

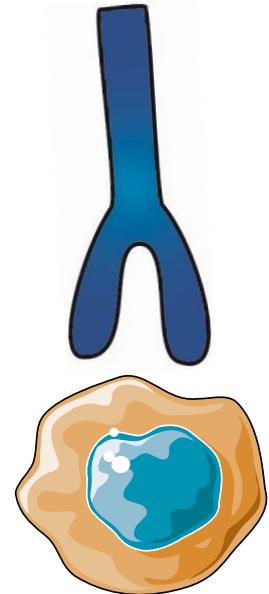
# Belgian Multidisciplinary Immunotoxicity Board

Marthe Verhaert, MD

Sandrine Aspeslagh, MD, PhD

# Paradigm change in cancer therapy

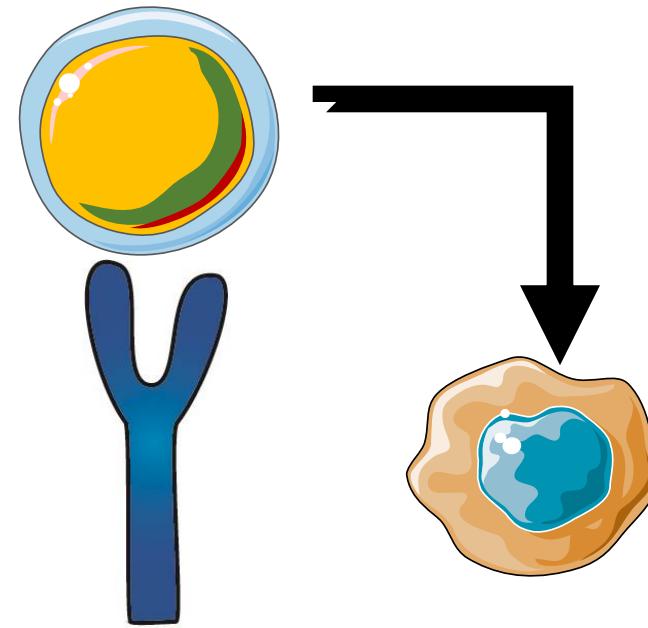
Target cancer cells



Tumor cell

Target the immune cells

Lymphocyte



# Immune checkpoint inhibition

## Anti-CTLA-4

Ipilimumab  
(BMS)



Tremelimumab  
(AZ)

Quavonlimab  
(Merck)

## Anti-PD-1

Nivolumab  
(BMS)



Pembrolizumab  
(Merck)



Spartalizumab (Novartis)

Cemiplimab (Sanofi)



Tyvyt Sintilimab, Tuoyi (Toripalimab),  
BITOX, BSMO annual meeting 2022  
Tislelizumab (CHINA)

## Anti-PD-L1

Atezolizumab  
(Roche/Genentech)



Durvalumab  
(AZ/Medimmune)



Avelumab  
(Pfizer)



LY3300054 (Lily)

