



**ImmunoScience Academy**

*Partnering for Education & Optimizing Treatment in ImmunoScience*

Workshop

# Managing treatment-associated adverse events

Mars, floor 1

**Sandrine Aspeslagh**, *Jules Bordet Institute*

Moderated by  
**Guy Jerusalem**, *CHU Liège*





**ImmunoScience Academy**

*Partnering for Education & Optimizing Treatment in ImmunoScience*

# Rare immune-related adverse events

Sandrine Aspeslagh



# Immune checkpoint blockers

## Anti-CTLA-4

**Ipilimumab  
(BMS)**

**Tremelimumab  
(AZ)**

## Anti-PD-1

**Nivolumab  
(BMS)**

**Pembrolizumab = MK3475  
(MSD)**

**PDR001 (Novartis)**

**Cemiplimab (Sanofi)**

**SHR (Chinese Ab\*)**

## Anti-PDL1

**Atezolizumab  
=MPDL3280A  
(Roche/Genentech)**

**Durvalumab=MEDI4736  
(AZ/Medimmune)**

**Avelumab  
(Pfizer)**

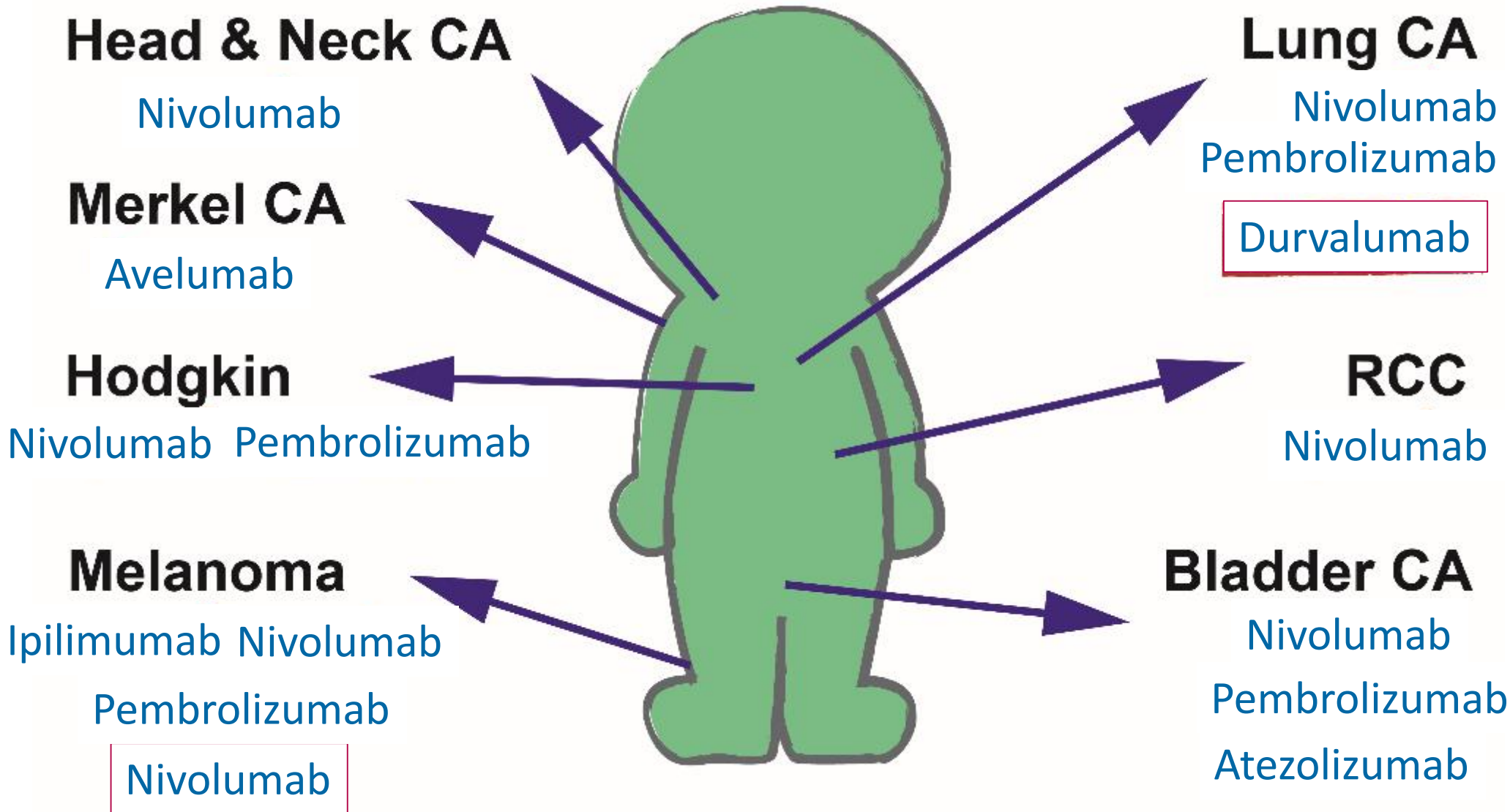
**LY3300054 (Lily)**

\*co-developed by Incyte Biosciences and  
Jiangsu Hengrui Medicine Corporation.

Ab, antibody; AZ, Astra-Zeneca; BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T-lymphocyte associated protein, MSD, Merck Sharp & Dohme; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.  
Sandrine Aspeslagh, personal communication, 2018.

Any off-label data shown are used to support the educational message of the presentation and not intended to endorse use of any drug in any way





**Reimbursement of immune checkpoint blockade, Belgium, November 2018**

CA, cancer; RCC, renal cell carcinoma.  
Sandrine Aspeslagh, personal communication, 2018.

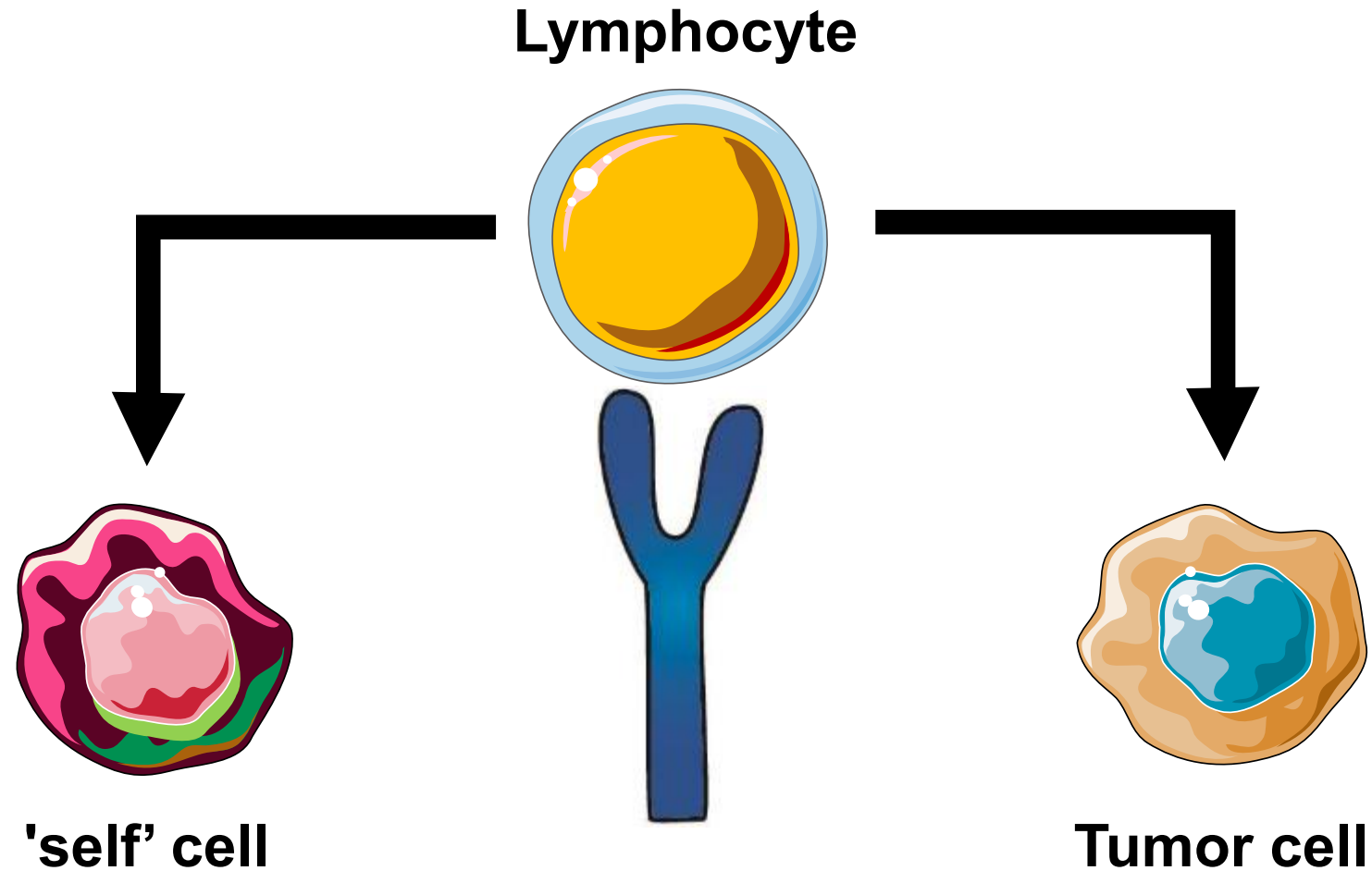
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# Who is in the room?

1. Medical oncologist
2. Radiation oncologist
3. Organ specialist who prescribes ICPI
4. Organ specialist who doesn't prescribe ICPI (and is more involved in the autoimmune problems)
5. Nurse
6. Other

