

# De nye Gigtsygdomme

Bent Deleuran

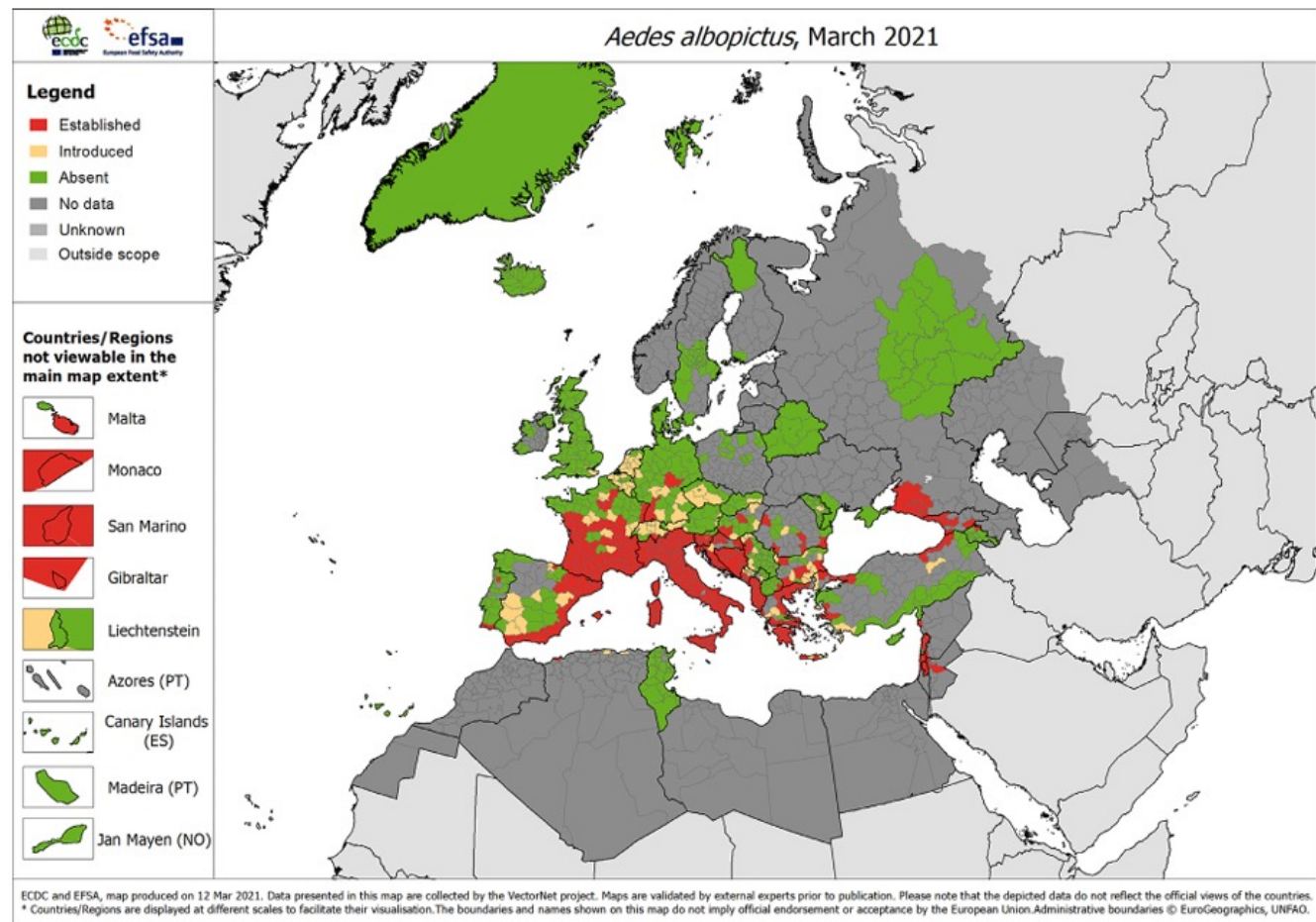
# De nye gigtsygdomme

- **irAE - immune related adverse events**
- "Genteknologiske inddelinger" af reuma-sygdomme
  - VEXAS
- Infektionsrelaterede gigtsygdomme – **Klima ændringer**
- De nye somatoforme sygdomme
- De nye gigt-behandlinger
  - Saphnelo – anti-type-1 Interferon antistof
  - Nye JAKi (TYK2)
  - Anti-FcRn
  - Anti..... ..

# Chikungunya, Dengue, West Nile fever



2021



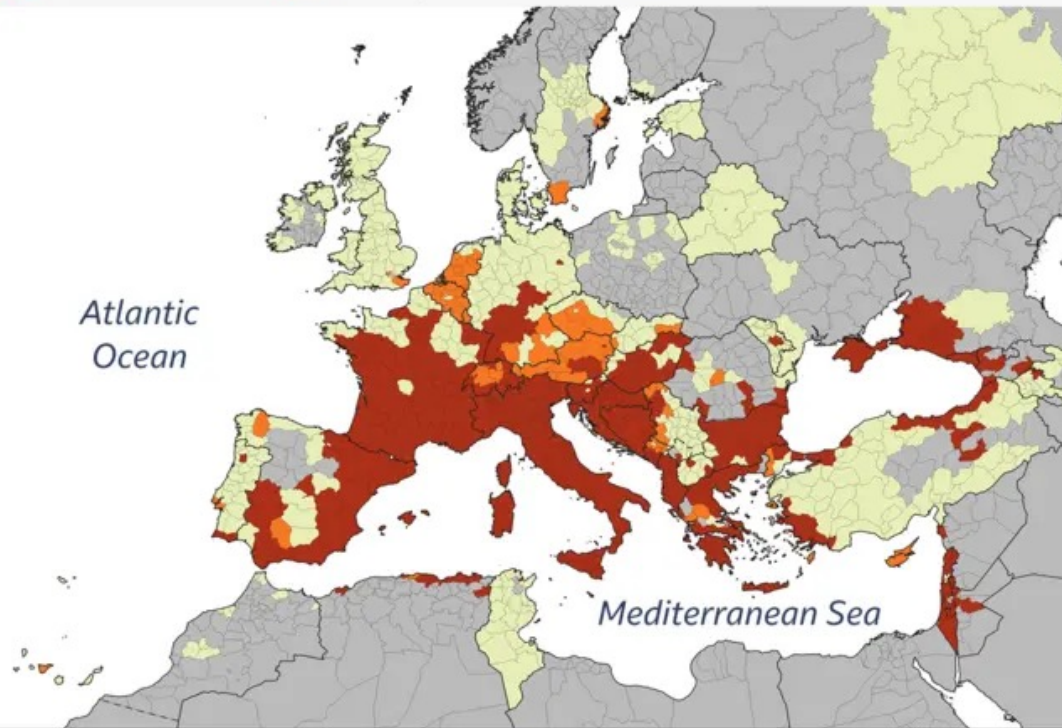
# Chikungunya, Dengue, West Nile fever



2024

Asian tiger mosquitoes continue to spread in Europe

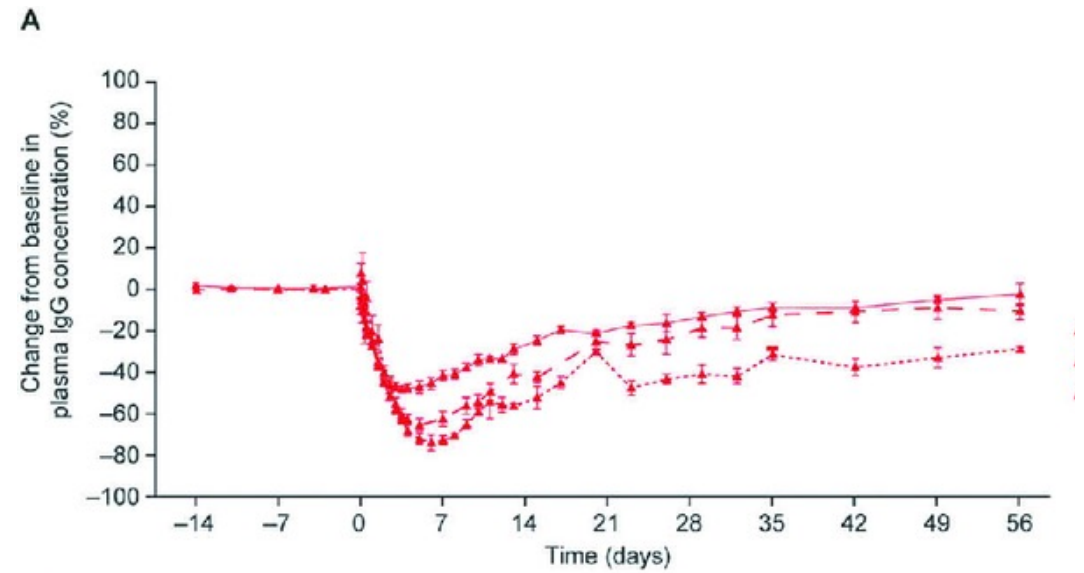
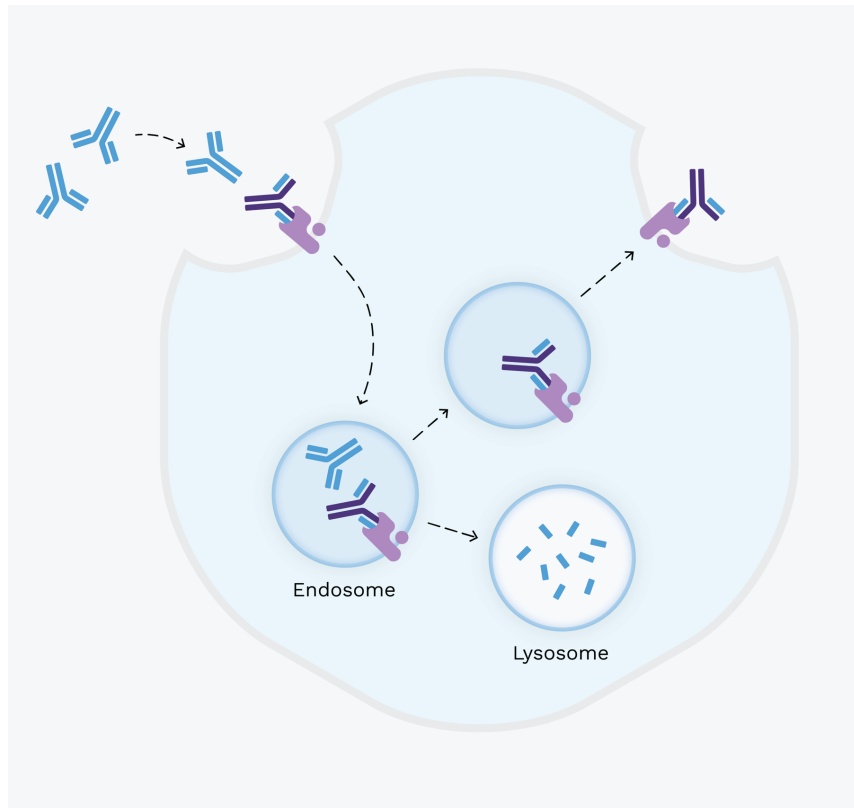
■ Established ■ Newly observed ■ Not seen ■ No data