# Head & Neck CA

OPDIVO™ KEYTRUDA®

# Oesophageal CA

OPDIVO™

# Hodgkin

OPDIVO™ KEYTRUDA®

# TNBC

TECENTRIQ®

# HCC

TECENTRIQ®  
anti-VEGF Ab

# Melanoma

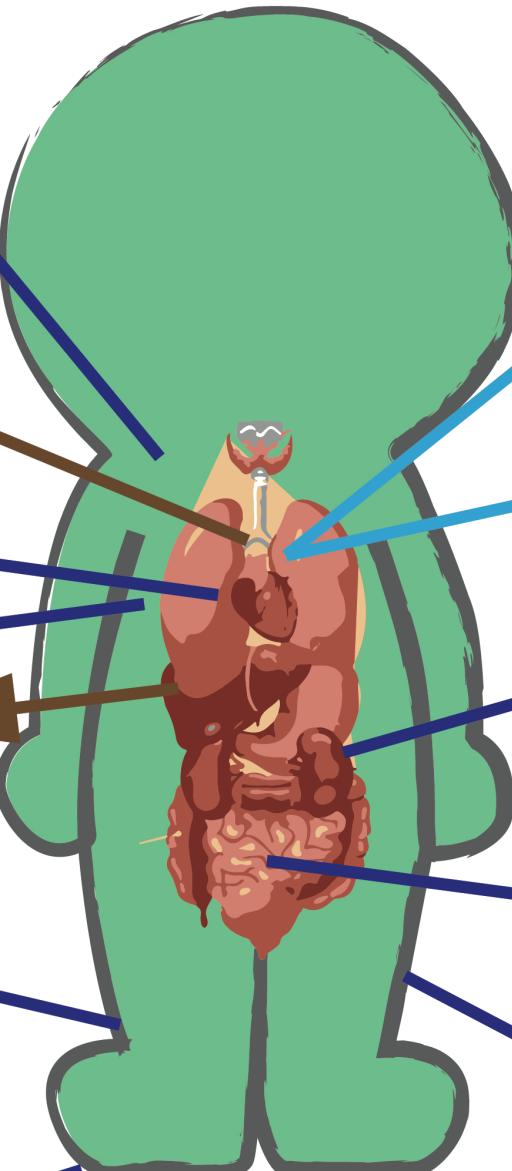
YERVOY™ OPDIVO™

KEYTRUDA®

OPDIVO™

# Merkel CA

BAVENCIO®  
avelumab 20 mg/mL



# NSCLC

YERVOY™ OPDIVO™  
KEYTRUDA® IMFINZI™  
TECENTRIQ®

# SCLC

IMFINZI™

# RCC

YERVOY™ OPDIVO™

Axitinib  
BAVENCIO®  
avelumab 20 mg/mL

KEYTRUDA®

# Bladder CA

OPDIVO™ KEYTRUDA®

BAVENCIO®  
avelumab 20 mg/mL  
TECENTRIQ®

# SCCS

LIBTAYO®  
(cemiplimab-rwlc)