# Only immunity against cancer cells?

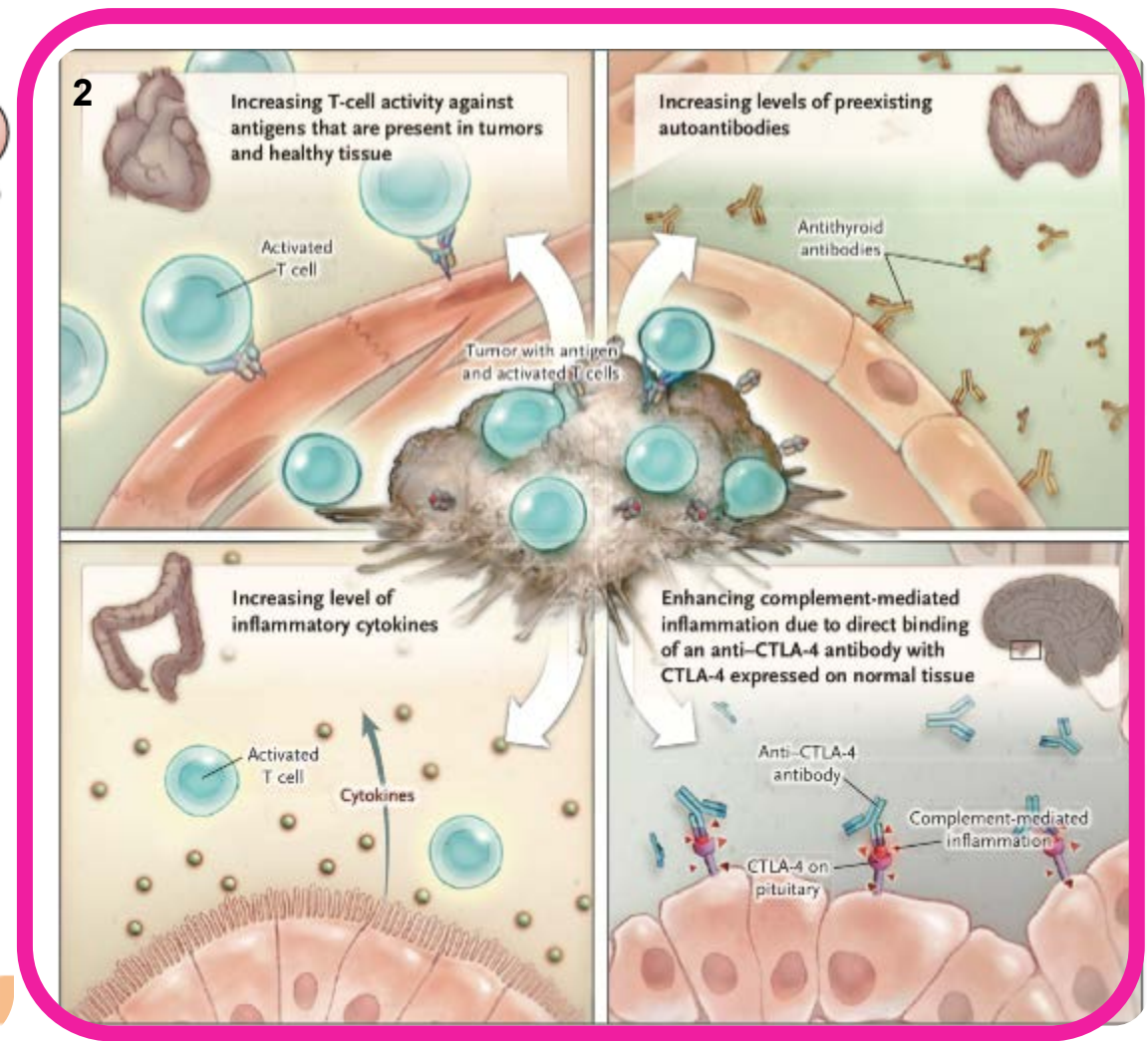
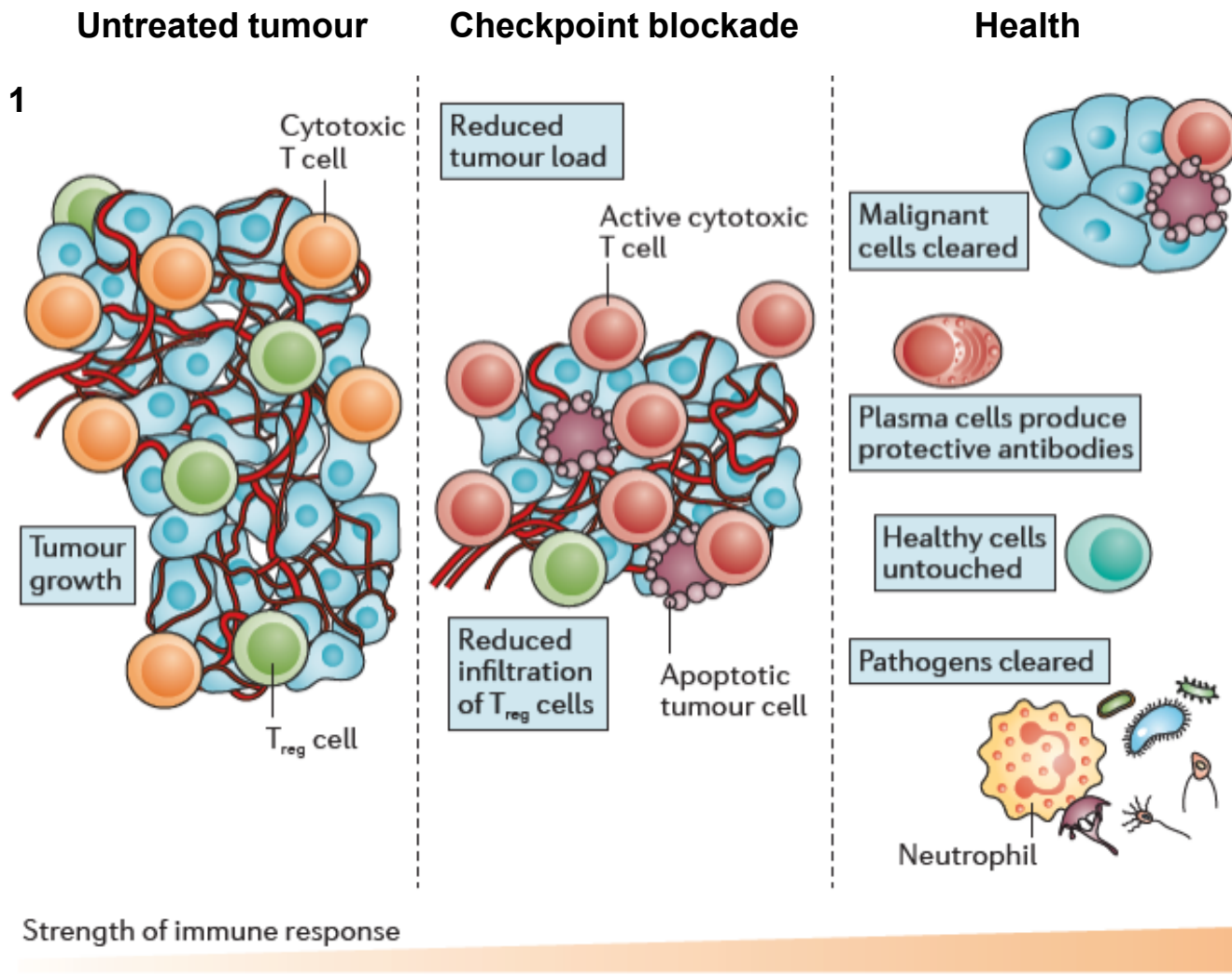


# Have you been confronted with rare side effects of immune checkpoint blockade in your patients?

**Rare: other than hepatitis, colitis, pneumonitis, skin reaction...**

1. Never
2. Yes, more than one patient per month
3. No, less than one patient per month

# Immune balance<sup>1,2</sup>

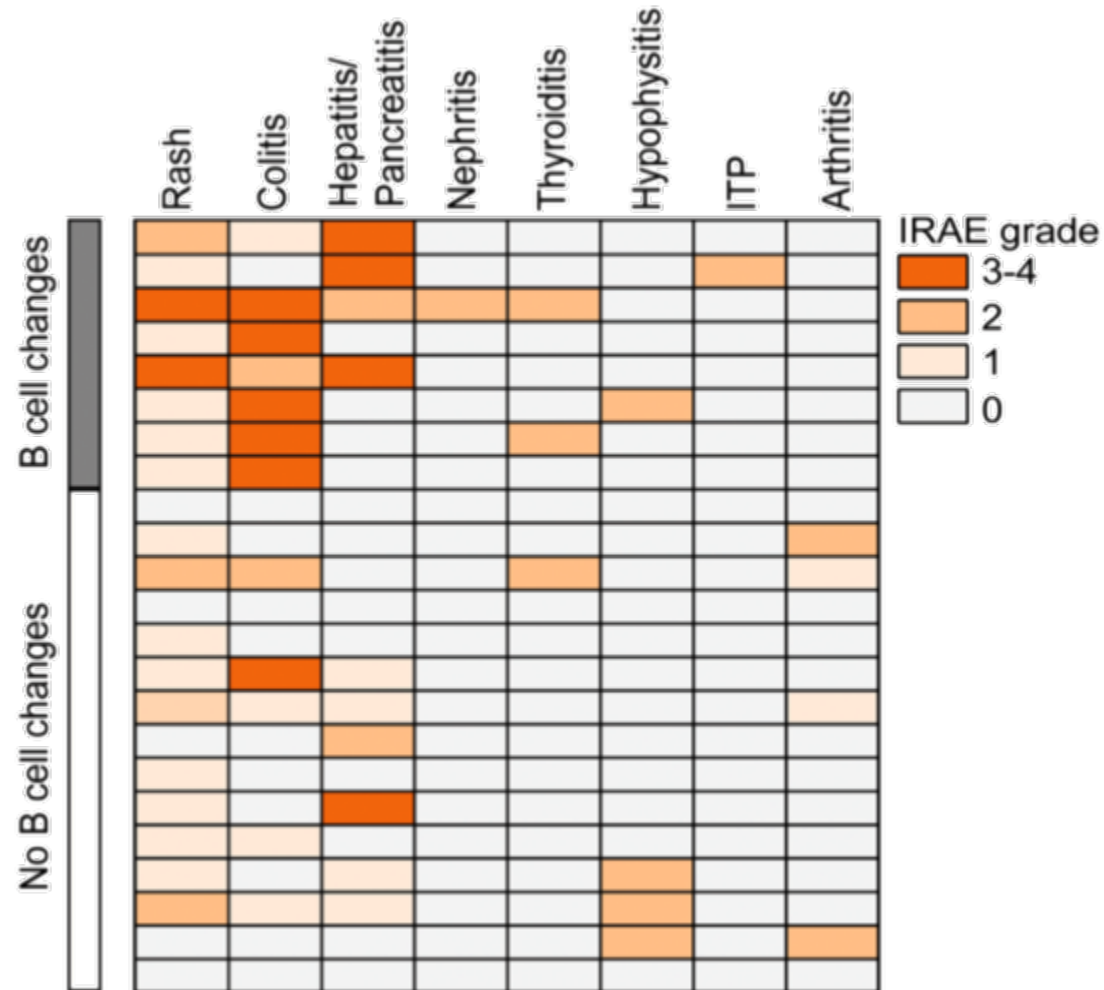


1. Van der Vlist et al. Nat Rev Immunol 2016;12:593–604. 2. Postow et al. 2018, N Engl J Med 2018;378;158–68.

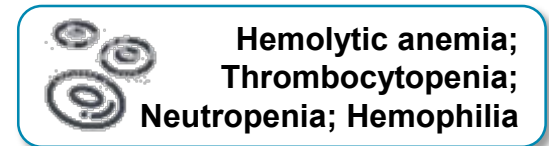
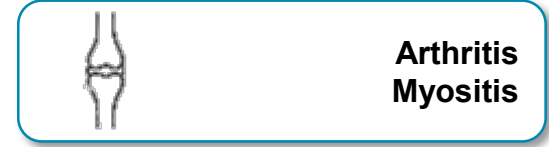
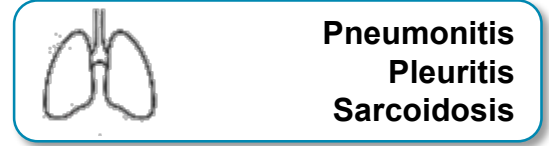
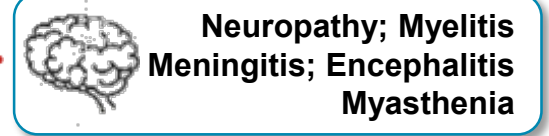
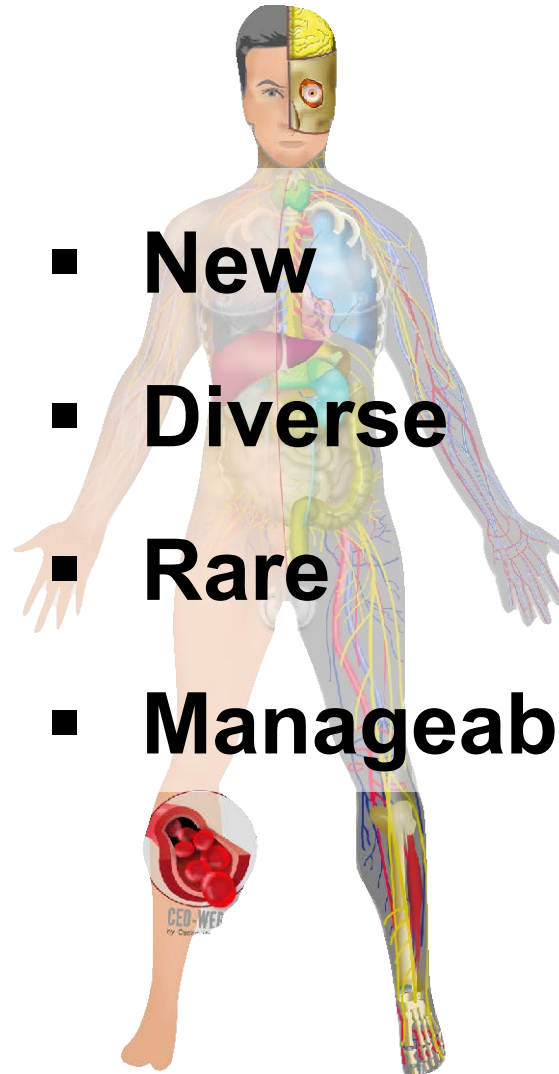
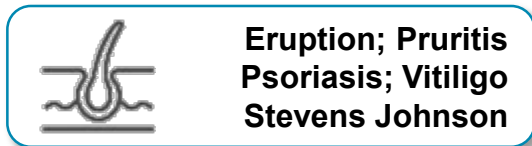
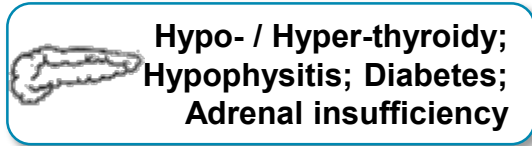