Source: European Centre for Disease Prevention and Control, May 2024

BBC

# Anti-FcRn - fjerne IgG, men ikke IgM, og IgA

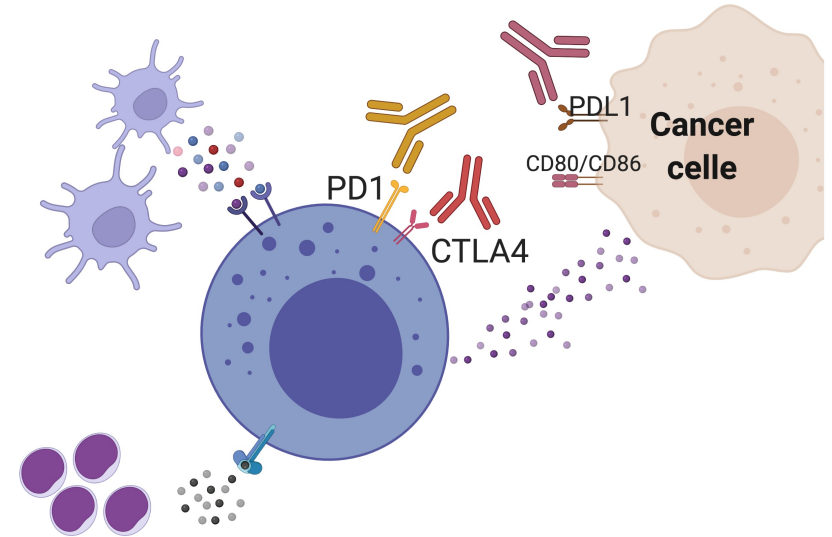
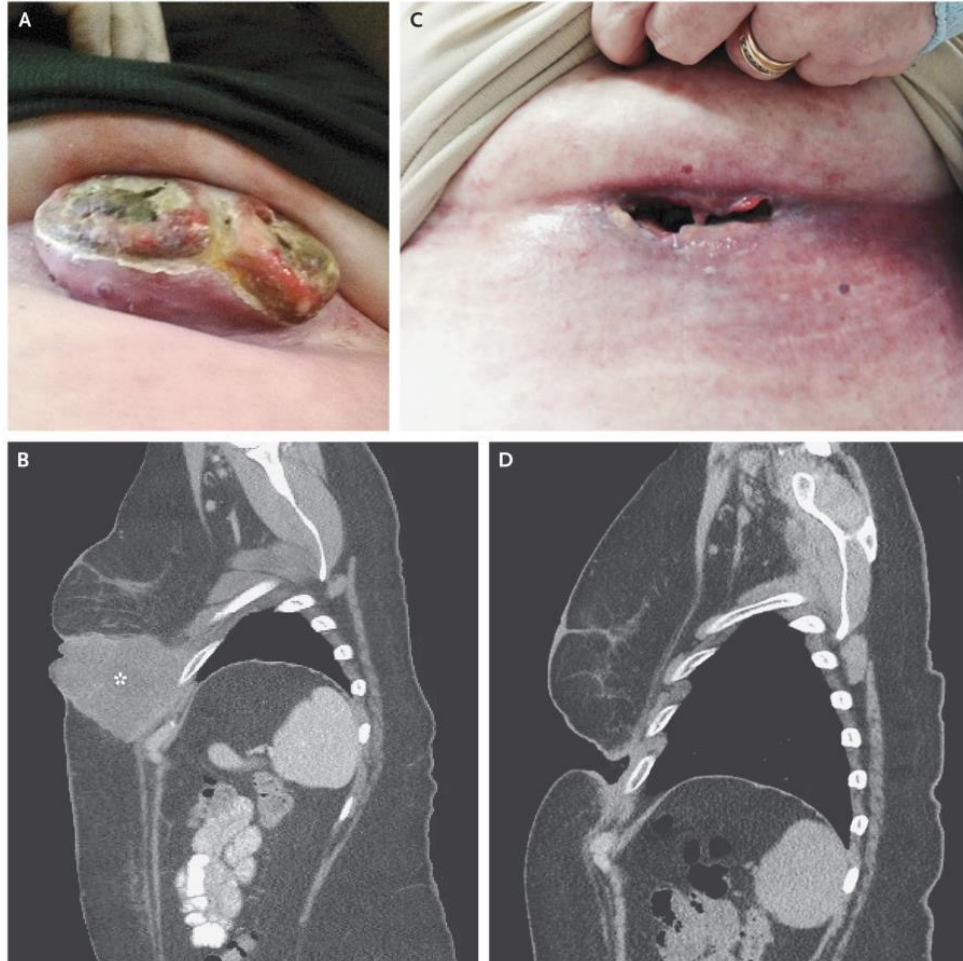


# **Immune related adverse events (irAE) i relation til Immune Checkpoint Inhibitors (ICI)**

Bent Deleuran

Biomedicine, Aarhus University  
Department of Rheumatology, Aarhus University Hospital

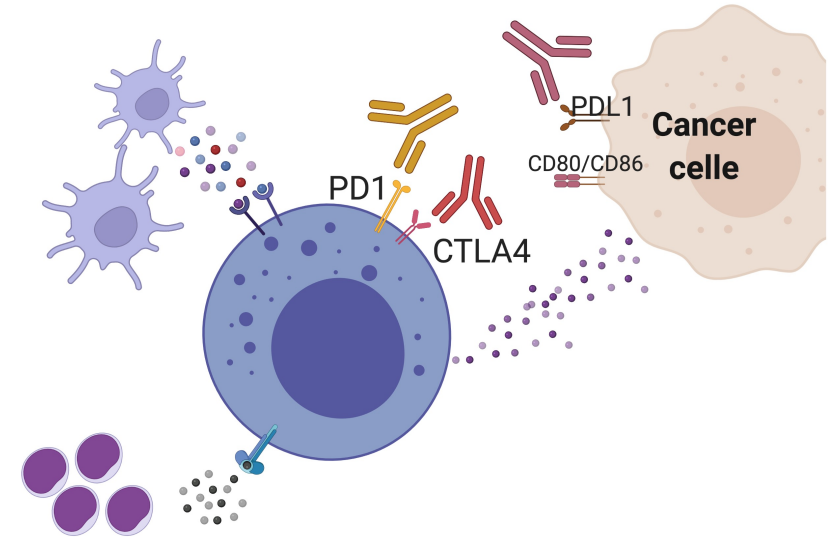
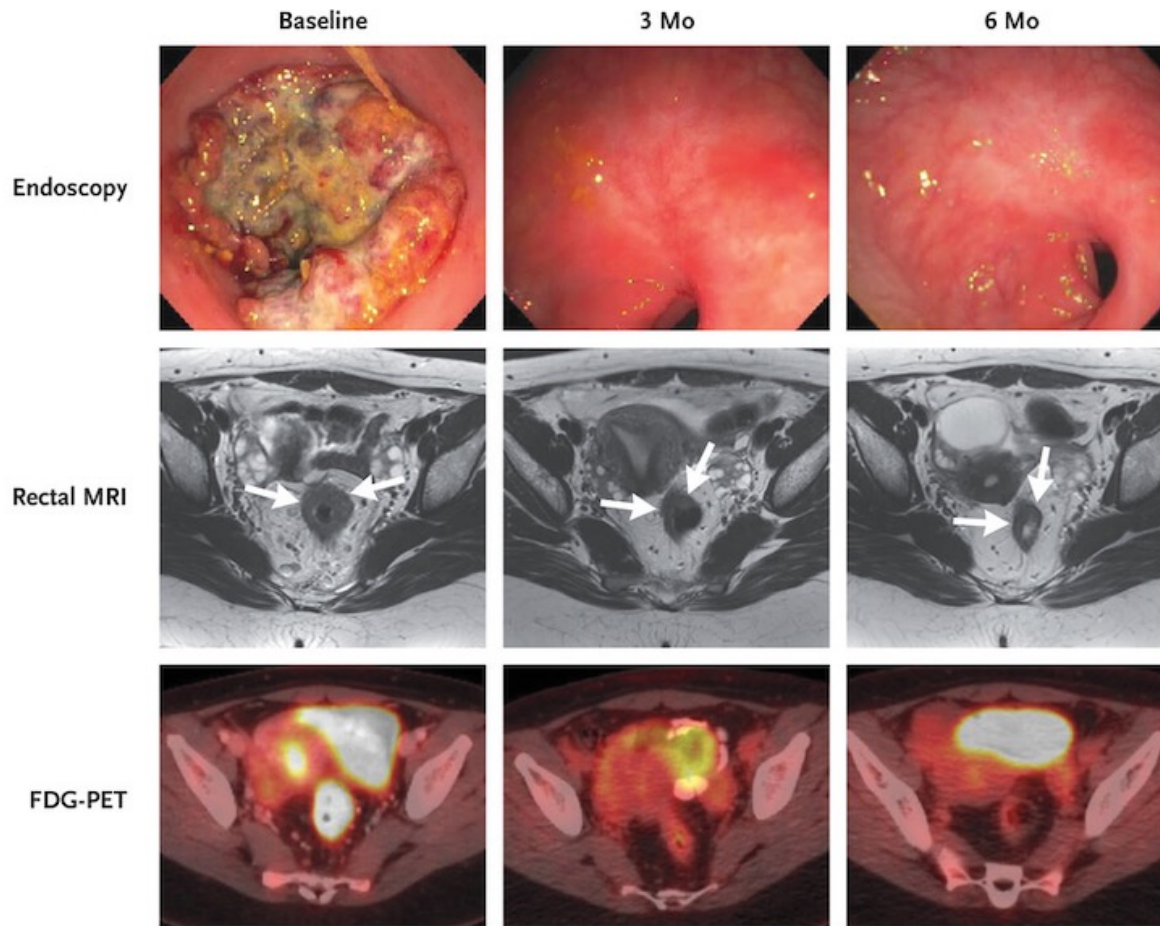
# Blocking checkpoint inhibition



N Engl J Med 2015;372:2073-2074



# Blocking checkpoint inhibition



Cercek et al. N Engl J Med 2022;386:2363-2376



Co-inhibitoriske/co-stimulatoriske molekyler  
**Afdelingernes udgifter bør tage hensyn til irAE**



