

- Cancer response:
  - 50% with irAE, 36% without
- Lower rate of irAE
  - if on baseline treatment/immunosuppression

- Deaths:
  - 2 irAE [1 IBD: TEN/sepsis , 1 psoriasis: colitis]
  - 3 unrelated to irAE

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130

Preexisting autoimmune disease –

- 75% overall rate of irAE –
  - 50% have a flare of their disease

- Yes, patients with autoimmune disease can receive CI
  - Stop immunosuppression at the time of CI initiation if at all possible
  - (Watch myositis patients carefully)

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130

Thank you

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Seropositivity and survival

A Progression-free survival with or without any antibody

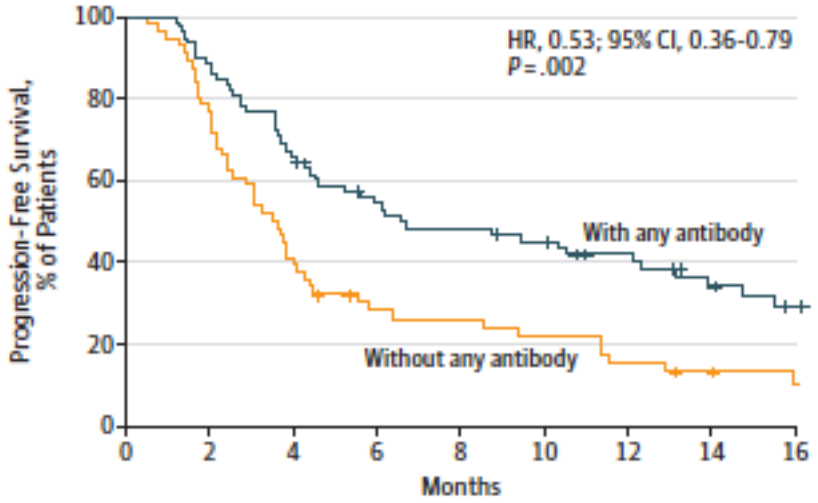


Figure 3. Overall Survival in the Cohort

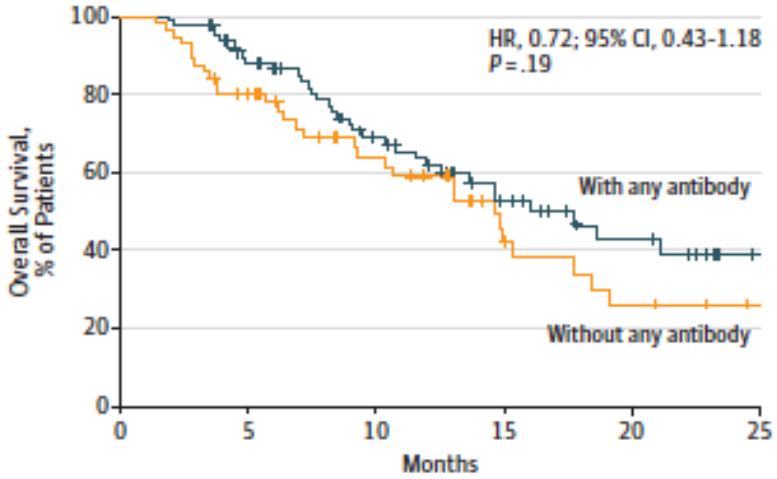


Table 1. Characteristics of 137 Patients Who Did or Did Not Develop irAEs During Nivolumab or Pembrolizumab Monotherapy

Characteristic	No. (%) of Patients With irAE (n = 66)	No. (%) of Patients Without irAE (n = 71)	P Value
Sex, male	54 (82)	51 (72)	.24[a]
Age, median (range), y	68 (36-88)	67 (31-84)	.61[b]
Preexisting antibody			
Any[g]	48 (73)	32 (45)	.002[a]
RF[h]	26 (39)	12 (17)	.006[a]
ANA[i]	29 (44)	19 (27)	.05[a]
Antithyroid[j]	15 (23)	10 (14)	.28[a]

Toi Y. 2018 JAMA Oncol.