# Early B cell changes predict autoimmunity following combination immune checkpoint blockade<sup>1</sup>



# Toxicity of immune checkpoint blockade agents<sup>1</sup>



1. Adapted from Champiat et al. Ann Oncol 2016;27:559–74.



# Case report: cytokine release syndrome

anti-PDL1+ immunomodulator

19/09/2016		20/09/2016						21/09/2016				
16:00	20:00	00:00	04:00	08:00	12:00	16:00	20:00	00:00	04:00	08:00	12:00	16:00
	143 mmHg			124 mmHg	157 mmHg	104 mmHg	115 mmHg ...		146 mmHg	109 mmHg		135 mmHg
	75 mmHg			75 mmHg	98 mmHg	65 mmHg	68 mmHg ...		82 mmHg	69 mmHg		84 mmHg
	88			75	47	78	86		100	77		101
	40 °C	38,5 °C	40,3 °C	37,6 °C	39,8 °C	38,7 °C	39,6 °C	38,6 °C	39,8 °C	38,5 °C		40,4 °C
	93 %			96 %	93 %	95 %	91 % 92 %		95 %	94 %		94 %
	0 L/min			0 L/min	0 L/min	0 L/min	0...		0 L/min	0 L/min		0 L/min

Day 7

Day 15

+/- 30 days later



- Ferritin >6000 ng/mL
- Fibrinogen < 2g/L
- TG nl
- ASAT/ALAT: Grade 3
- Anemia Grade 1

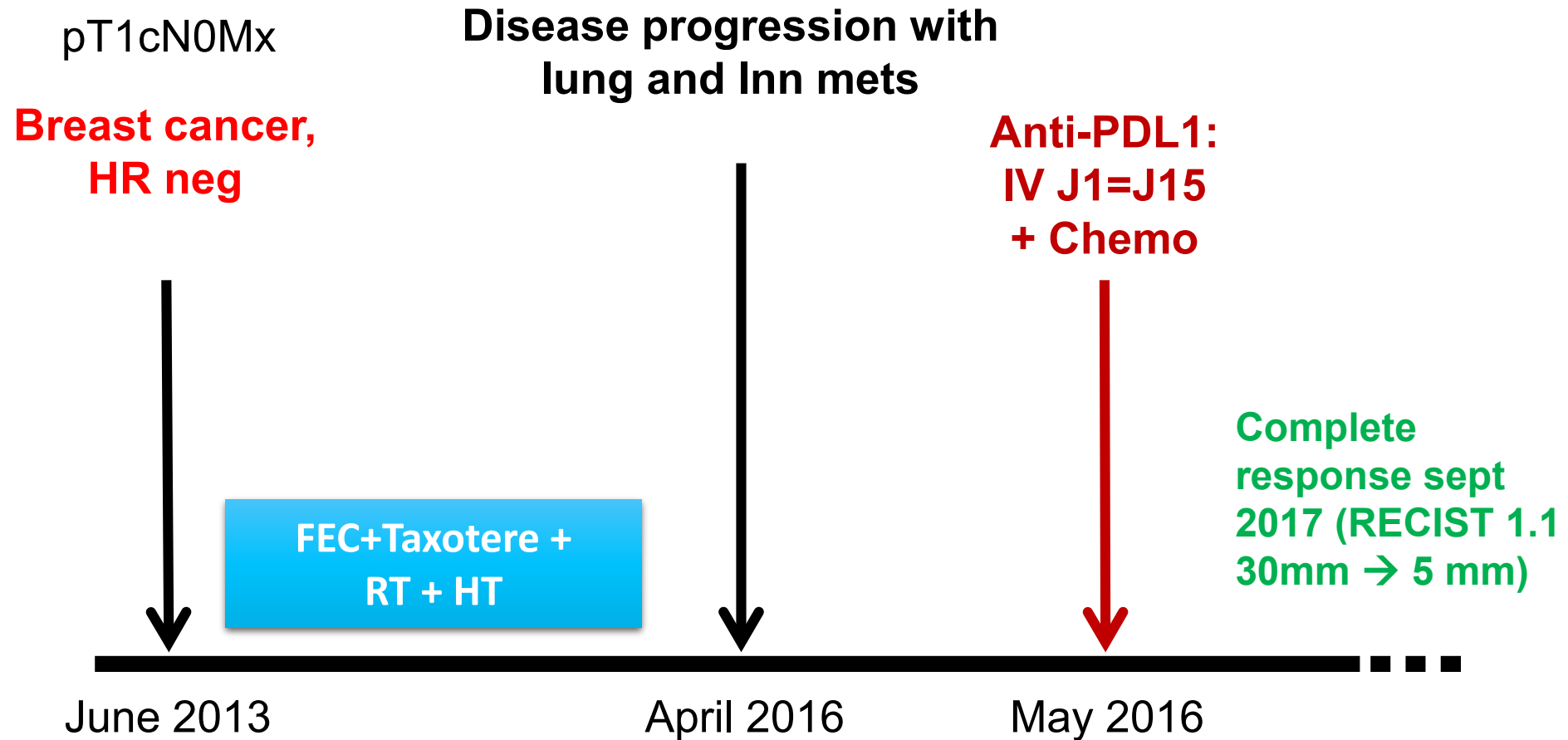
- Respiratory distress**
- ICU:
  - → Corticosteroids (1mg/kg)
  - Resolution within 24h
  - Corticosteroids were decreased rapidly

- Restart anti-PDL1

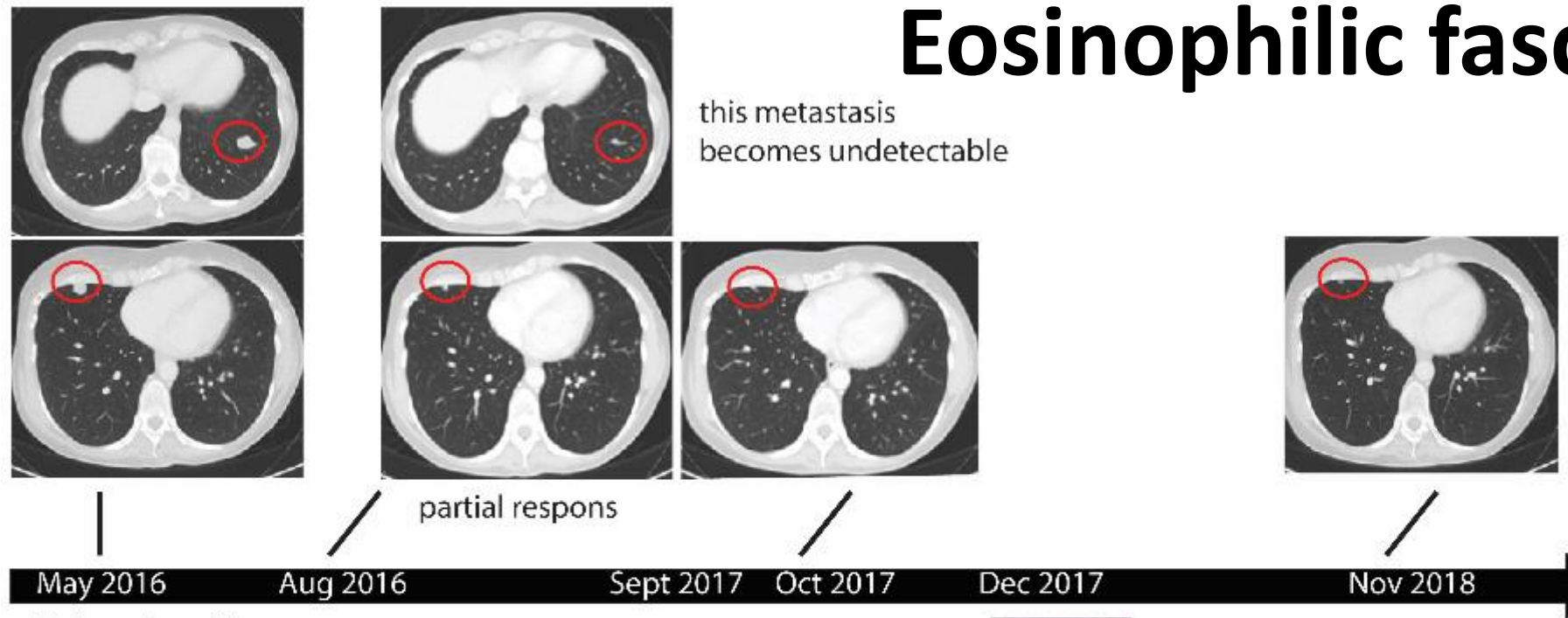
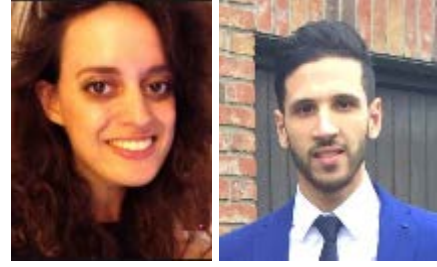
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose <sup>2</sup> of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)



# An example from the clinic



# Eosinophilic fasciitis



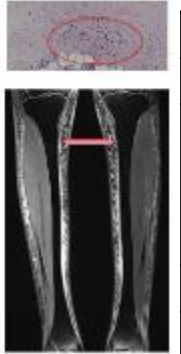
this metastasis becomes undetectable

partial respons



Nabpaclitaxel/  
Atezolizumab

stop Nabpaclitaxel  
stop Atezolizumab



Autoimmunity	
Anti-CCP	1.4 U/mL
Reference value:	Negative Uncertain Positive
<7	
7 - 10	
>10	
Rheumatoid factor	< 11.30 U/mL
	0-40
Antinuclear Antibodies (ANF)	
ANF fluorescence pattern	Speckled
ANF intensity (dilution 1:40)	+1
Reference value (negative to positive scale)	-1 to +5

Images provided courtesy of Sandrine Aspeslagh, will be submitted soon: Wissam Y et al.  
CCP, cyclic citrullinated peptide

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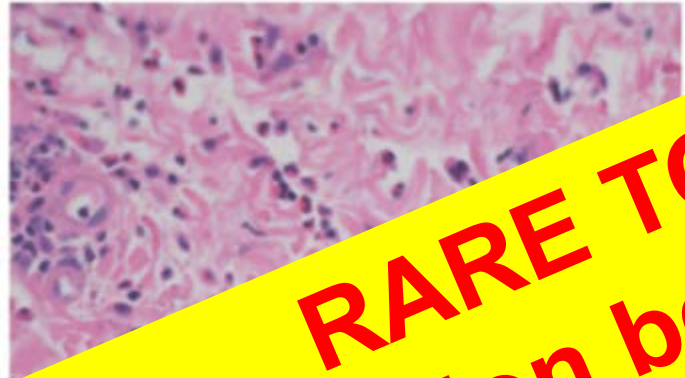
# Eosinophilic fasciitis and acute encephalopathy toxicity from pembrolizumab treatment of a patient with metastatic melanoma<sup>1</sup>