ADJUVANT

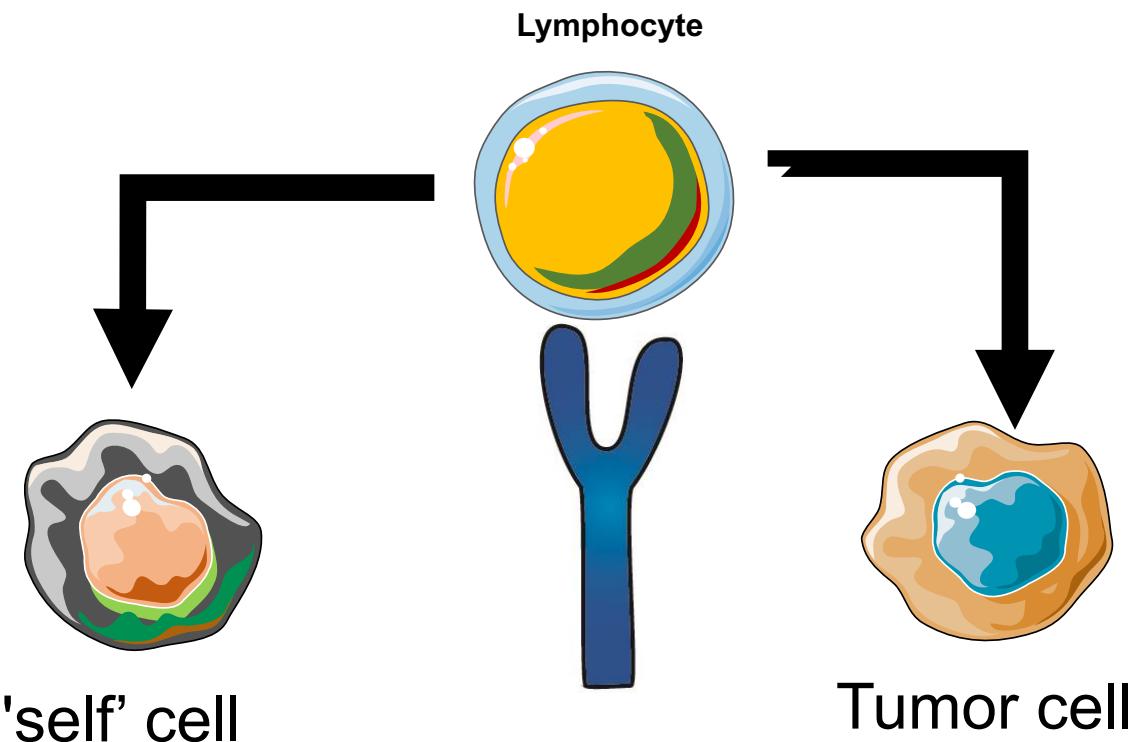
PDL1 high

+ Chemo

+ TKI

+ anti-VEGF Ab

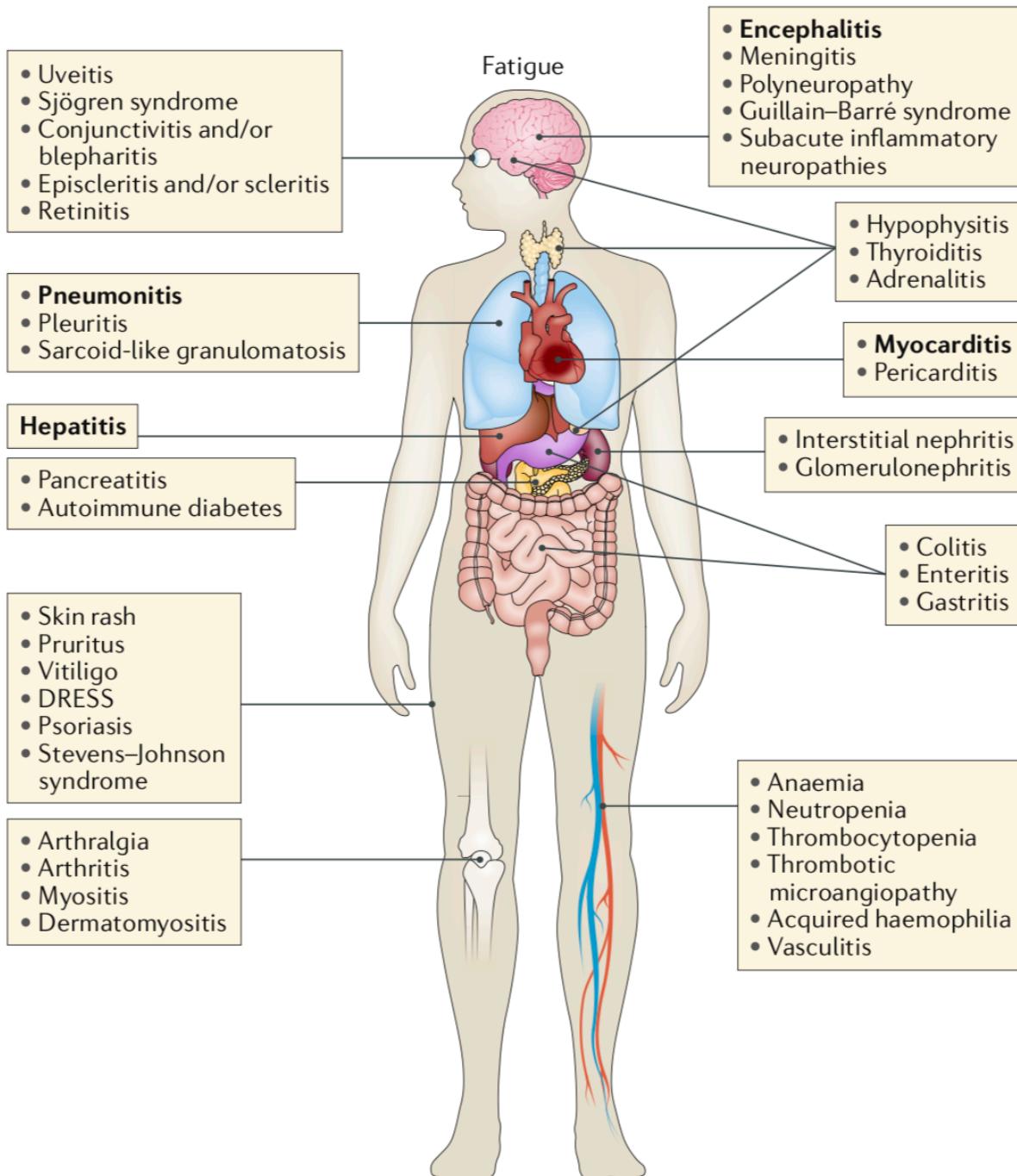
# Only immunity against cancer cells?