Seroconversion overall - 19.2% (19/99)
(ipilimumab)

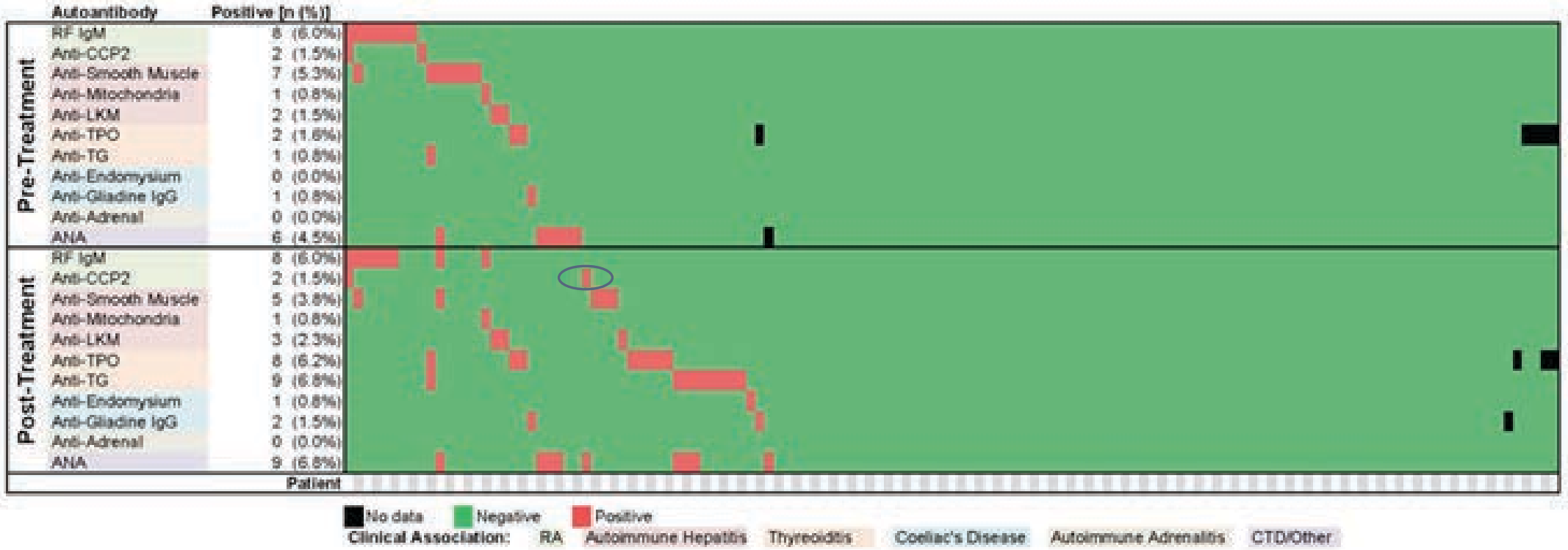
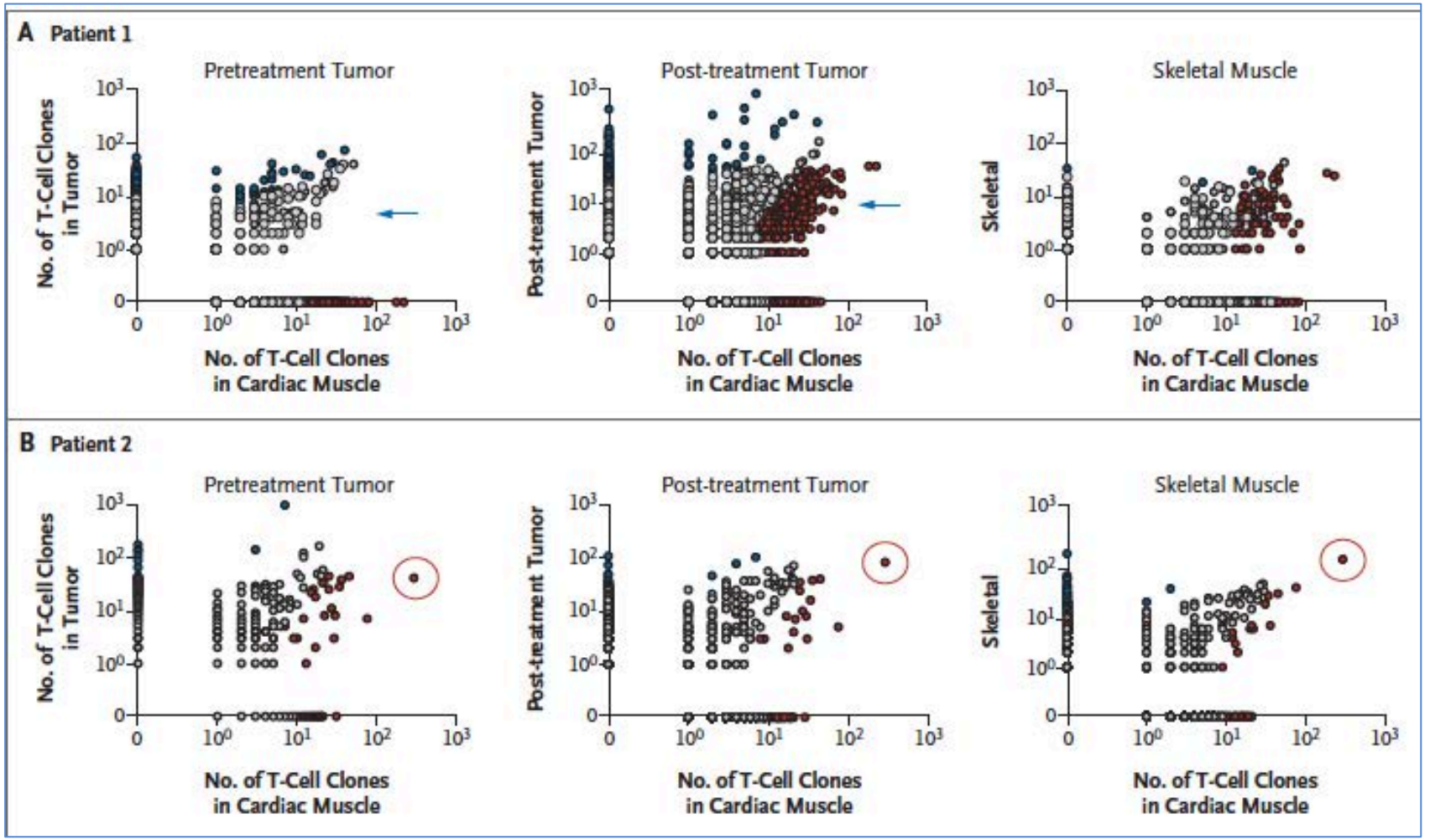