# Co-inhibitoriske/co-stimulatoriske molekyler

## Afdelingernes udgifter bør tage hensyn til irAE

### Eksempel:

- Incidens af renal celle karcinom i RM: 150/år
- Patienter i ICI behandling er 100/år
- Medicinudgift til behandling i RM: 100 million/år
- Omkring 10 af disse vil blive henvist for en gigtsygdom

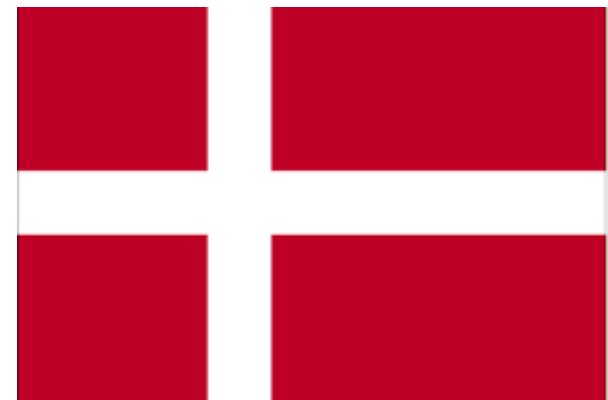


# Co-inhibitoriske/co-stimulatoriske molekyler

## Afdelingernes udgifter bør tage hensyn til irAE

Eksempel:

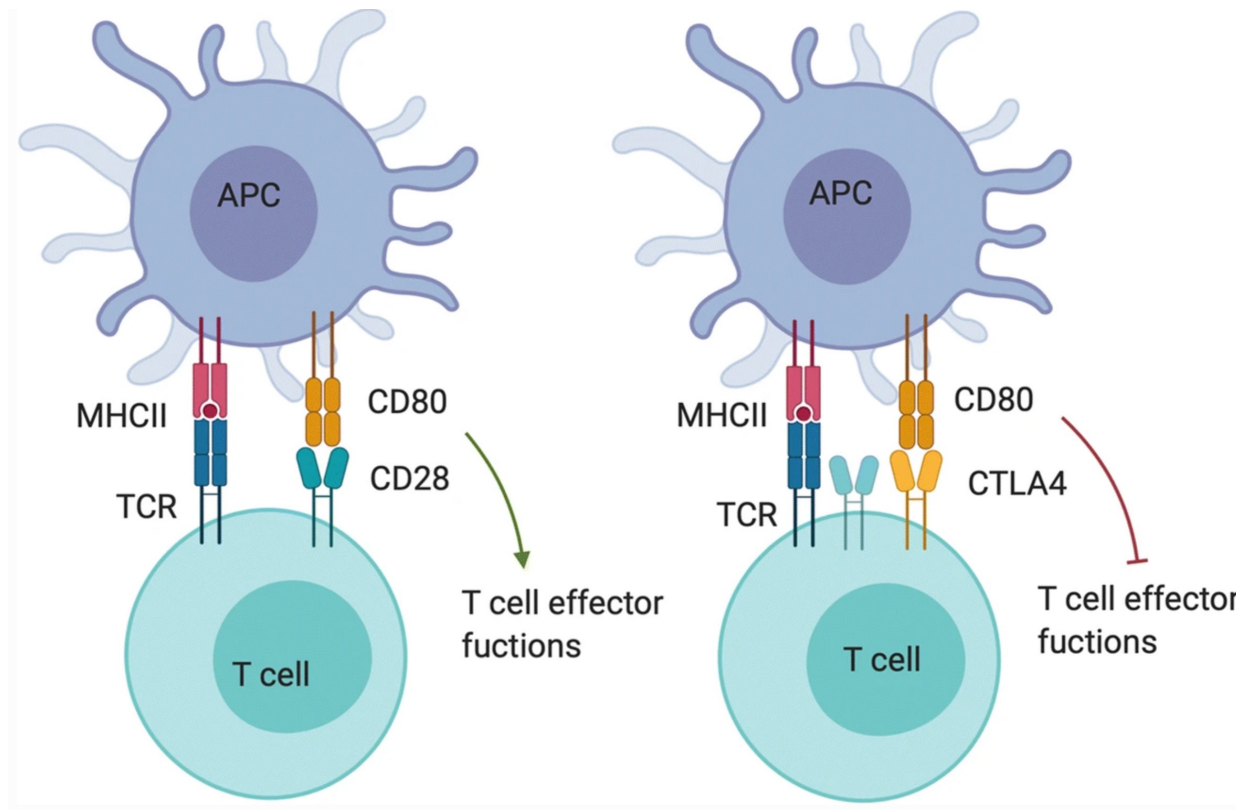
- Lungekræft i Danmark: ca. 2400/år
- ICI behandling tilbud ca. 1500-2000
- Medicinudgift til behandling i RM: 1 milliard/år
- Omkring 200 vil blive henvist for en gigtsygdom



# Indikation for Immune checkpoint inhibitor (ICI)

- Lungekræft
- Malignt melanom
- Hodgkins lymfom
- Urotelial cancer
- Hoved-hals cancer
- Renalcelle cancer
- Colorektal cancer
- Esofagus cancer
- Triple-negativ brystkræft
- Endometrie cancer
- Cervix cancer
- Adenokarcinom i ventrikel eller den gastroesophageale overgang
- Galdegangscancer
- *Og mange andre er på vej*

# Immunsystemet – meget simpelt



Stinne Ravn Greisen & Bent Deleuran  
Current Rheumatology Reports volume 23, : 22 (2021)