MRI: upper arm

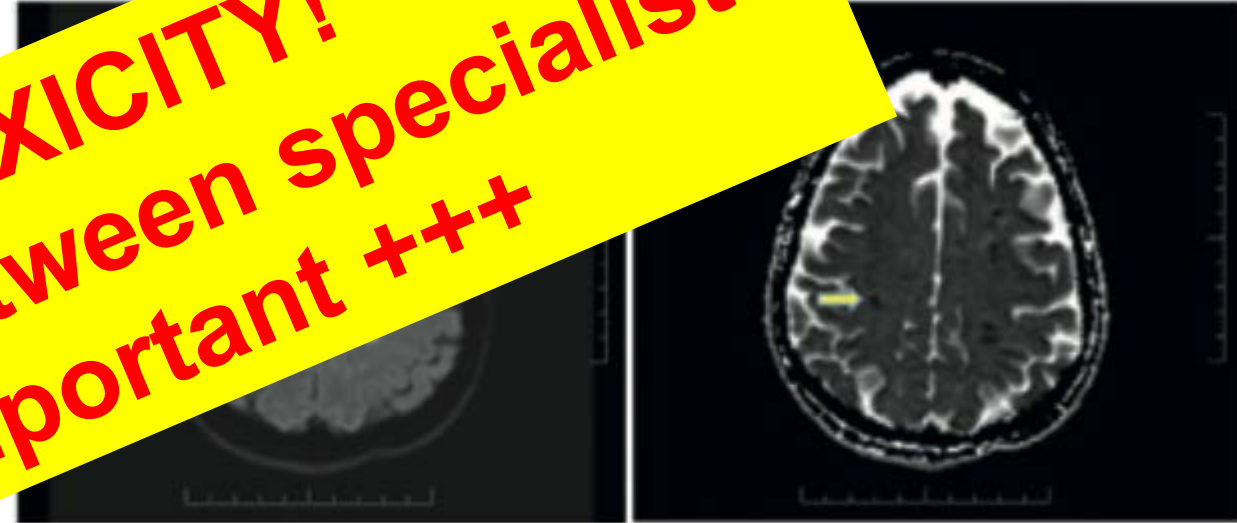


Marked fascial edema

Muscle biopsy



MRI of acute encephalopathy



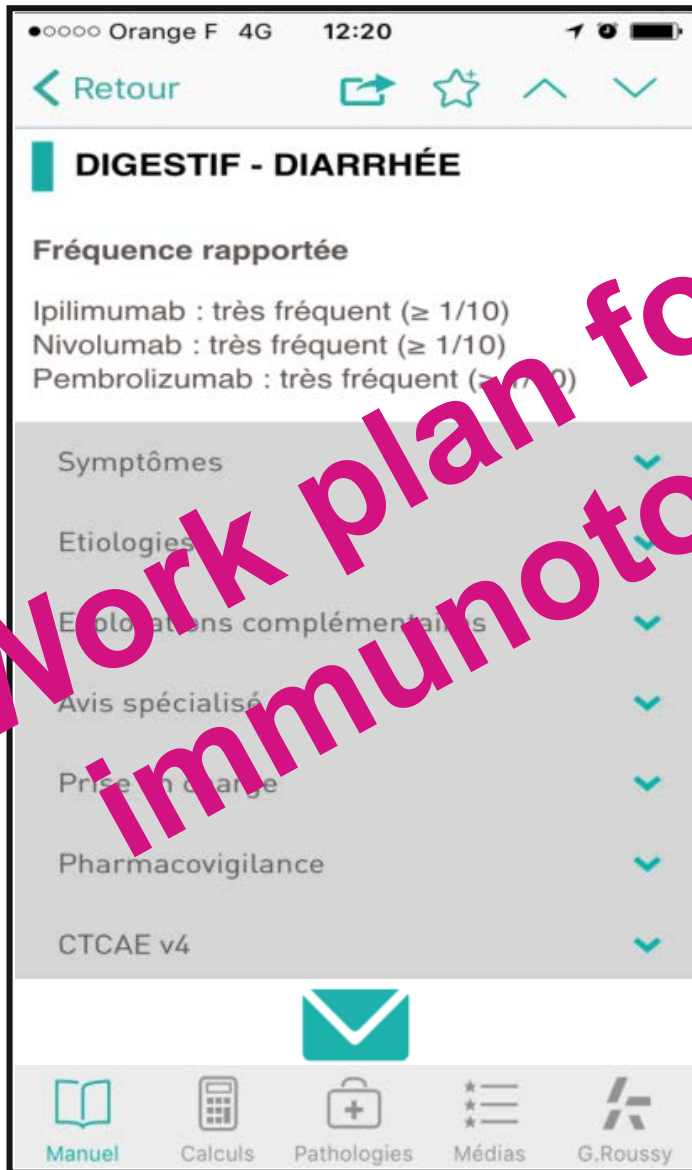
Small lesions restricting diffusion in bilateral cerebral hemispheres

Decreased signal at the emplacement of the lesions

**RARE TOXICITY!**  
**Collaboration between specialists**  
**is very important +++**

1. Khoja et al. Cancer Immunology Research 2016;4:175–78.





## Symptoms

- clinical signs/ATC
- Grading

## Etiology

- frequent etiology in oncology
- suspected immune problem?
- other causes

## Explorations

- biological analysis
- imaging
- serology (infectious causes)
- immune analysis

## Organ specialist

- need for organ specialist?
- know your organ specialist

## Handling

- According to severity
- Corticoids indication
- multidisciplinary discussion
- surveillance



# Recommendations

## Immune related adverse events (irAE)

In case of preexisting autoimmune disorder, discussion with the organ specialist (eg rheumatologist), who follows the patient, is indicated.



Joint pathology →



Colitis →



Skin toxicity →



Hepatitis →



Nephritis →



Neurologic →



Pneumonitis →



Endocrine →



Muscle pathology →





Great collaboration with  
KBVR/SRBR

# Joint pathology<sup>1</sup>



## Arthralgia

- No clinical swelling
- Joint pain
- Stiffness

## Inflammatory arthralgia

- Pain at rest
- Awakening at night
- Early morning stiffness >30 minutes
- No clinical swelling

## Arthritis

- Signs of inflammation
- Joint swelling
- Awakening of pain at night
- Early morning stiffness (>30min)
- Pain at rest
- Multiple joints may be affected

Arthralgia →

Arthritis →

In case of preexisting autoimmunity  
contact the organ specialist who treats  
the autoimmune disorder



Great collaboration with  
KBVR/SRBR

# Arthritis<sup>1</sup>

## Symptom Grade

- Moderate or severe pain, limiting instrumental activities of daily living and may disable self care
- Signs of inflammation such as joint swelling
- Awaking of pain at night
- Early morning stiffness (>30min)
- Multiple joints may be affected
- Evaluate pain with visual analogue scale

Severity of pain is not a criterium for escalating treatment, treatment will rather be defined by the type and amount of joints affected

## Management escalation pathway

- Escalate analgesics and use NSAID (If not contraindicated)
- Prednisone (10-20mg) to be started ideally after consultation with rheumatologist
- Withhold ICPI until resolution of symptoms
- Intra-articular injections only if infection was ruled out
- Consider methotrexate or salazopyrine if steroid refractory or for steroid sparing purposes

## Assessment and Investigations

- Always do X-ray (consider arthropathy, pre-existing arthropathy, metastasis or baseline evaluation)
- If possible, try to objectify arthritis (e.g. by ultrasound or arthrocentesis)
- Complete rheumatological history regarding differential diagnosis
- Examination of all joints
- Always consider joint aspiration especially when fever or severe inflammation to rule out septic arthritis and crystalarthropathies

### Autoimmune panel:

- ACPA
- RF
- ANF
- ANCA

○ Joint biopsy can be done in collaboration with certain centres for scientific purposes

**PISCO study will be  
launched soon**



# Organize platform for rare and lethal toxicity on the BSMO website

- ▶ Exchange between oncologists and organ specialists
- ▶ Learn from each other as a community: build a platform
- ▶ Underreporting in literature
  
- ▶ ...

**Email me if you have a case**

[sandrine.aspeslagh@bordet.be](mailto:sandrine.aspeslagh@bordet.be)  
[Sandrine.aspeslagh@uzbrussel.be](mailto:Sandrine.aspeslagh@uzbrussel.be)  
(1st of February)



# Clinical case

## Disease history

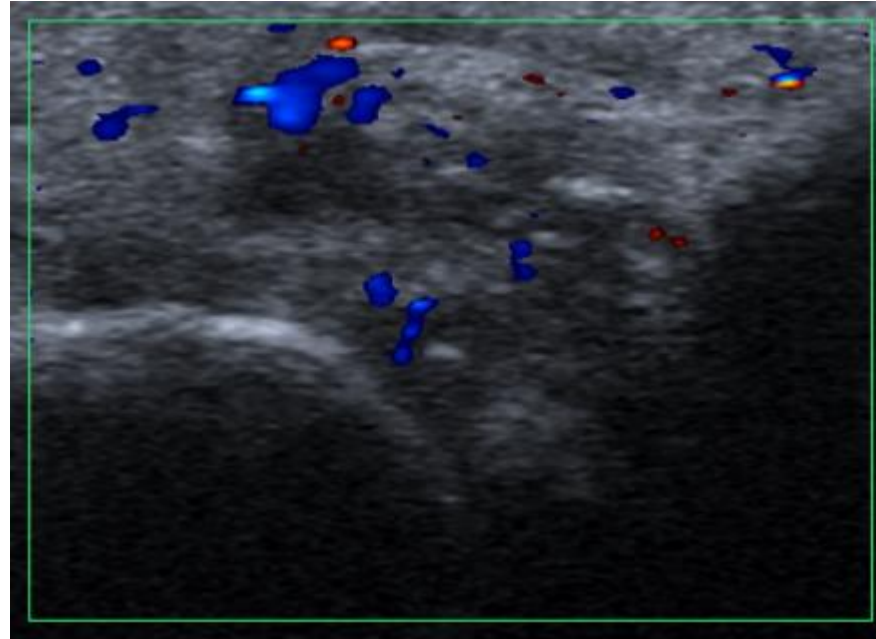
- Dec 2013 Melanome stade IIIB, BRAFV600E, neoadj dabra-trame
- Oct 2017: local relaps: surgery + nivo adj (2): hepatitis G2: corticoids and stop anti-PD1
- Sept 2018: arthritis
- Oct 2018: local relaps: surgery

## Patient history

- DM type II, AHT, hypothyroidism

## Family history

- Daughter with psoriasis



## Patient data

- Clear synovitis:
- Articular puncture can be made for scientific purposes

**Ideal patient for  
PISCO study**

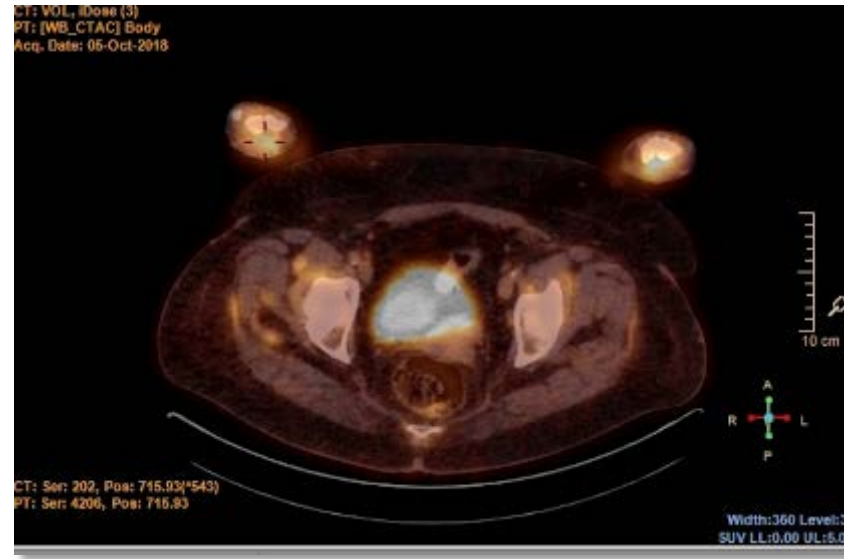
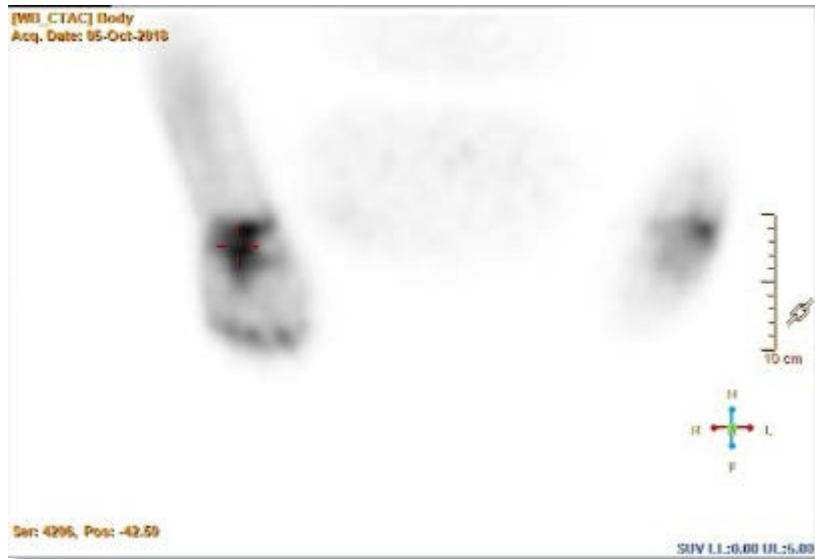
BSMO-KBVR/SRBR