Figure 1. Heatmap of antibody positivity pre- and post-ipilimumab treatment. Not shown: all patients were anti-ENA negative at baseline, while at follow-up, two patients became anti-ENA positive, specifically anti-SSA positive.

De Moel 2018 ACR ABSTRACT #23

Myositis & Myocarditis –T cell clones

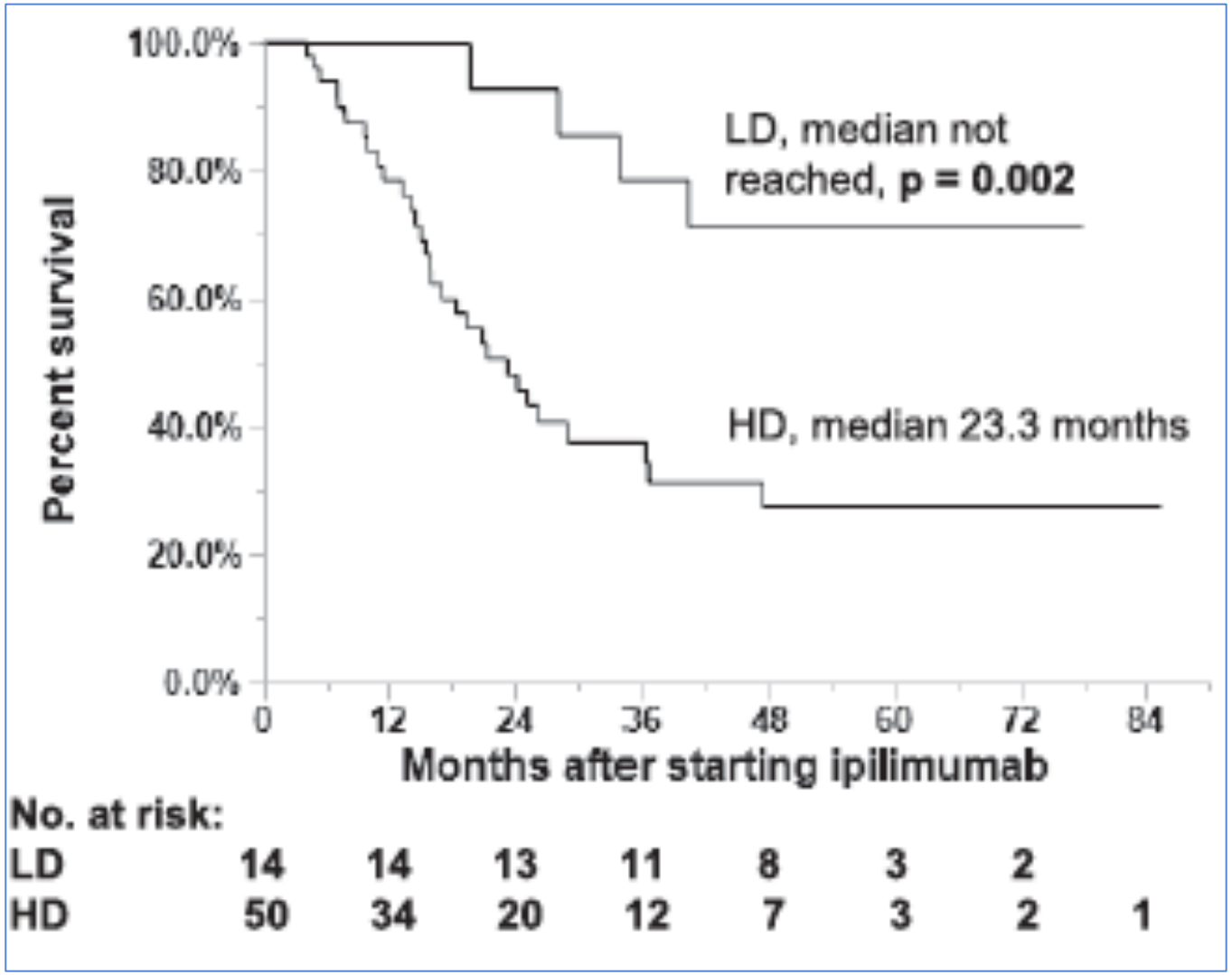


Johnson. N Engl J Med 2016;375:1749-55.