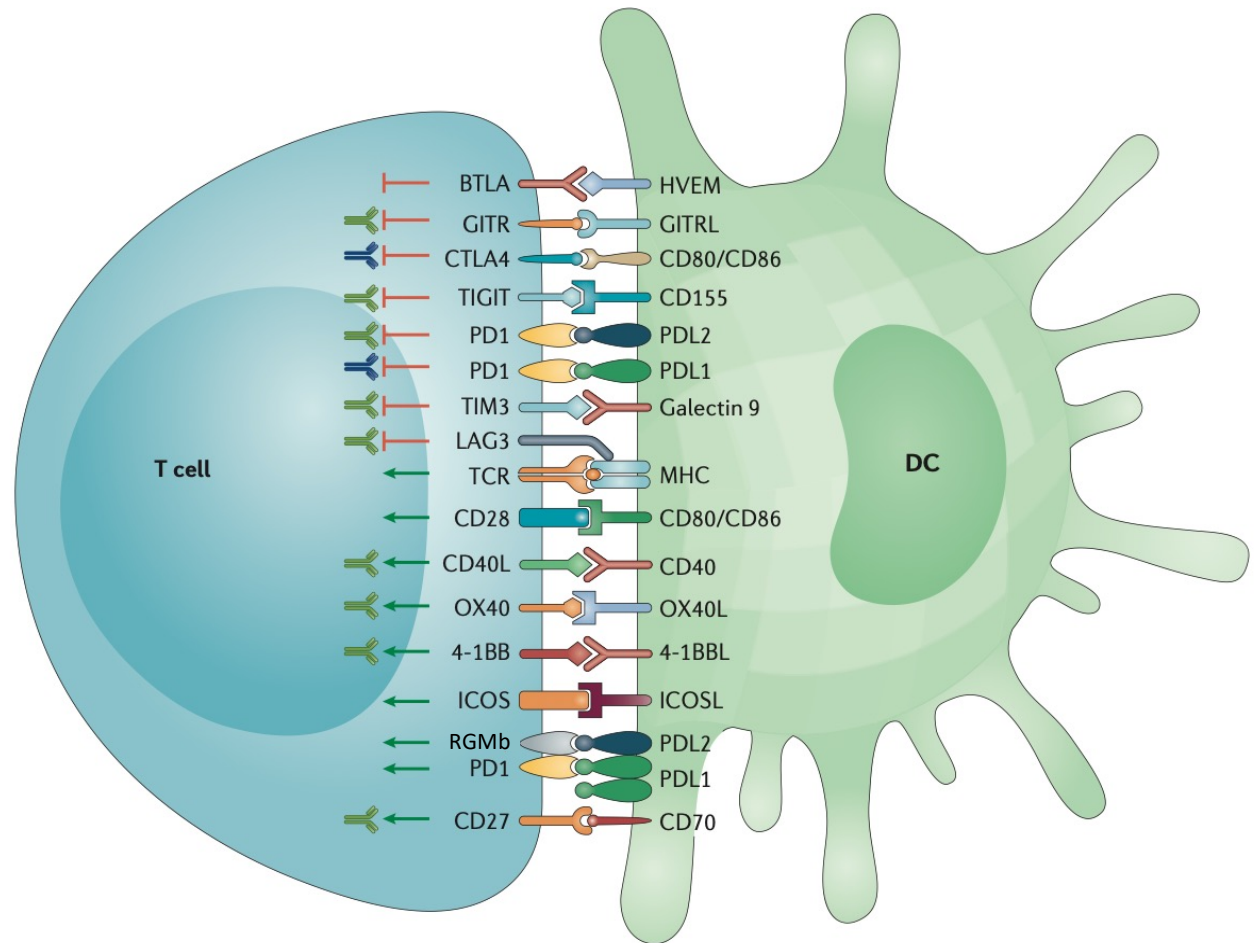
# Immunsystemet – meget simpelt

<https://youtu.be/GIUu239FWMg>



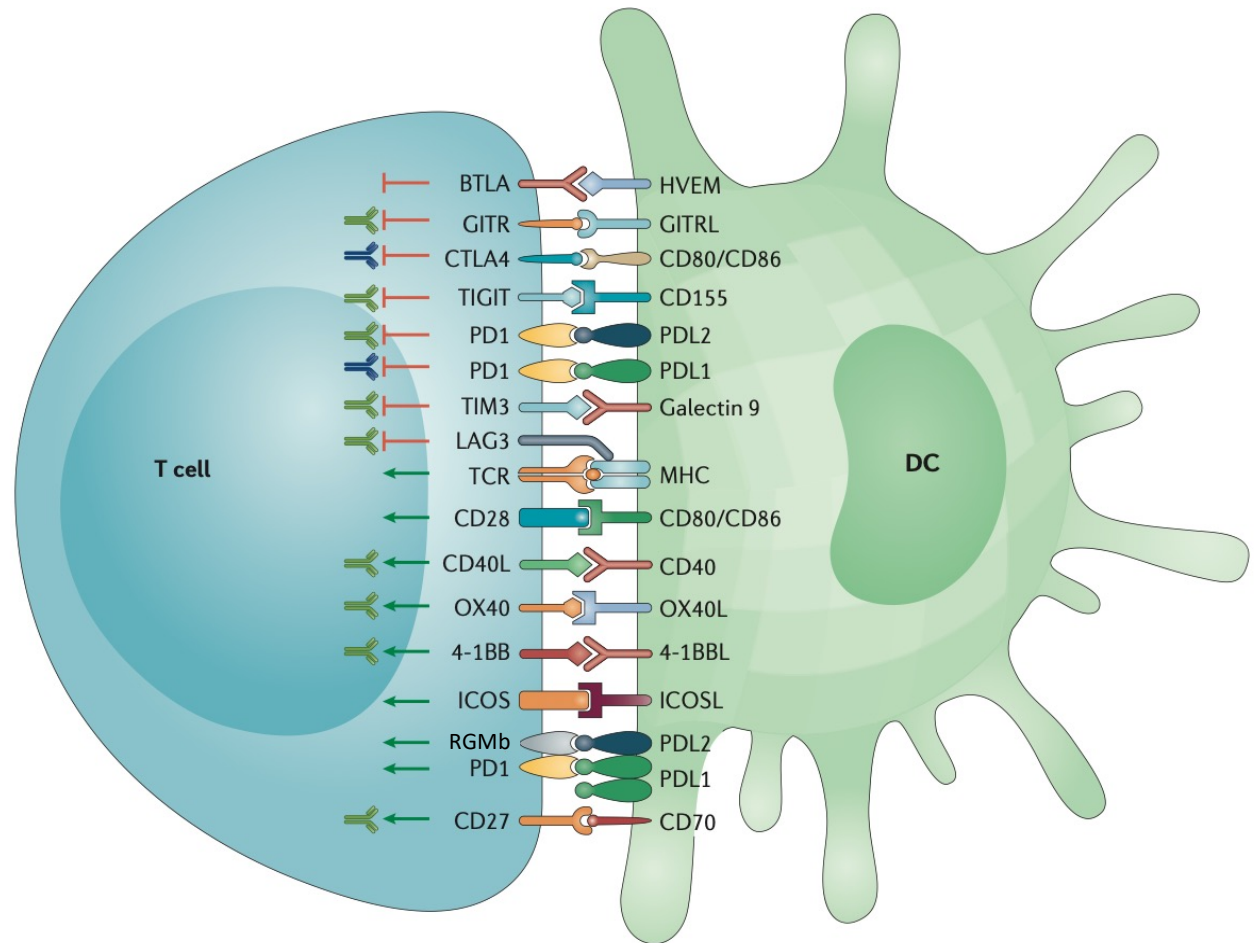
# Co-inhibitoriske/co-stimulatoriske molekyler

- Mange forskellige
- De kan have forskellige organ præference
- Virker forskelligt

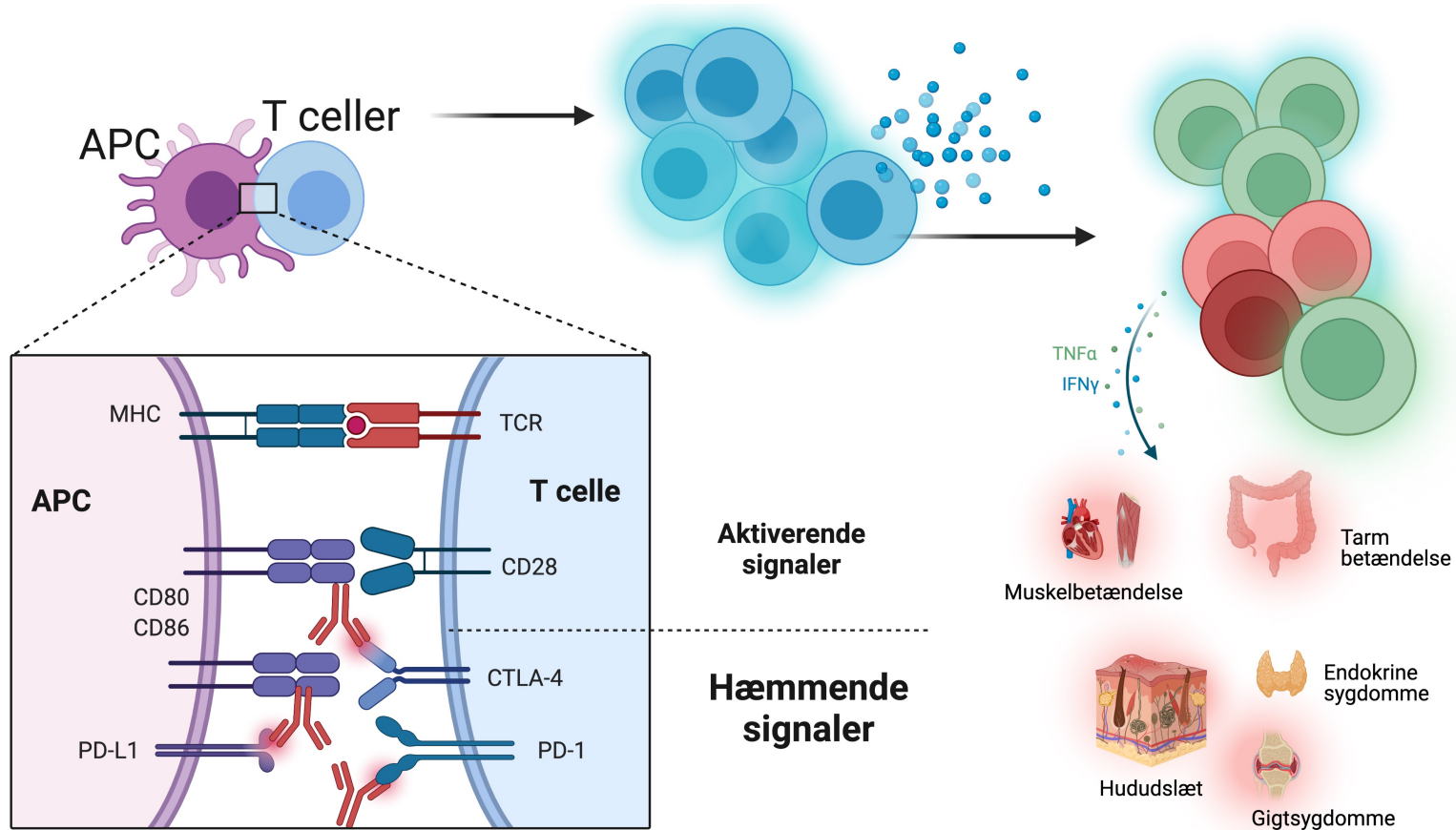


# Co-inhibitoriske/co-stimulatoriske molekyler

- Af de viste molekyler er 3 aktuelt i brug (blå)
- **Resten er på vej**

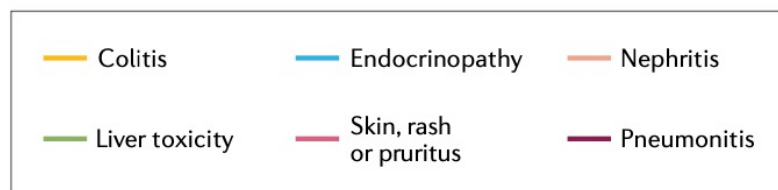
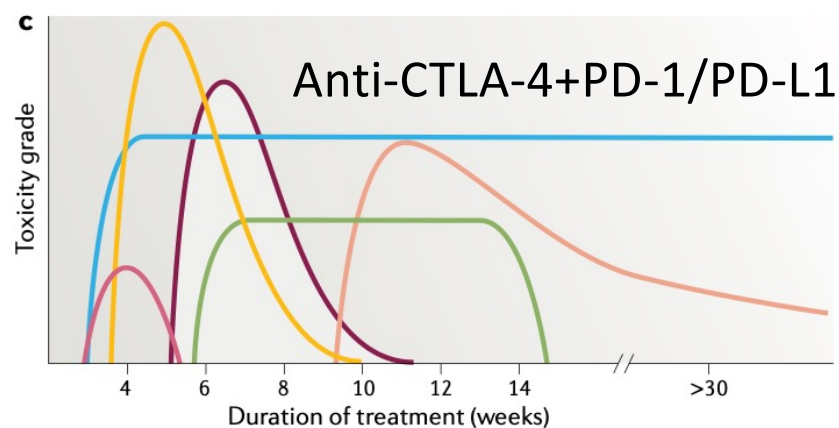
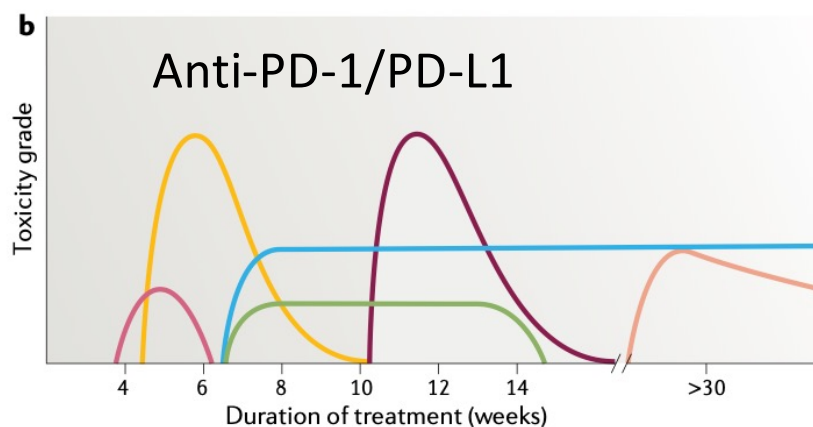
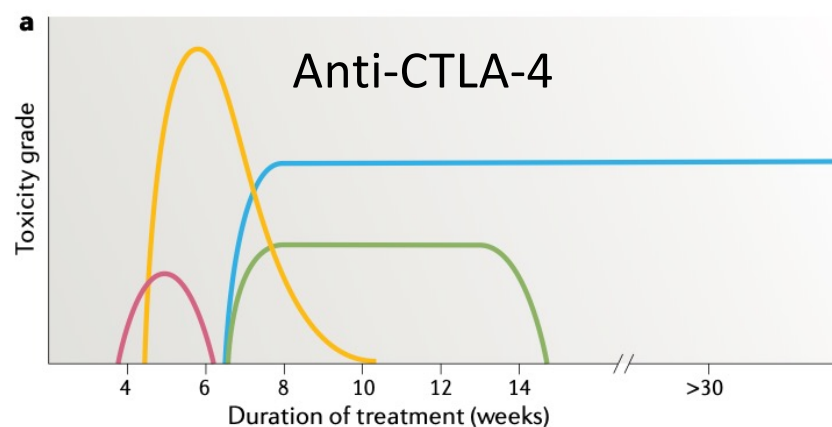


# Immune related adverse events (irAE)



# Immune related adverse events (irAE)

## Brug af flere forskellige checkpoint inhibitor antistoffer giver større sandsynlighed for bivirkninger





# irAE rapporteret fra stort set alle organer

Kan involvere alle specialer



## NEUROLOGIC

- Posterior Reversible Encephalopathy
- Neuropathy
- Guillian-Barre Syndrome
- Myelopathy
- Autoimmune Encephalitis
- Aseptic Meningitis
- Myasthenia gravis
- Transverse Myelitis
- Non-specific symptoms: headache, tremor, lethargy, memory disturbance, seizure