PI: Dr. Laurent Meric de Bellefon



# Polyarthrititis 7 months after stopping nivolumab

PET images



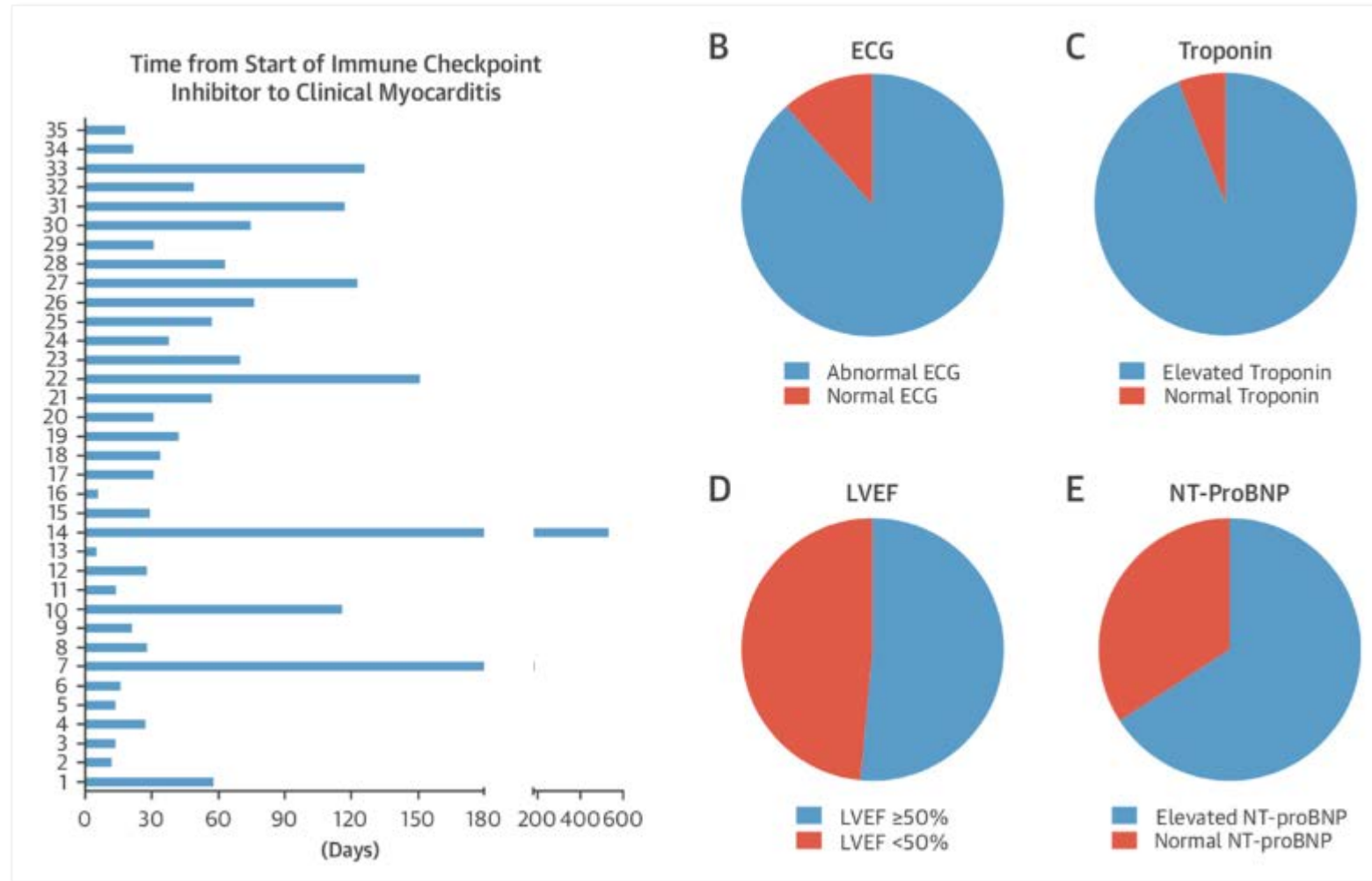
Clinical improvement,  
Resolution of inflammation  
MTX 15mg + corticoids (tapered)



# What symptoms can make you think about cardiac toxicity?

- ▶ Dyspnea
- ▶ (Pulmonary) infection that remains problematic
- ▶ Thoracic oppression

# Myocarditis in patients treated with ICIs



ICI, immune checkpoint inhibitor

1. Mahmood et al. J. Am. Coll. Cardiol. 2018;71:1755–1764

Any off-label data shown are used to support the educational message of the presentation and not intended to endorse use of any drug in any way



# Case report: myocarditis

anti-PDL1+ immunomodulator

## Medical History:

- Cutaneous Lupus
- Hashimoto Thyroiditis
- Sarcoidosis (not confirmed)

Day 30

Day 40

Day 60

- **Dyspnea grade 1 + Hypoxia grade 2 (88%)**, cough + crackling lung sounds
- Hemocultures; lab tests; Viral serology: negative; brain scan, ORL consult, lumbar puncture, BAL: negative
- **Chest CT scan:** Initial lung condensation at the LLL suspicion of chest infection.
- **ECG:** negative T waves but negative troponin and BNP

- **Negative T waves and low ST trait with increased troponin and BNP:** suspicion of immune myocarditis
- **Echocardiography:** FE 45%
- → Steroids 1mg/kg

- LVEF 69%: decrease steroids





## Polymyalgia rheumatica

- Typically inflammatory girdle (shoulder and pelvic)
- Stiffness and pain

Polymyalgia rheumatica →

## Myositis

- Muscle weakness Muscle pain
- CK elevation

### Alarm symptoms:

- Diaphragm paralysis
- Myocarditis
- Swallowing troubles
- Diplopia
- Dyspnea due to respiratory muscle involvement

Myositis →

## Myasthenia gravis

- Fluctuating muscle weakness (proximal limb, trunk, ocular, e.g. ptosis/diplopia or bulbar) respiratory muscles may also be involved

### Fatigability:

- Muscle weakness is induced and aggravated by exercise

Myasthenia gravis →

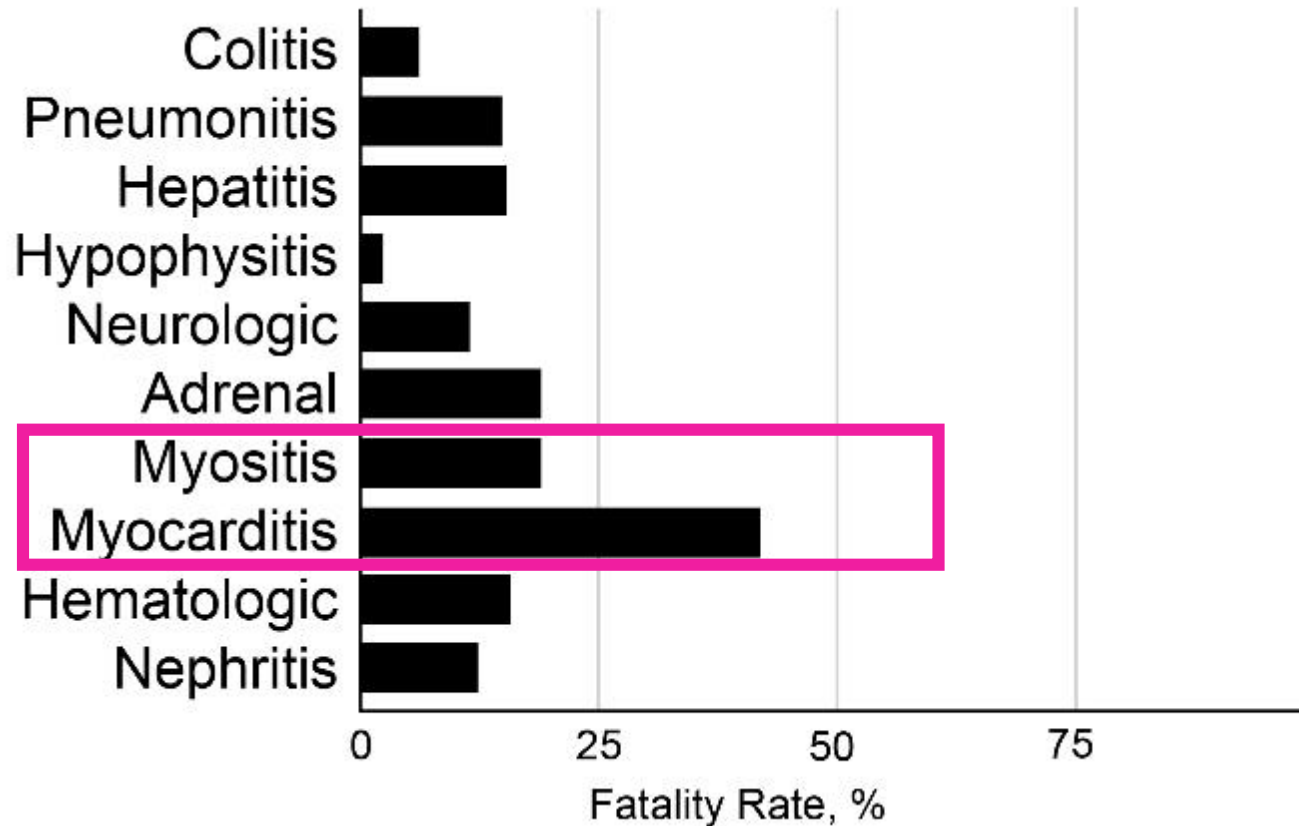
\*Rheumato-onco taskforce KBVR/SRBR (Yves Piette, Ellen Delanghe) Gauthier Remiche, ULB Erasme Olivier Lambotte, AP-HP, Hôpital Bicêtre, Service de Médecine Interne et Immunologie Clinique, Paris, France, Dimitri Psimaras, Praticien Hospitalier Département de Neurologie Mazarin, GHPS, Paris, France



# What are the main risks with immune related myositis?

- ▶ Associated cardiac toxicity
- ▶ Diafragm paralysis
- ▶ No response to corticoids
- ▶ All of the above

# Fatal toxic effects associated with immune checkpoint inhibitors a systematic review and meta-analysis<sup>1</sup>



1. Wang et al. JAMA Oncol 2018;doi:10.1001/jamaoncol.2018.3923.



# Retrospective study of consecutive patients diagnosed with irMyositis

## Tests

Electromyoneurography – n

**Myopathic process<sup>a</sup>** 9/9

Abnormal motor/sensory conduction 1/9

**Decrement on RNS** 0/8

Laboratory tests - n (%)

**Abnormal Troponin T** 7/9

**Anti-AChR antibodies** 0/7

Myositis-associated antibodies<sup>b</sup> 0/7

Cardiac MRI with contrast - n (%)