Steroids: dosing and safety

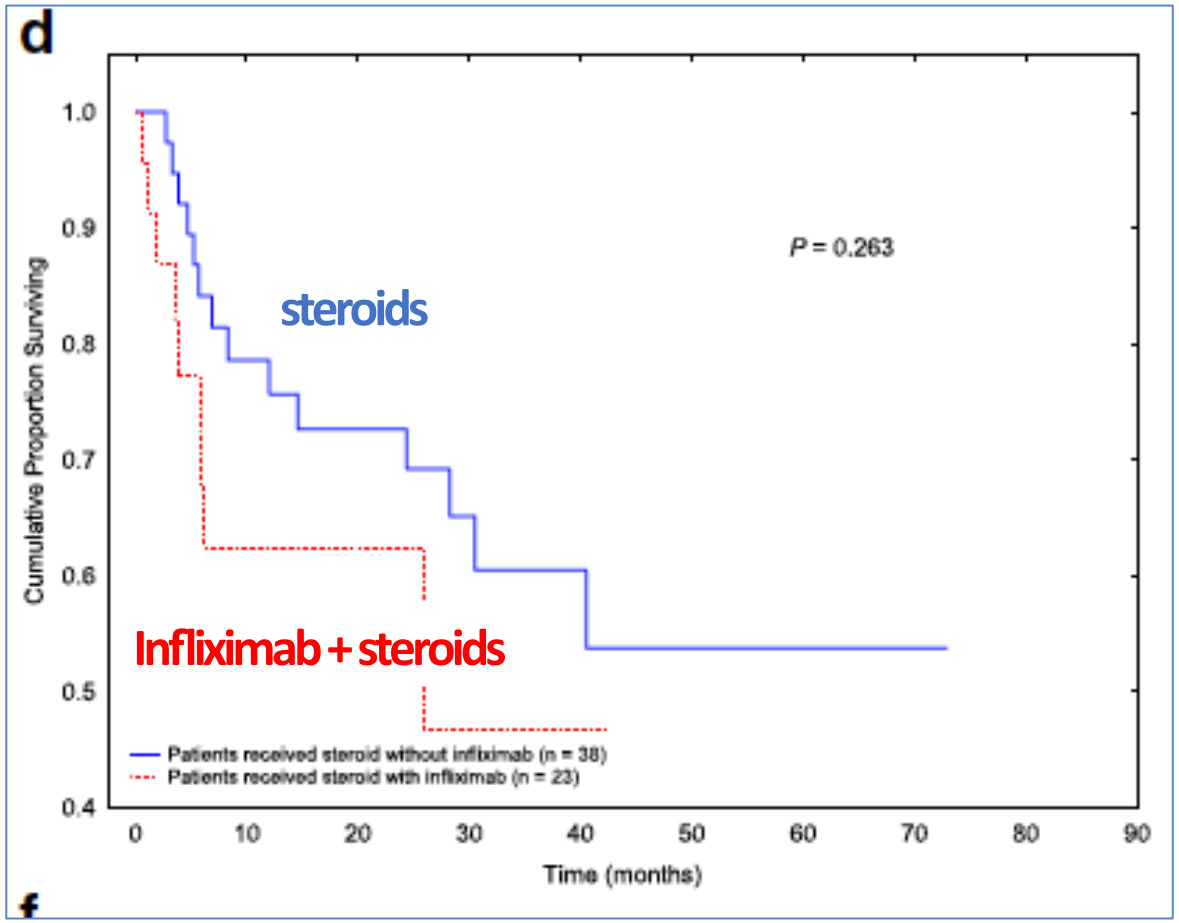
- Low dose - probably safe
- High dose - may impact cancer survival