## RESPIRATORY

- Cough/dyspnea
- Laryngitis
- Pneumonitis
- Bronchitis
- Pleuritis
- Sarcoid-like granulomatosis

## RENAL



- Tubulointerstitial nephritis
- Acute renal failure
- Lupus nephritis
- Granulomatous lesions
- Thrombotic microangiopathy

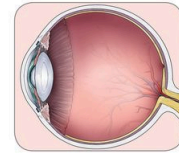
## HEMATOLOGIC

- Autoimmune hemolytic anemia
- Red cell aplasia
- Thrombocytopenia
- Leukopenia/Neutropenia
- Acquired hemophilia
- Myelodysplasia

## DERMATOLOGIC

- Rash/Pruritis
- Mucositis
- Psoriasis
- Vitiligo
- Bullous pemphigoid
- Steven-Johnson syndrome
- DRESS syndrome

## OCULAR



- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Optic neuritis
- Blepharitis
- Retinitis
- Peripheral ulcerative keratitis
- Vogt-Koyanagi-Harada

## CARDIOVASCULAR

- Myocarditis
- Pericarditis
- Pericardial effusion
- Arrhythmia
- Hypertension
- Congestive heart failure

## ENDOCRINE

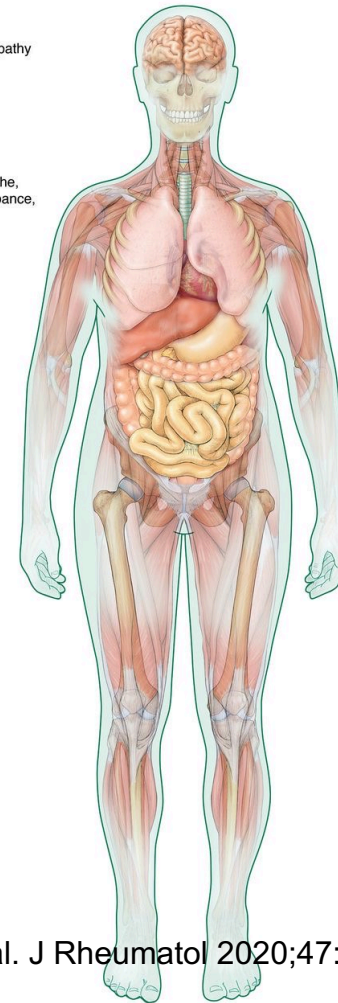
- Hyper or hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

## GASTROINTESTINAL

- Diarrhea
- Gastritis
- Colitis
- Ileitis
- Pancreatitis
- Hepatitis

## RHEUMATOLOGIC

- Arthralgias/Myalgias
- Inflammatory Polyarthritis
- PMR-like
- Psoriatic Arthritis
- Oligoarthritis
- Vasculitis
- Sicca Syndrome
- Sarcoidosis
- Inflammatory myositis
- Resorptive bone lesions and fractures



Shahin Jamal et al. J Rheumatol 2020;47:166-175

# irAE rapporteret fra stort set alle organer

Kan involvere alle specialer



Hvem skal se patienter med irAE?

***Patienten i centrum!***

Højt specialiserede patienter:

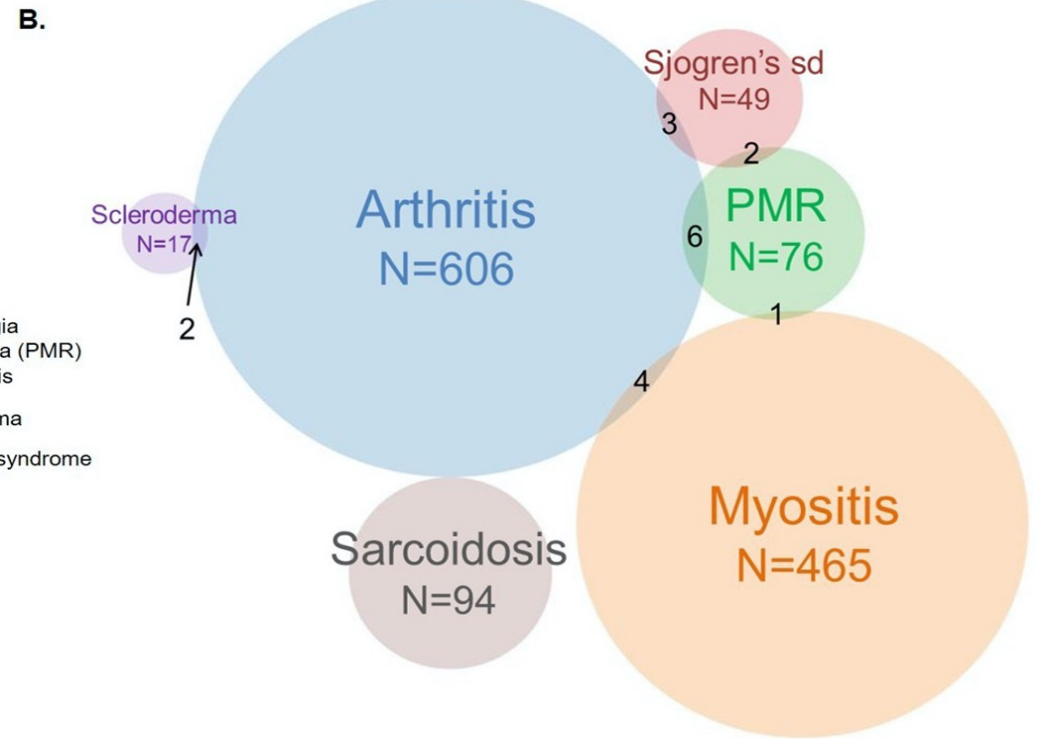
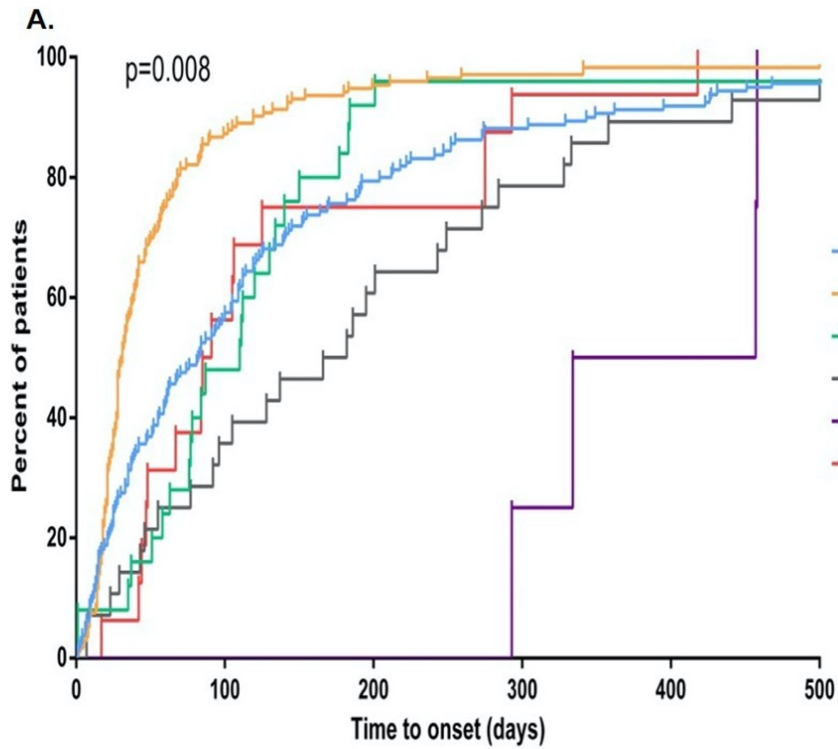
- Myositis/Myocarditis
- Pneumonitis

Lavt specialiserede patienter:

- Myxødem
- Smerter



# irAE over tid



# irAE og Reumatologi - AUH



- Myositis, myokarditis, myopati
- Polymyalgi lignende symptomer
- Periartrose
- Artrit
- Accelereret erosiv OA/ degenerative sygdomme
- Recidiv af cancer
- Ikke definerbar inflammatorisk sygdom

tis  
5

**Førte til stop i behandling med “Checkpoint” i >50% af tilfældene**

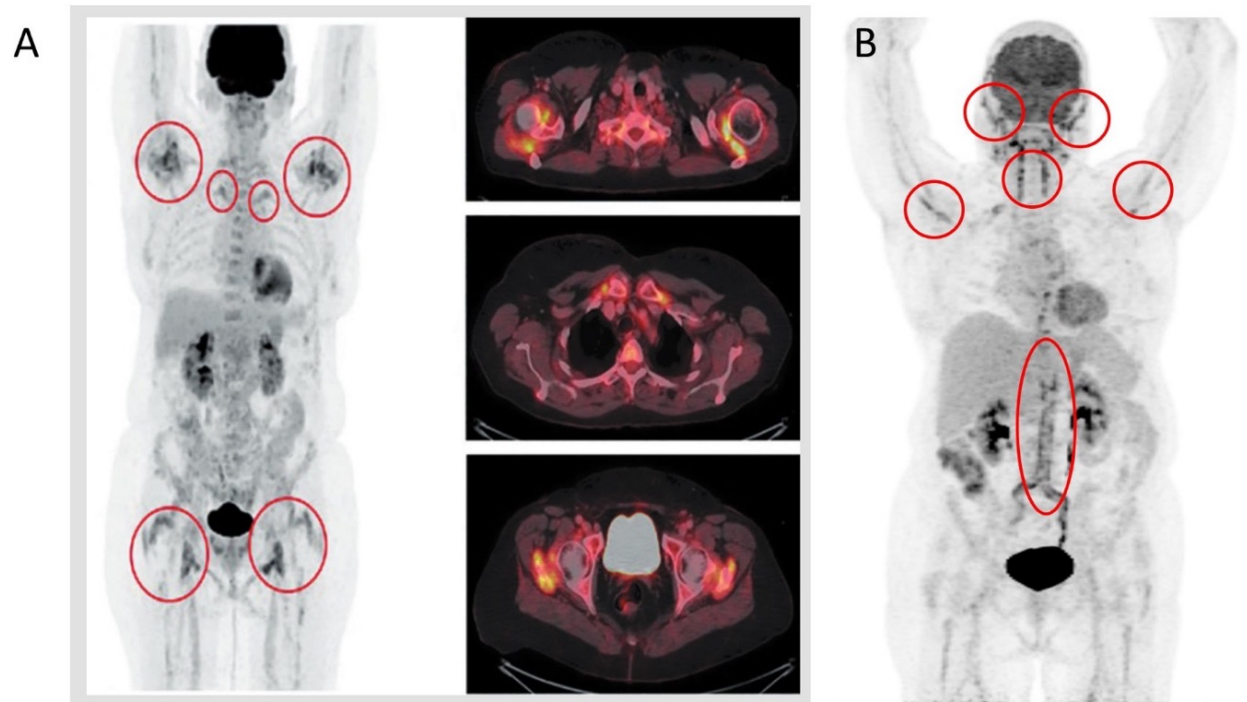
Autoimmun Rev. 2020 Aug;19(8):102586.