Subepicardial enhancement 2/4

## Histopathological assessments n=9

**Necrotic or regenerating fibers – n** 9/9

Multifocal 7/9

Focal 2/9

**Abnormal MHC-1 expression- n** 8/8

Sarcoplasmic C5b-9 deposits - n 8/8

Endomysial infiltrates - n 9/9

**CD68 Positive cells** 9/9

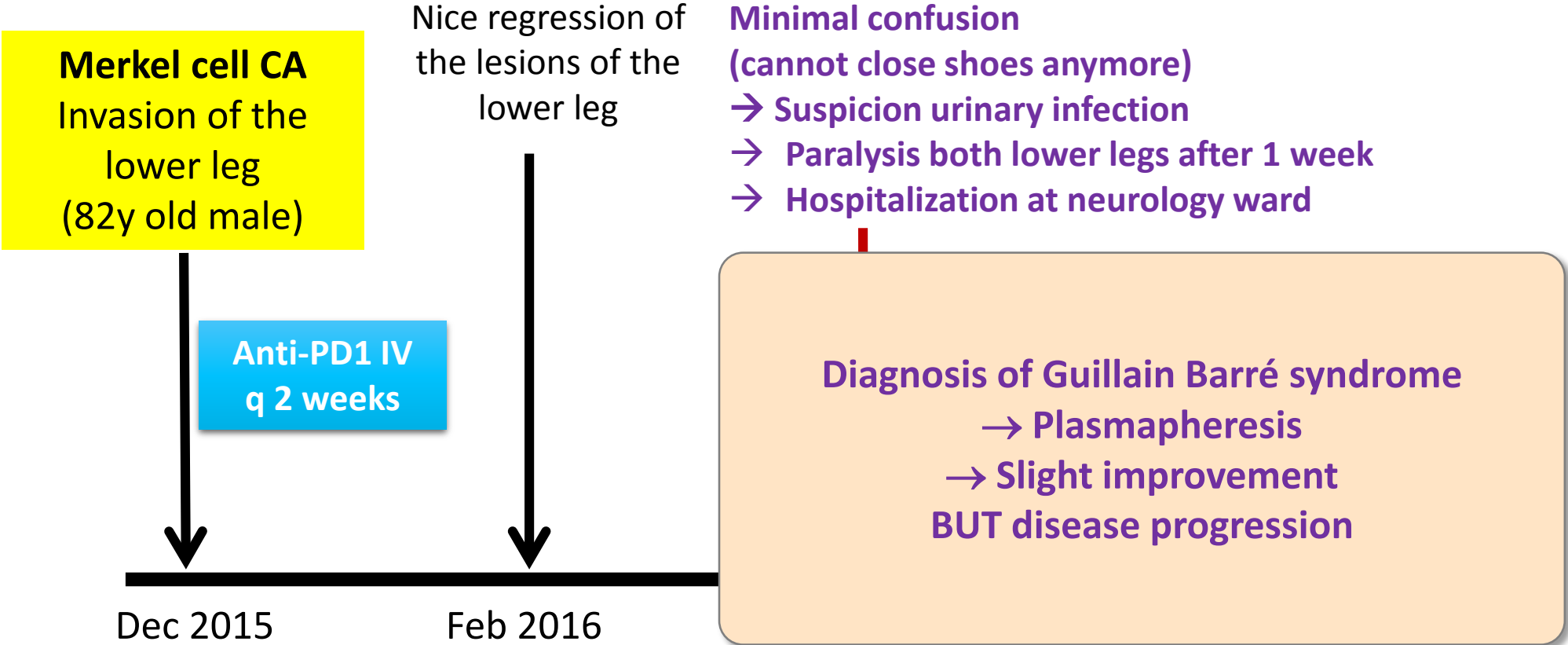
CD3 Positive cells 9/9

**CD8/CD4 ratio > 1** 9/9

**PD-1+ lymphocytes- median [range)** 20% [5-40]



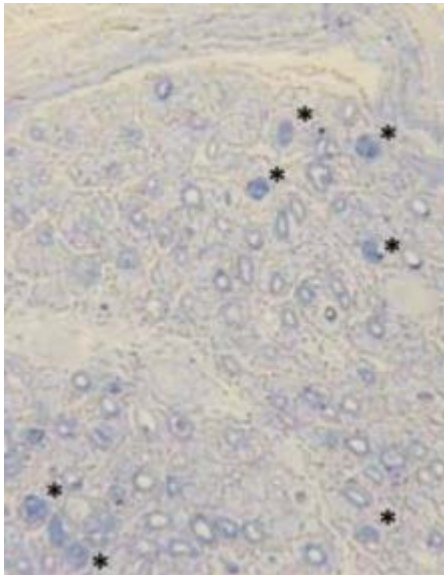
# Clinical case



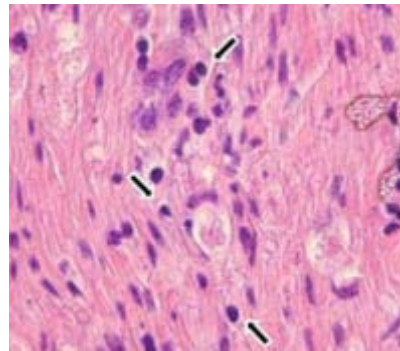
# Nivolumab-induced chronic inflammatory demyelinating polyradiculoneuropathy mimicking rapid-onset Guillain-Barre syndrome: a case report<sup>1</sup>

## Sural nerve biopsy

Loss of small- to medium-sized myelinated nerve fibres; presence of myelin ovoid, oriented by asterism



Mild infiltration of lymphocytes (↑)

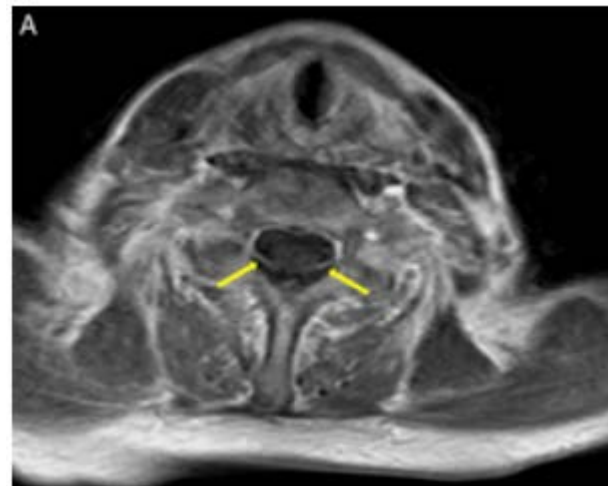


Disentangled nerve fibres showed segmental demyelination



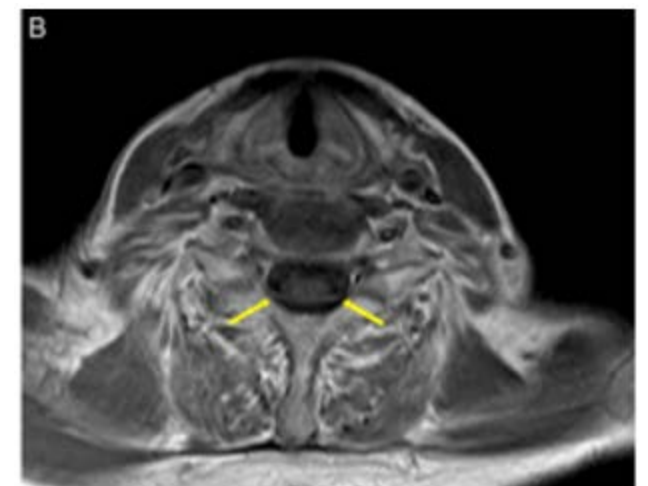
## Posterior nerve root of cervical spinal cord

Pre-intravenous immunoglobulin infusion



Enhancement consistent with inflammatory polyradiculoneuropathy

Post-intravenous immunoglobulin infusion

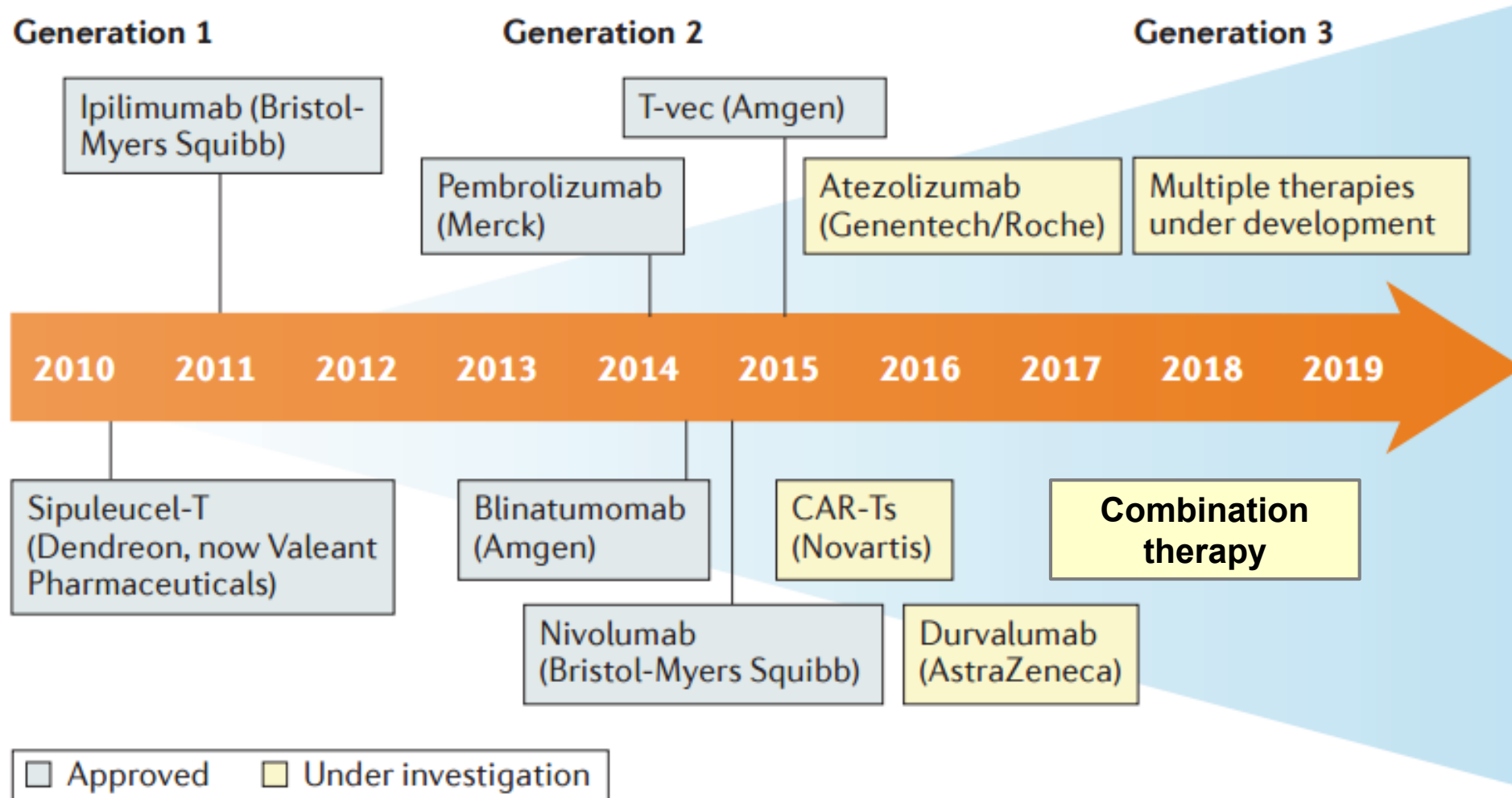


Absence of enhancement

1. Tanaka et al. Jpn J Clin Oncol 2016;46:875–78.



# Future of immunotherapy

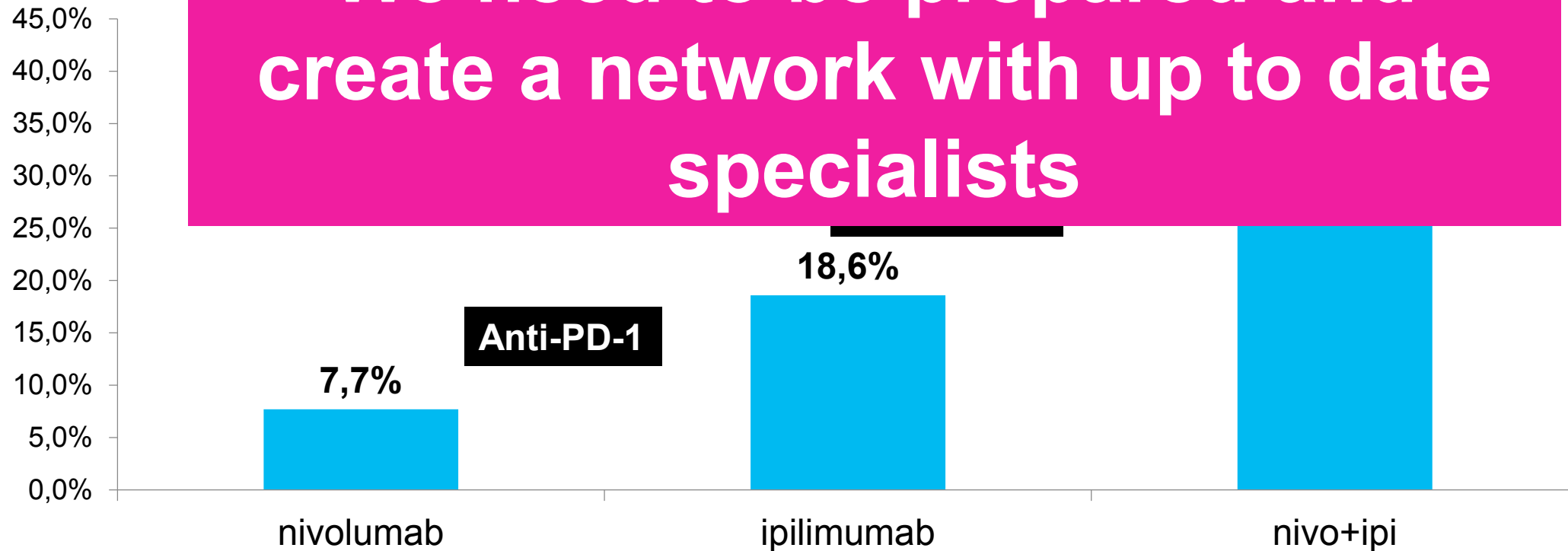


Adapted from Hoos et al Nat Rev Drug Discov 2016;15:235–47.