- Risks
  - infection, osteoporosis



Faje. Cancer 2018

TNF inhibitors - safety

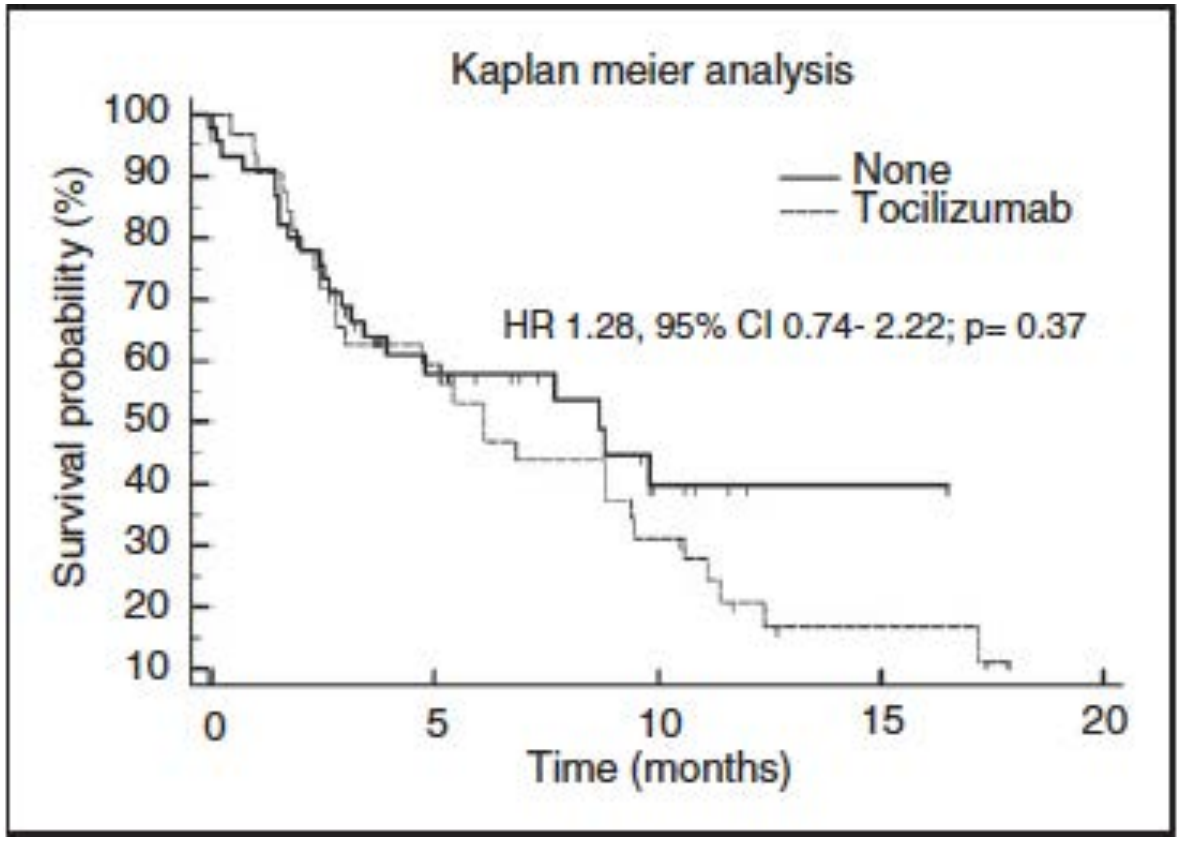


- No difference in survival
  - Steroids vs. steroids + infliximab
  - Study not powered

327 patients, multiple CI, multiple cancers

Wang. J ImmunoTherapy 2018; 6(37)

IL-6R blockade



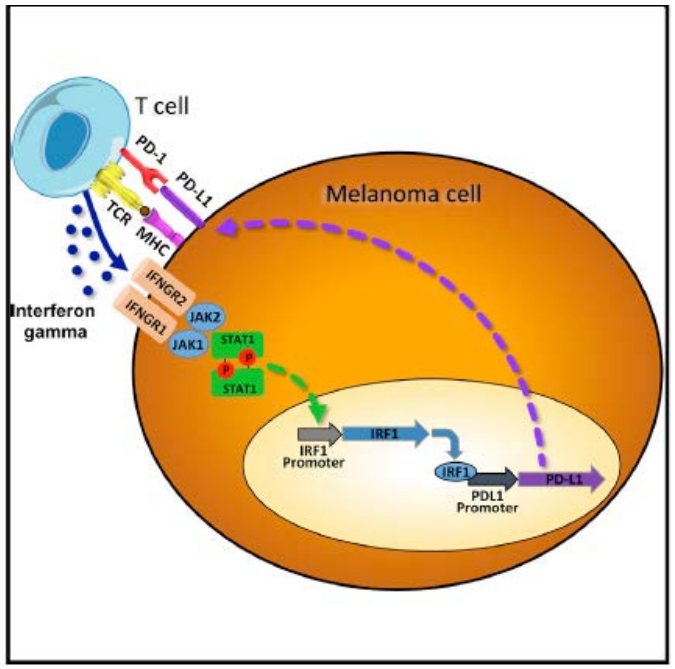
- Safety unknown
  - Watch for colonic perforation
  - Much less experience than with TNFi
- **Reserve for refractory cases**

Multiple malignancies (most NSLC) - nivolumab

Stroud. J Oncol Pharm Practice 2017

Safety of JAK/STAT blockade?

- Indirect evidence suggests they may NOT be safe.
  - Avoid JAK/STAT inhibitors for CI-associated irAE



- JAK/STAT important for regulation of PD-1 ligands and IFN-g signaling in tumors
- **JAK1/2 mutations can cause anti-PD-1 resistance**

Zaretsky JM. N Engl J Med 2016;375:819-29
Shin DA. Cancer Discov. 2017;7(2): 188–201