# irAE og Reumatologi - Polymyalgia rheumatica

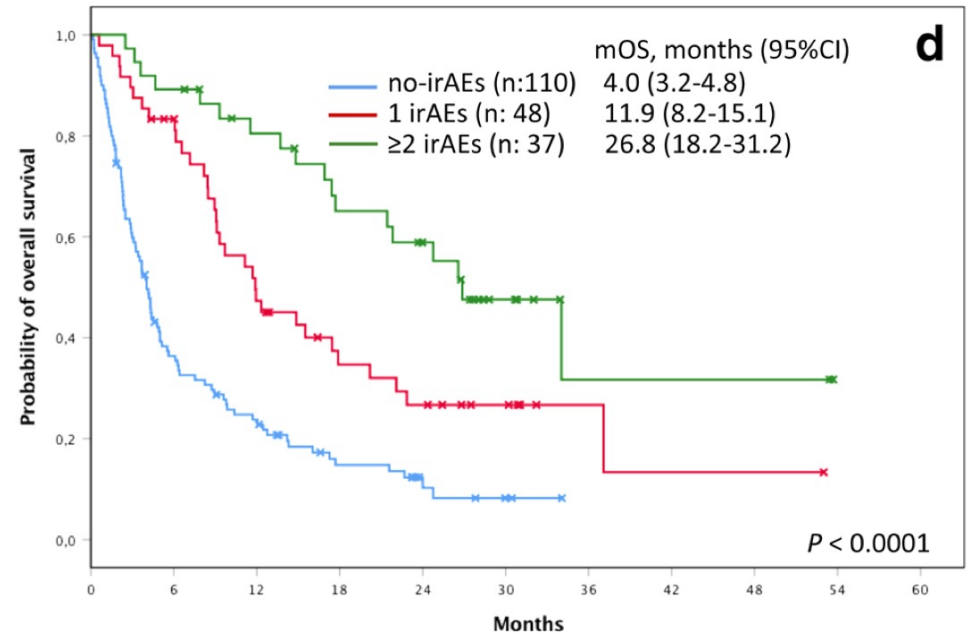
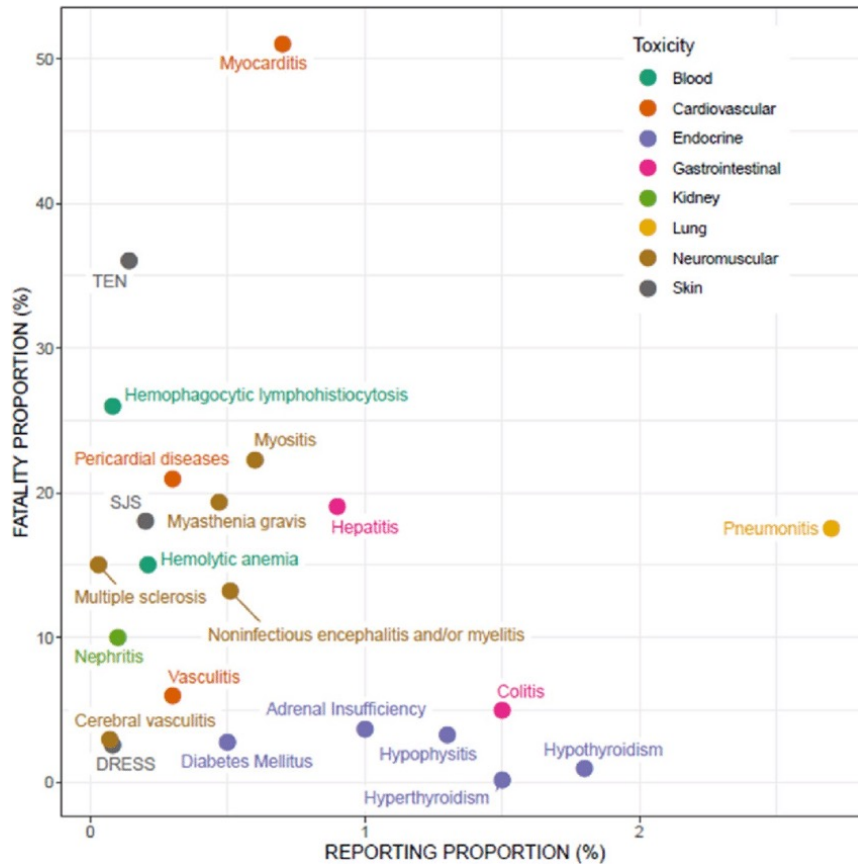
FDG-PET udføres hyppigt

FDG-PET er meget følsom  
overfor PM/AT

FDG-PET kan udføres op til 3  
dage efter start på  
prednisolon, men ikke efter 10  
dage