# The more combinations, the more toxicity?

**We need to be prepared and create a network with up to date specialists**



1. Larkin et al. N Engl J Med 2015;373:23–34. 2. Larkin J et al. N Engl J Med 2015;373:23–34\_Supplementary information.



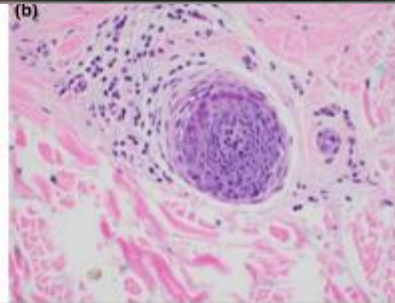
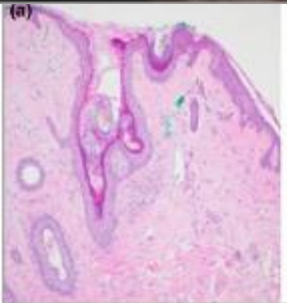


# Bizarre toxicity?

## Hairloss



Zarbo et al, 2017, BJD



## Repigmentation



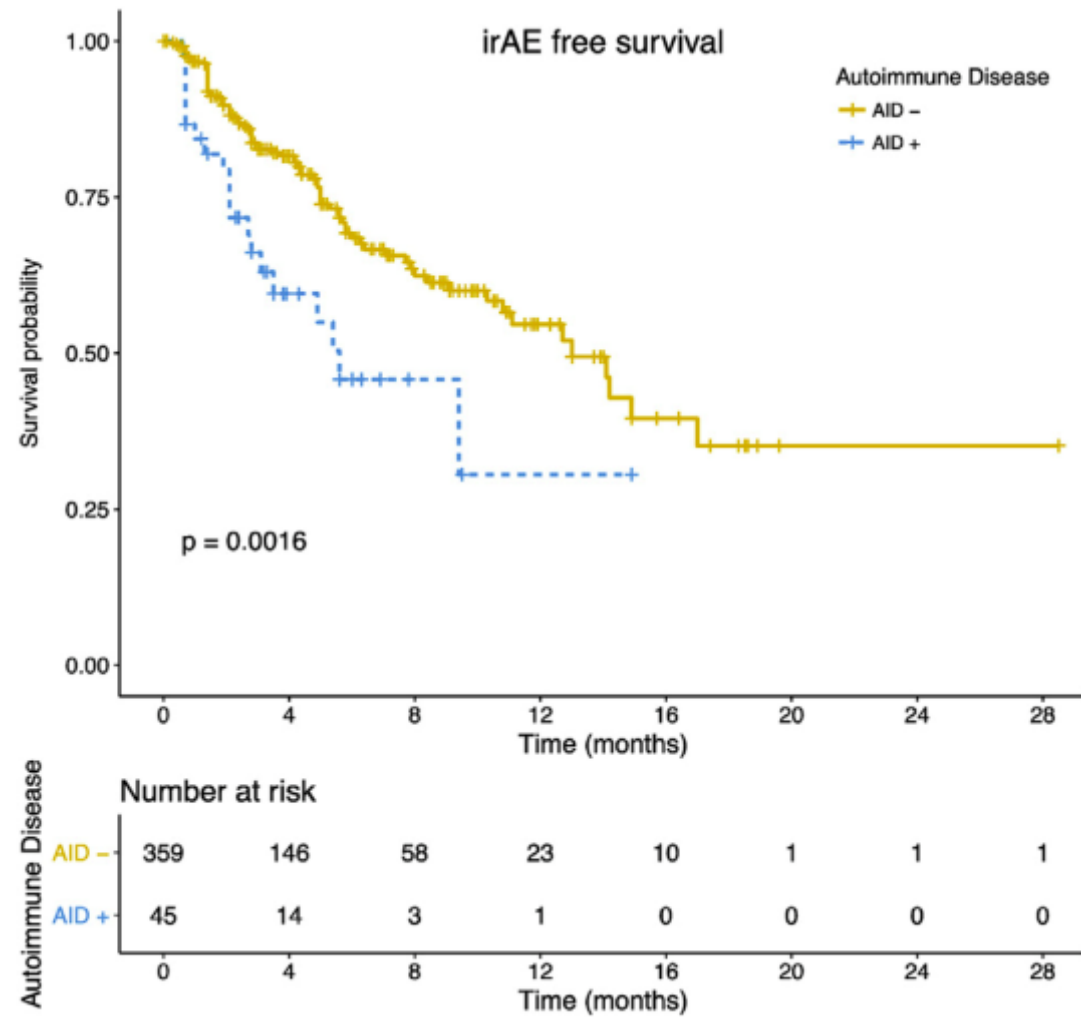
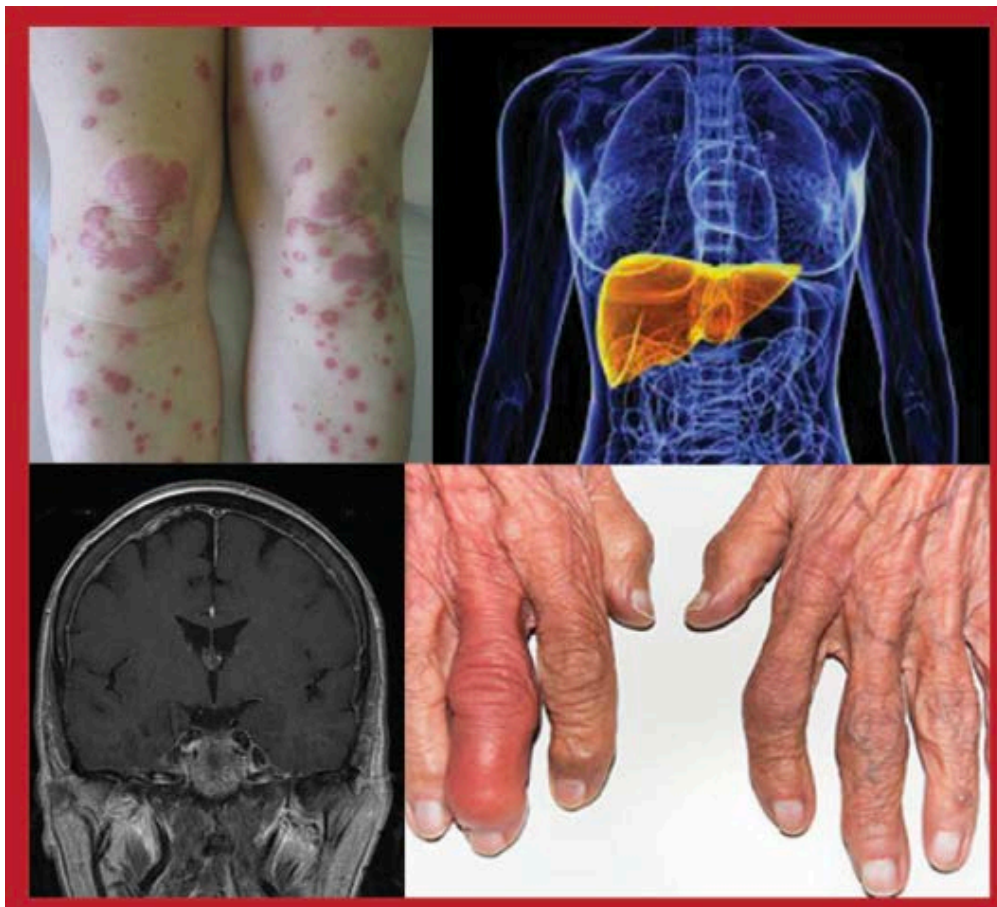
1. Zarbo et al. Br J Dermatol 2017;176:1649–52. 2. Rivera et al. JAMA Dermatol 2017;153:1162–1165.



# Have you been collaborating with other specialists for patients with preexisting autoimmune disorders?

- ▶ Never
- ▶ Yes in order to discuss possibility of starting immune checkpoint blockade
- ▶ Yes in addition I have seen autoimmune disease getting worse

# Patients with preexisting autoimmune disease<sup>1</sup>



1. Danlos et al. Eur J Cancer 2018;91:21–29.



# Case report: arthritis

## Medical History:

- RA since 2009: (ACPA +)
  - 2009:10mg MTX
  - 2009-10: Adalimumab: stop for intolerance
  - 2013-15: Etanercept: didnt work
  - 2015: Tocilizumab (anti-IL6)
  - 2016: Abatacept (CTLA4-Ig)
  - 2017: stop Abatacept due to Merkel cell CA diagnosis
- Type II diabetes mellitus (insulin)

anti-PD-1  
(14 Sept)

July 2018

Sept 2018

Inguinal Inn and  
local

Merkel Cell  
carcinoma  
resection



*[octreoPET today  
at 3pm]*



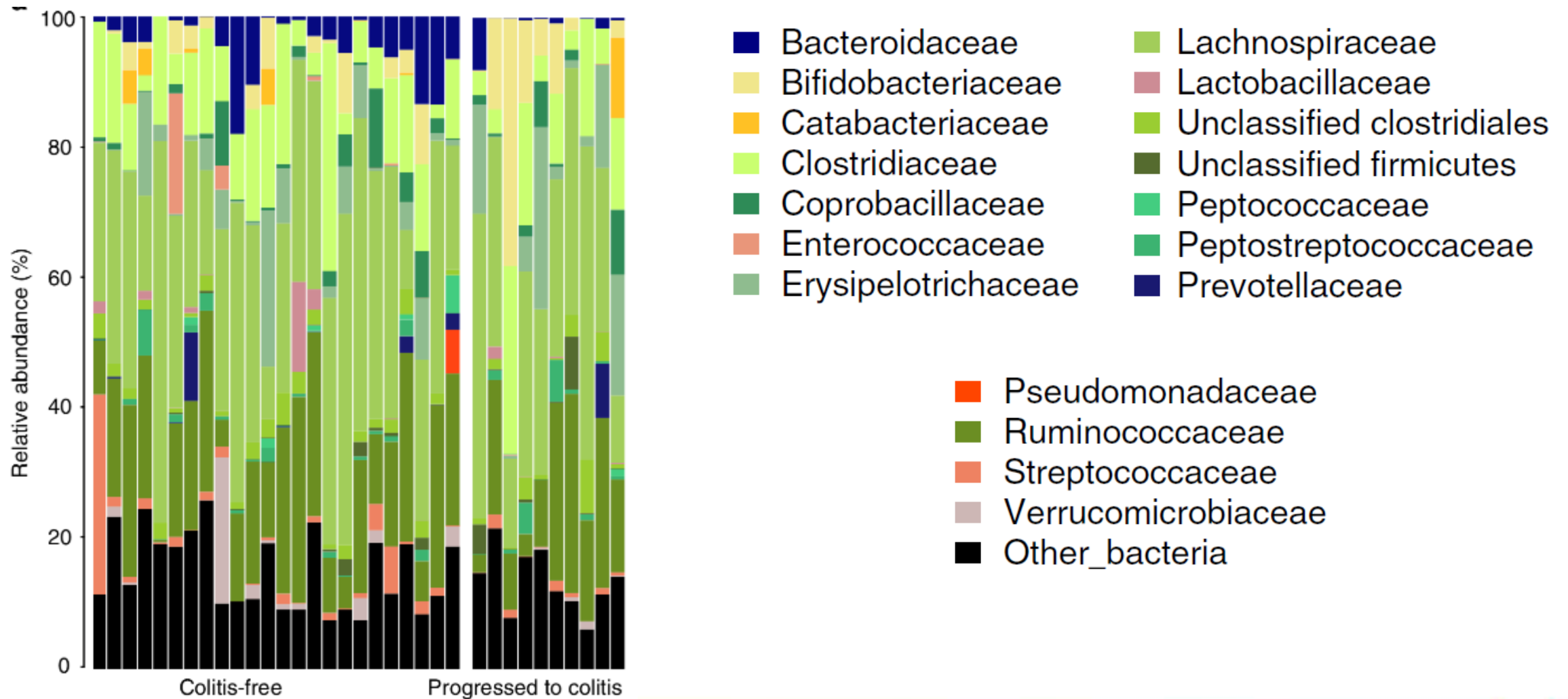
# Which patient characteristics might indicate irAE occurrence?