# Immune related adverse events (irAE)

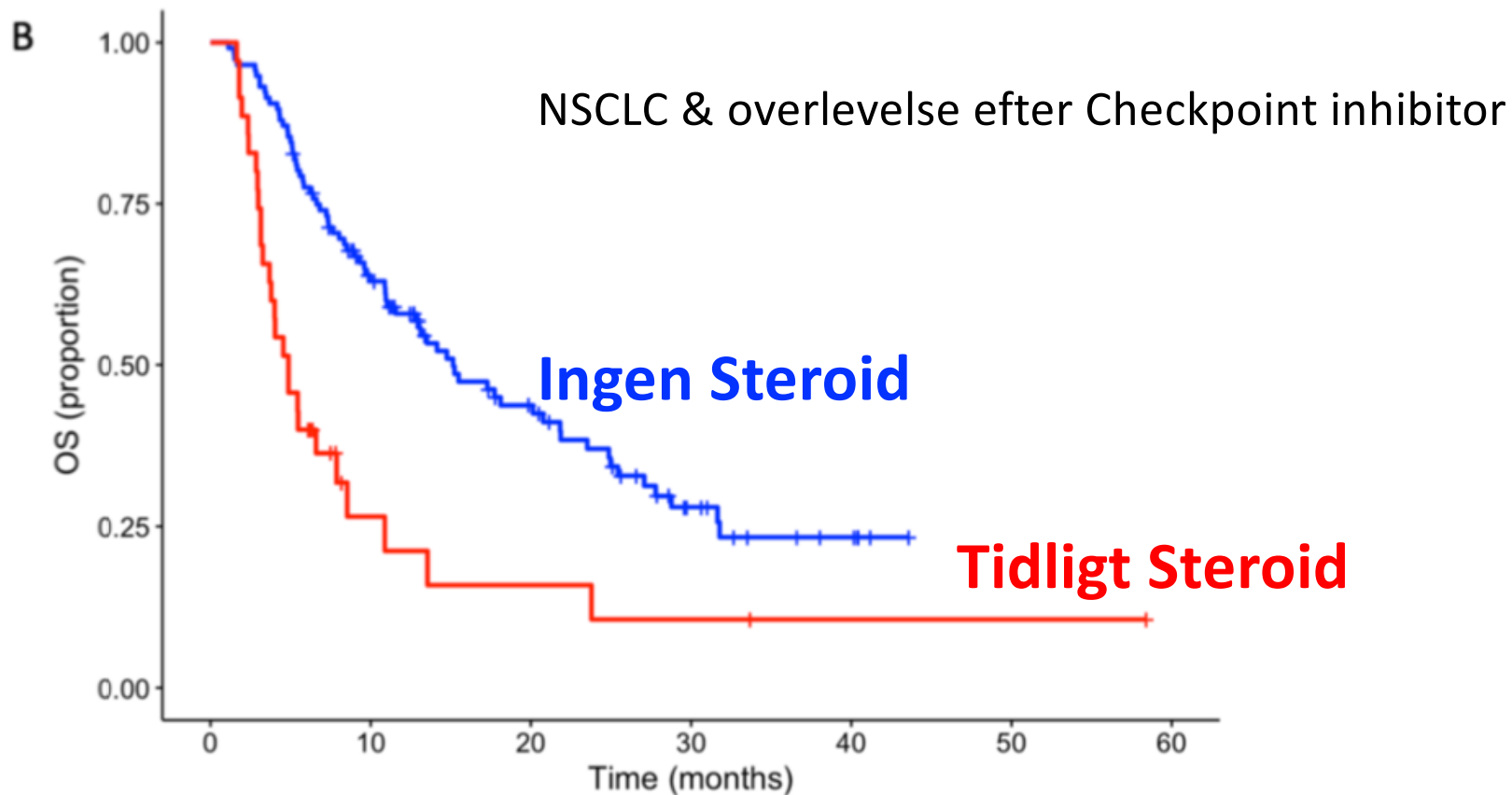


**Milde - til moderate irAE er forbundet med en øget overlevelse**

Journal of Cancer Research and Clinical Oncology (2019) 145:479–485

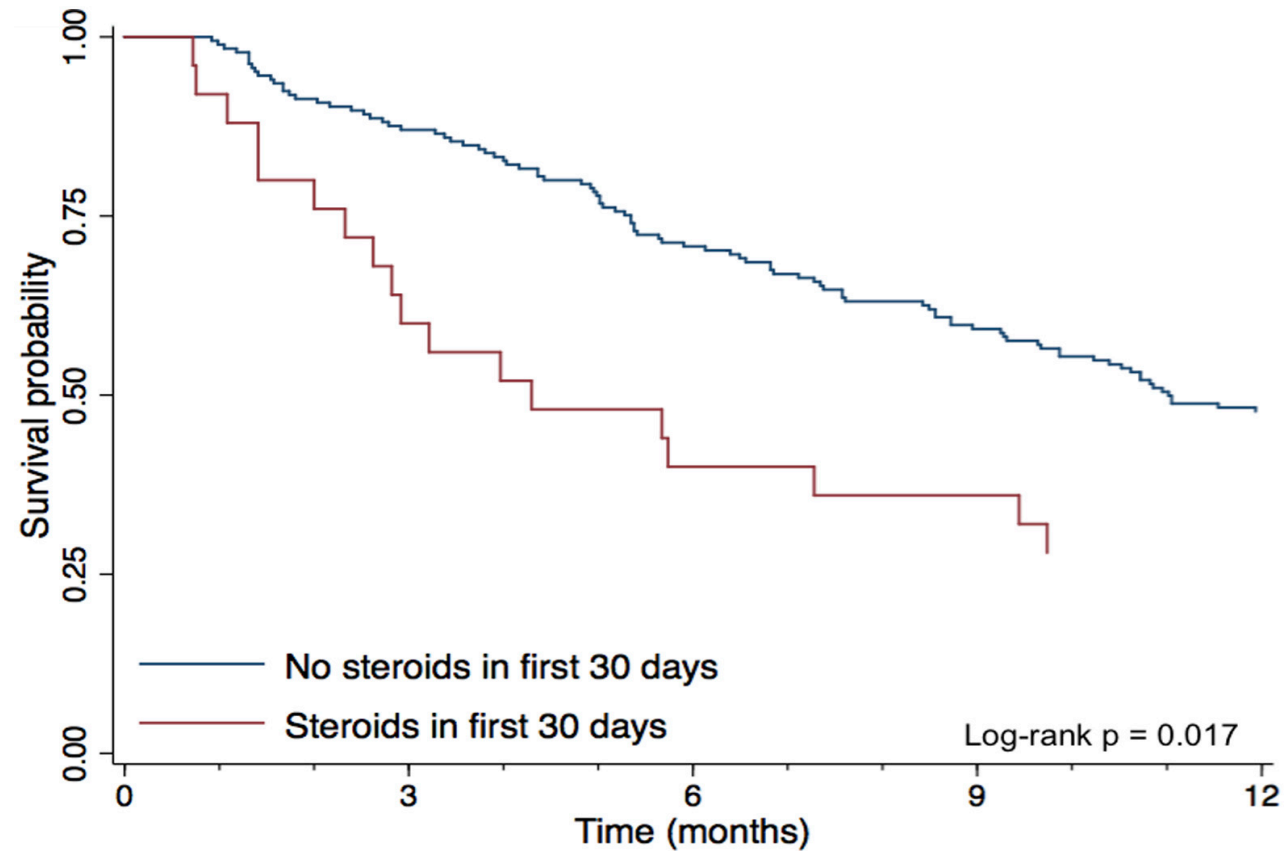
Targeted Oncology (2020) 15, pages 449–466

# irAE og Reumatologi - Behandling



Fucà G, et al. ESMO Open 2019;4:e000457.

# irAE og Prednisolon - overlevelse

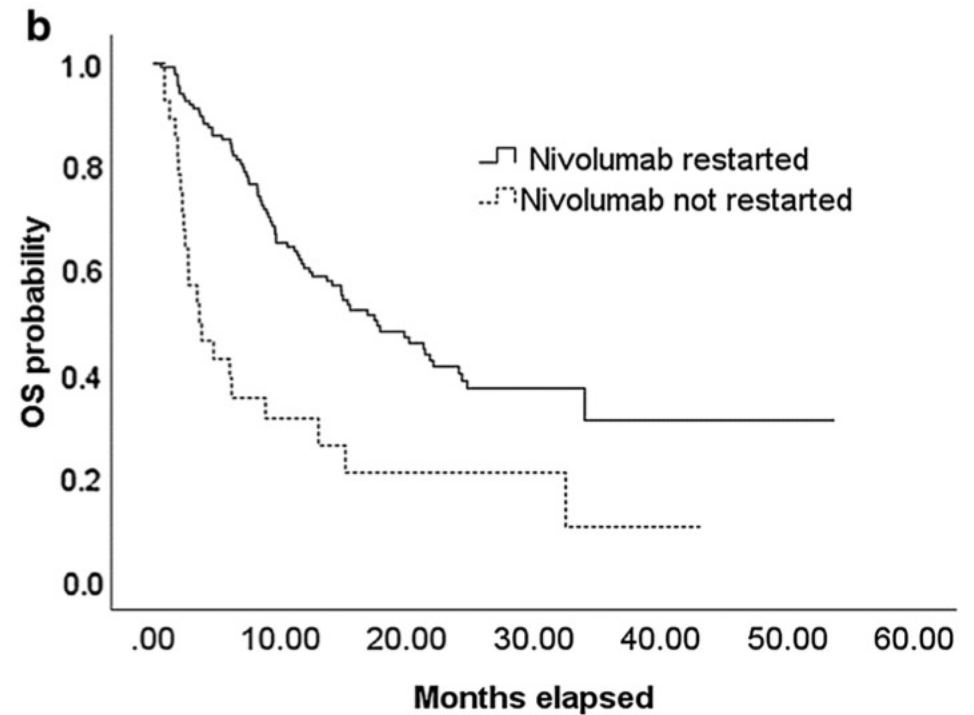
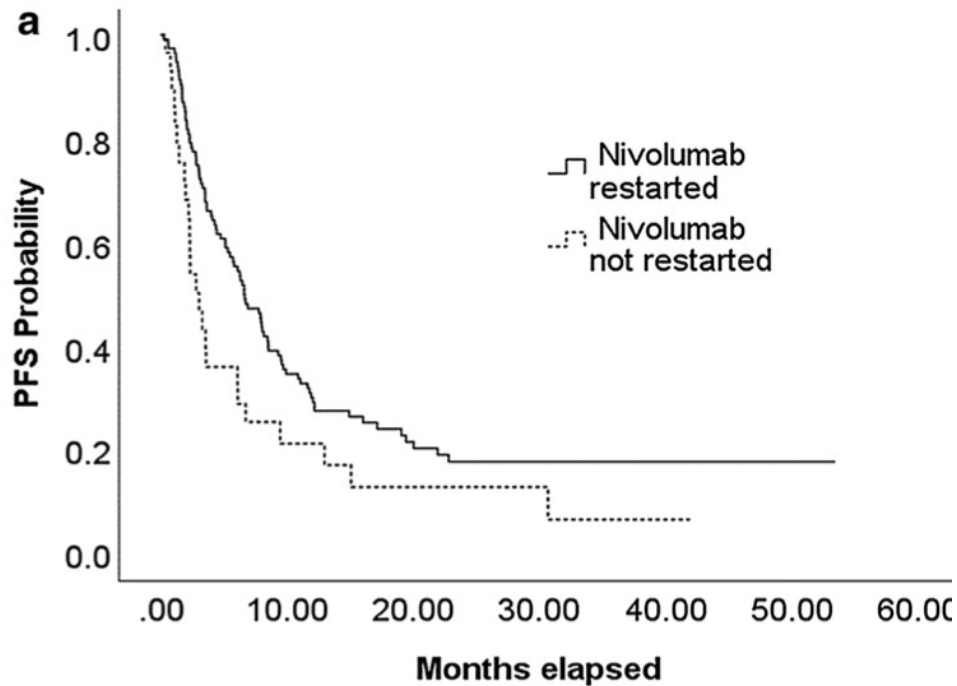


Scott et al. *Journal of Thoracic Oncology* 2018 131771-1775DOI: (10.1016/j.jtho.2018.06.004)



# Nytter det noget at behandle irAE?

Lungecancer

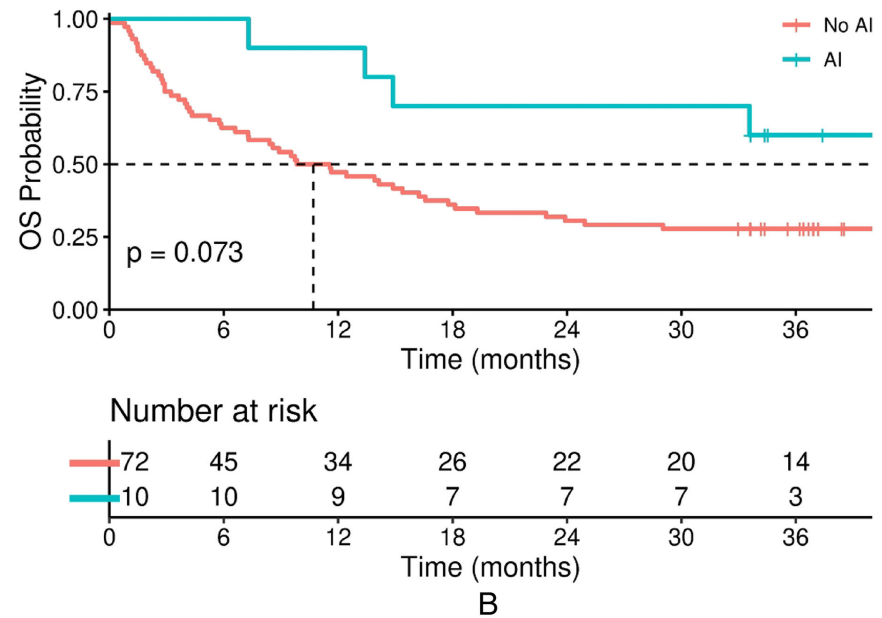
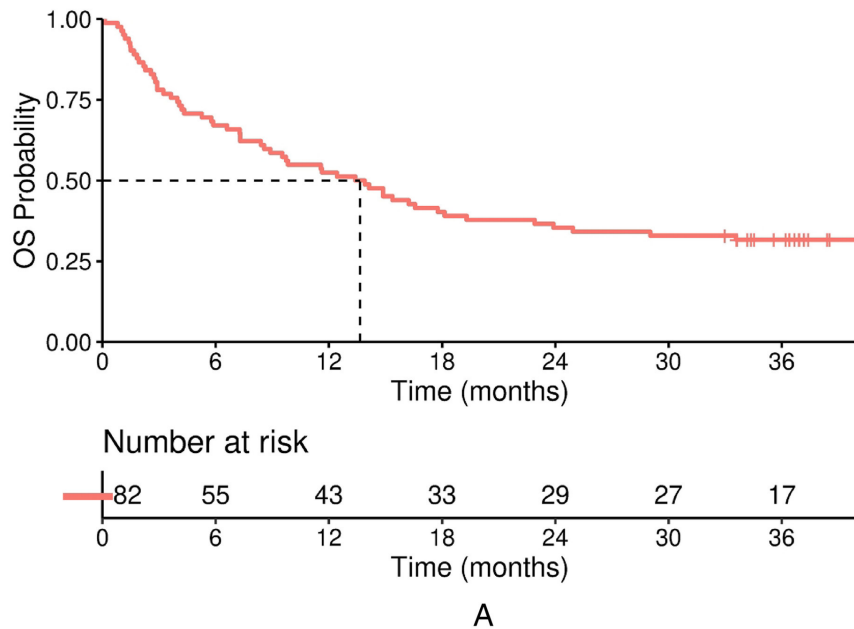


Naqash et al. Cancer Immunology, Immunotherapy (2020) 69:1177–1187

# Profylaktiske tiltag for at undgå irAE



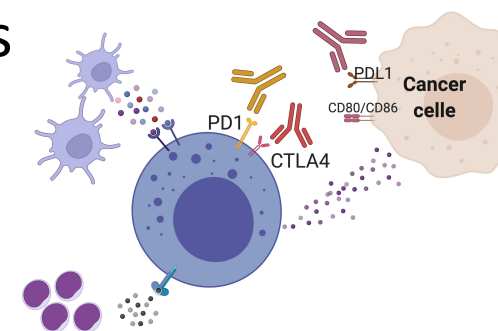
# Har man en autoimmun sygdom – så har man en bedre prognose ved behandling med en checkpoint inhibitor



## irAE ved onkologisk sygdom

### Individualiseret behandling (Points to consider)

- Brug lokalbehandling, hvis muligt
- Så lav dosering af systemiske kortikosteroider, som muligt
- Så hurtig tilbagevenden til checkpoint inhibitor behandlingen, som muligt
- Hurtigt tilråde ophør af checkpoint inhibitor behandlingen, hvis nødvendigt
- Livstruende irAE skal behandles hurtigt med højdosis kortikosteroider
  - Evt. i kombination med IVIG og plasmaferese



irAE ved onkologisk sygdom

## Individualiseret behandling (Points to consider)

- Brug lokalbehandling, hvis muligt



# irAE og behandling af reumatiske sygdomme

## Ingen sikre data

Som udgangspunkt - hvis det påvirker et vaccinationsrespons vil det også påvirke et checkpoint inhibitor respons

## Anbefaling

- Hvis muligt, hurtigt at opnå Prednisolon dosis  $\leq$  **10 mg/dag**
- cDMARD HCQ, SZP, MTX
- bDMARD – anti-TNF antistoffer og anti-IL-6R antistoffer

# irAE og behandling af reumatiske sygdomme

## Ingen sikre data

Som udgangspunkt - hvis det påvirker et vaccinationsrespons vil det også påvirke et checkpoint inhibitor respons

## Anbefaling

- Hvis muligt, hurtigt at opnå Prednisolon dosis  $\leq$  **10 mg/dag**
- **cDMARD, HCQ, SZP, MTX – TID!**
- bDMARD – anti-TNF antistoffer og anti-IL-6R antistoffer



# irAE og behandling af reumatiske sygdomme

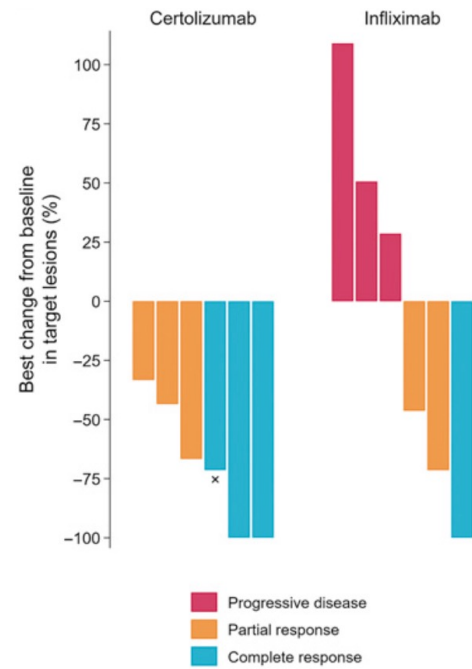
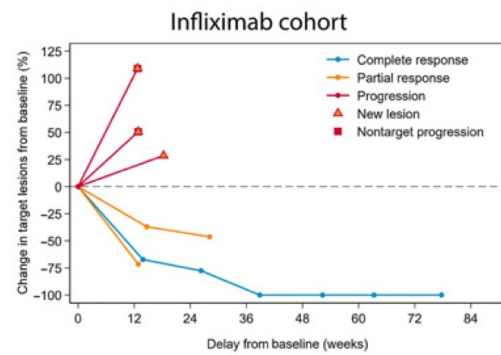
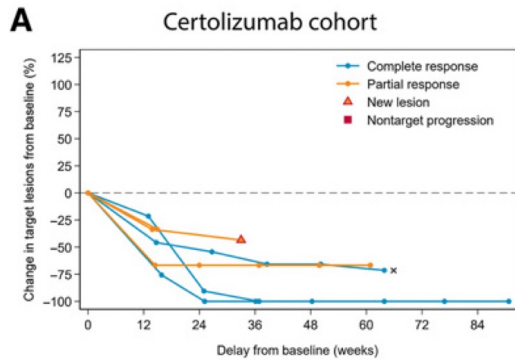
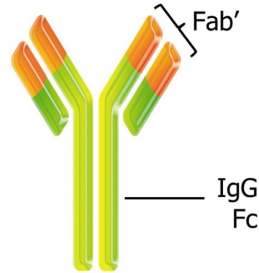
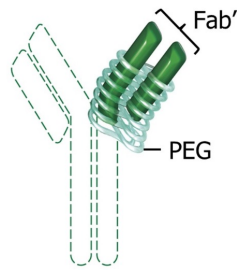
## Ingen sikre data

Som udgangspunkt - hvis det påvirker et vaccinationsrespons vil det også påvirke et checkpoint inhibitor respons

## Anbefaling

- Hvis muligt, hurtigt at opnå Prednisolon dosis  $\leq 10$  mg/dag
- cDMARD, HCQ, SZP, MTX – TID!
- **bDMARD – anti-TNF antistoffer og anti-IL-6R antistoffer**

# irAE og bDMARD – anti-TNF $\alpha$ antistof behandling



## Phase Ib Nivolumab and Ipilimumab with Infliximab or Certolizumab in Patients with Advanced Melanoma

Montfort et al. Clin Cancer Res 2021;27:1037–47

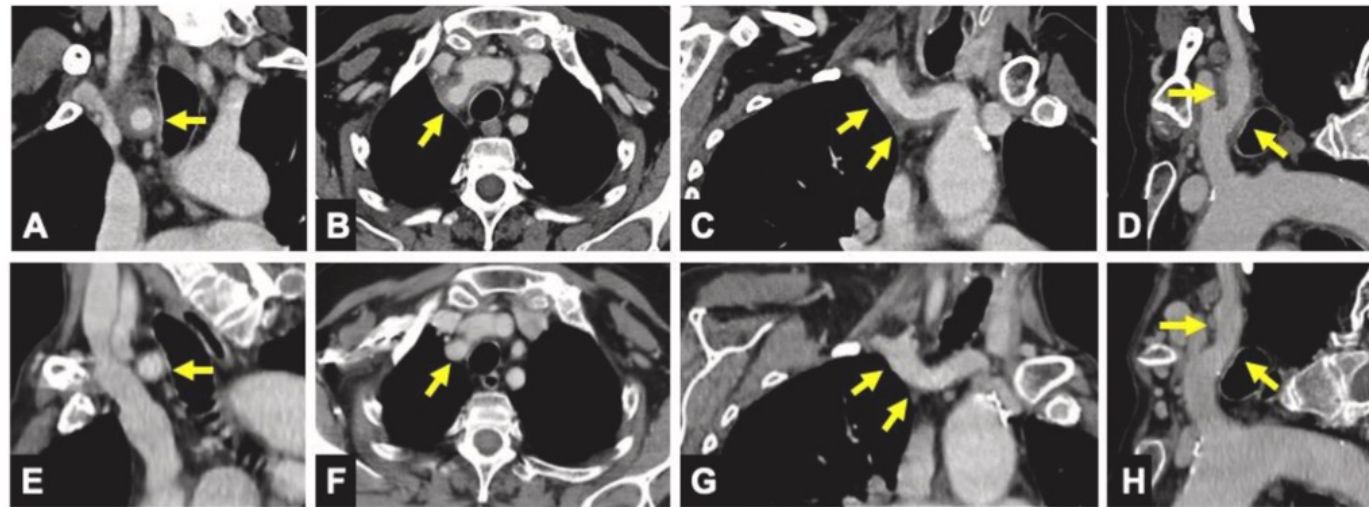
Porter et al Journal of Reproductive Immunology. 2016; 116: 7-12

# irAE og bDMARD – anti-IL-6R antistof behandling

Meta analyse

*” Tocilizumab also seems to be characterized by a remarkable safety profile that extends to the underlying malignancy.*

*Our data support a combined therapeutic approach based on ICI continuation alongside tocilizumab”*



# irAE og behandling generelt

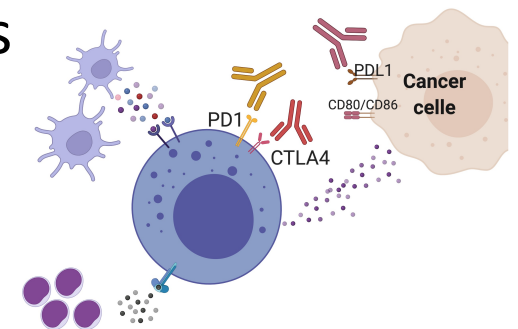
## – personlige overvejelser

Grad	Checkpoint inhibitor behandling	Inflammations behandling
1 - Mild	Fortsæt	Lokal behandling, NSAID, Paracetamol
2 - Moderat	Fortsæt	Lokal behandling (Prednisolon < 10mg/dg)
3 - Svær	Pause	anti-TNF/anti-IL-6R, evt. cDMARD og Prednisolon < 10 mg/dg
4 - Livstruende	Ophør	Høj dosis prednisolon, evt. IVIG
5 - Dødelig		

## irAE ved onkologisk sygdom

### Individualiseret behandling (Points to consider)

- **Brug lokalbehandling, hvis muligt**
- Så lav dosering af systemiske kortikosteroider, som muligt
- Så hurtig tilbagevenden til checkpointinhibitor behandlingen, som muligt
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irAE ved onkologisk sygdom

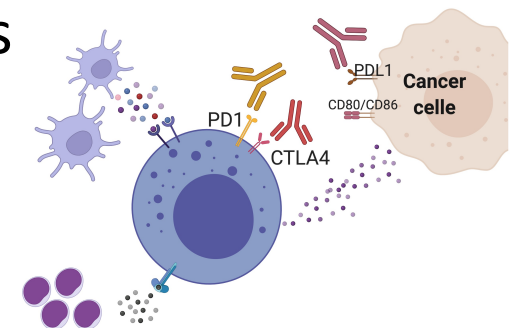
## Individualiseret behandling (Points to consider)

- Brug lokalbehandling, hvis muligt
- Så lav dosering af systemiske kortikosteroider som muligt

**Ca 50% - 66% kan vende tilbage til immunterapi – i et eller andet omfang**

nødvendigt

- Livstruende irAE skal behandles hurtigt med højdosis kortikosteroider
  - Evt. i kombination med IVIG og plasmaferese





# Sygeplejerske, irAE – udfordringer og kompetencer

- Hurtig behandling er ofte en nødvendighed
- Mange yngre patienter
- Vi følger ikke vejledninger for RA/PsA osv.
- Vi er ofte en service afdeling til Onkologisk afdeling

# irAE og reumatologi/immunologi

I er velkomne til at kontakte os

[SRG@biomed.au.dk](mailto:SRG@biomed.au.dk)



[bd@biomed.au.dk](mailto:bd@biomed.au.dk)