- ▶ Microbiome intestinal microbiota
- ▶ Preexisting autoimmune syndrome
- ▶ Age
- ▶ Lymphocyte count

# Microbiome



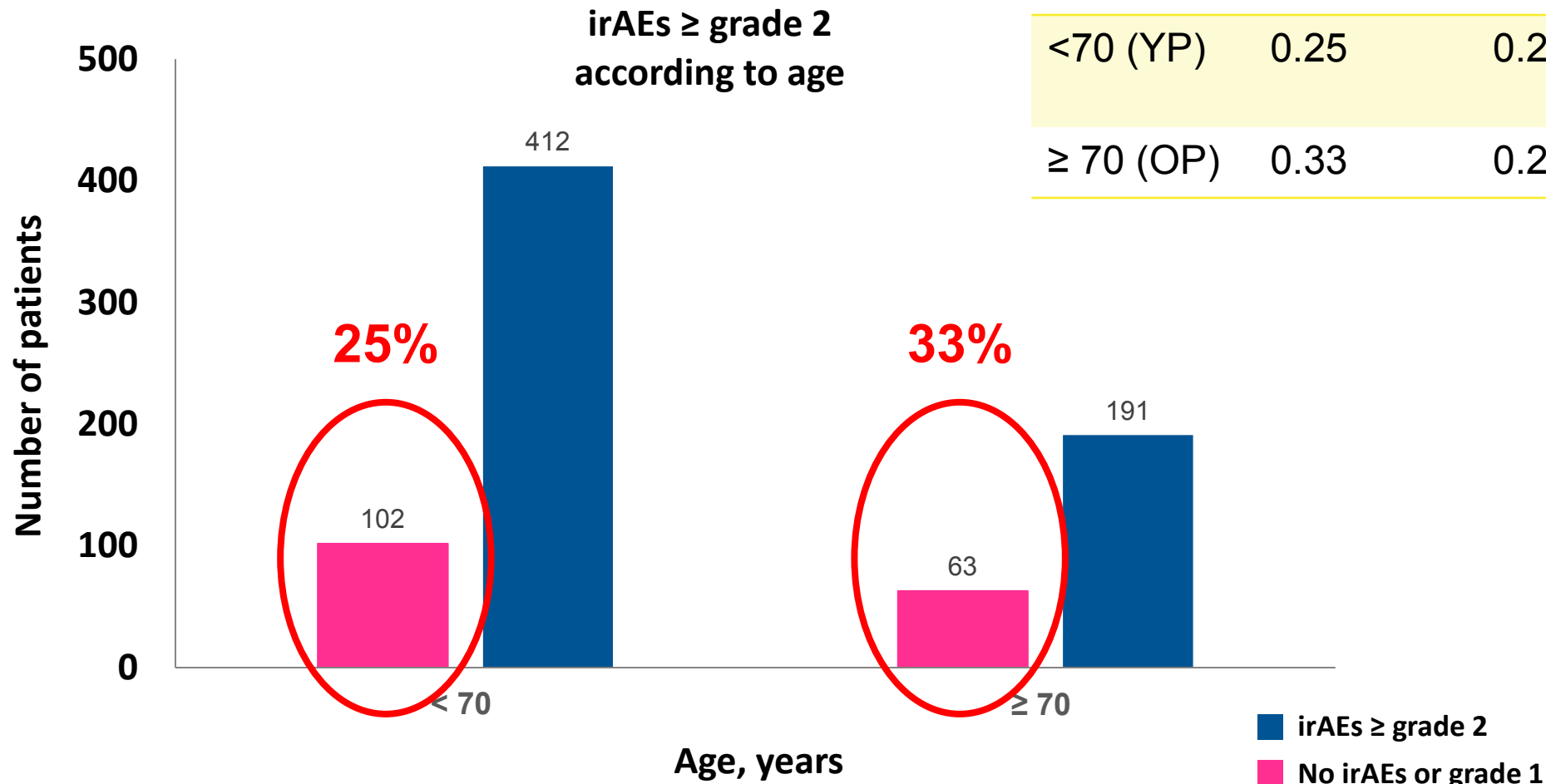
# Microbiota and toxicity<sup>1</sup>



1. Dubin et al. Nature Communications 2016;7:10391.



# Age and toxicity



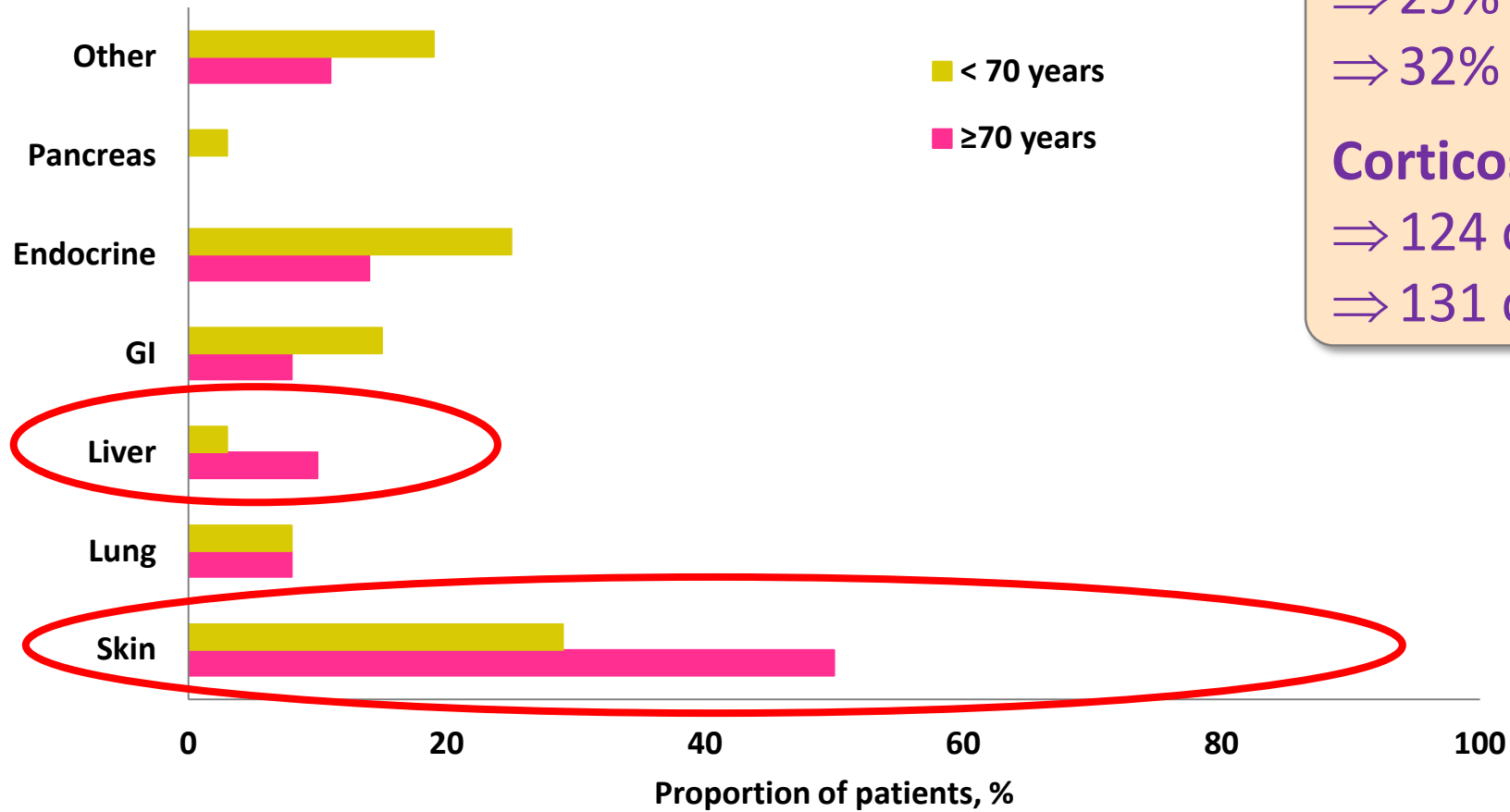
	irAEs	95% CI	p
<70 (YP)	0.25	0.21- 0.29	0.035
$\geq$ 70 (OP)	0.33	0.26 - 0.40	





# Types of irAE

Type of toxicities according to age



## Corticosteroids use:

⇒ 29% in ≥70 years

⇒ 32% in <70 years

## Corticosteroid use, median

⇒ 124 days for OP

⇒ 131 days for YP



# Future perspectives: how to handle irAEs



Immunotoxicity board

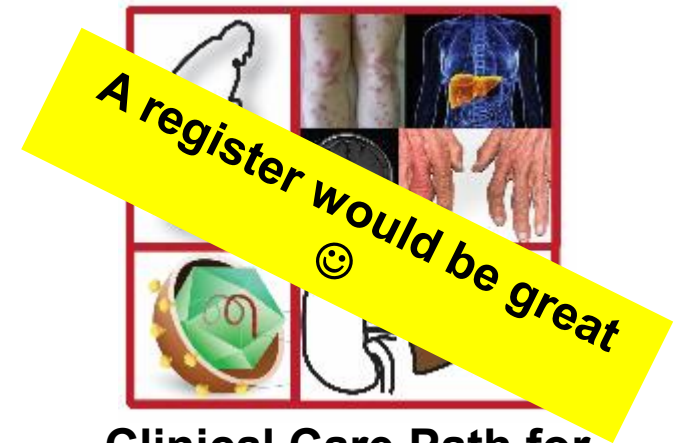
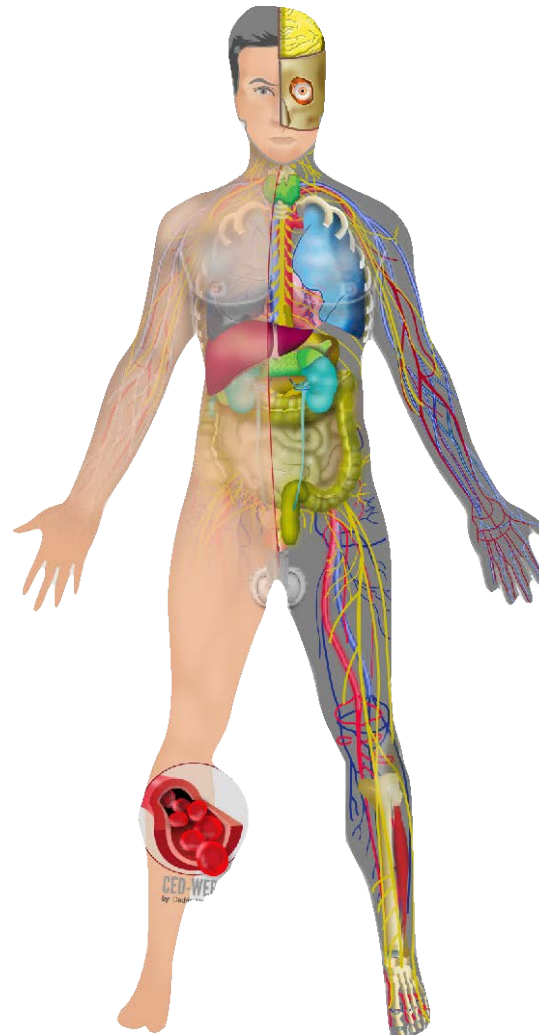
Great collaboration with KBVR/SRBR and BNS



BSMO Immunotaskforce



Translational Research



Clinical Care Path for dysimmunity patients

ENSEIGNEMENTS  
IMMUNO-ONCOLOGIE



Prospective analysis of autoimmune serology



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