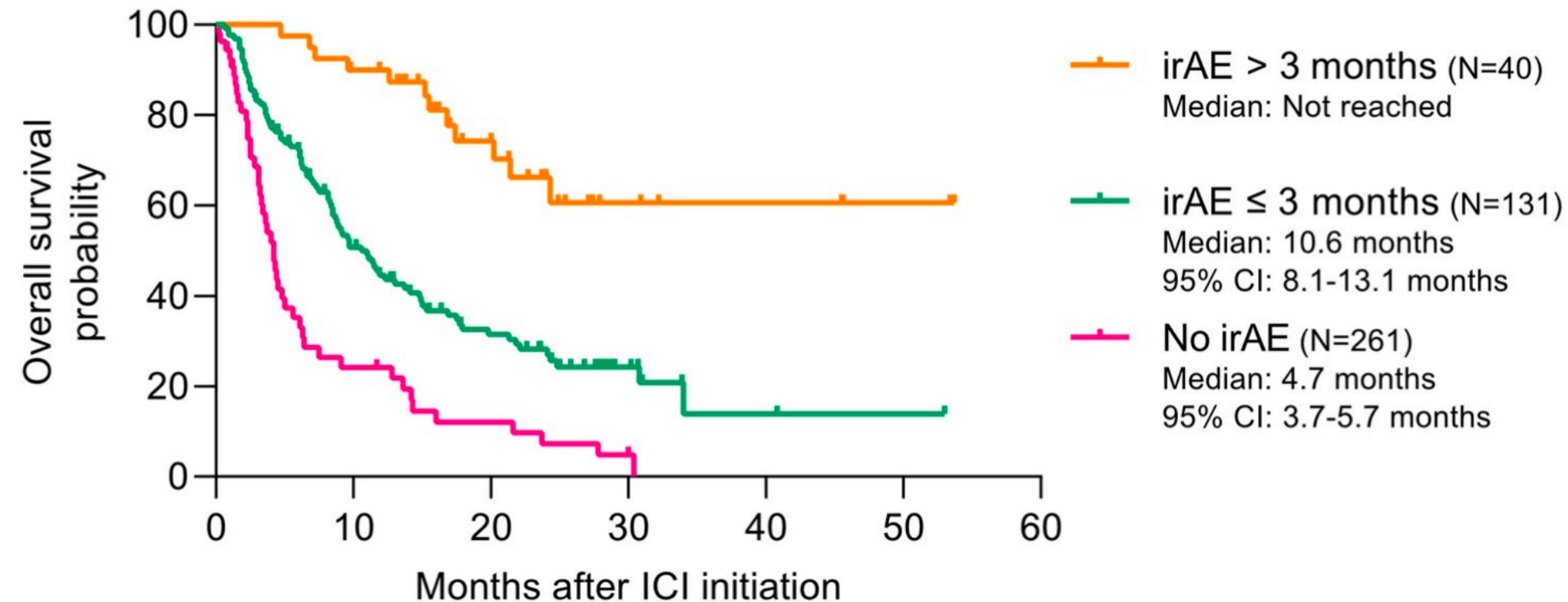
Immune related adverse event  
IrAE

# All organs can be affected by IrAE

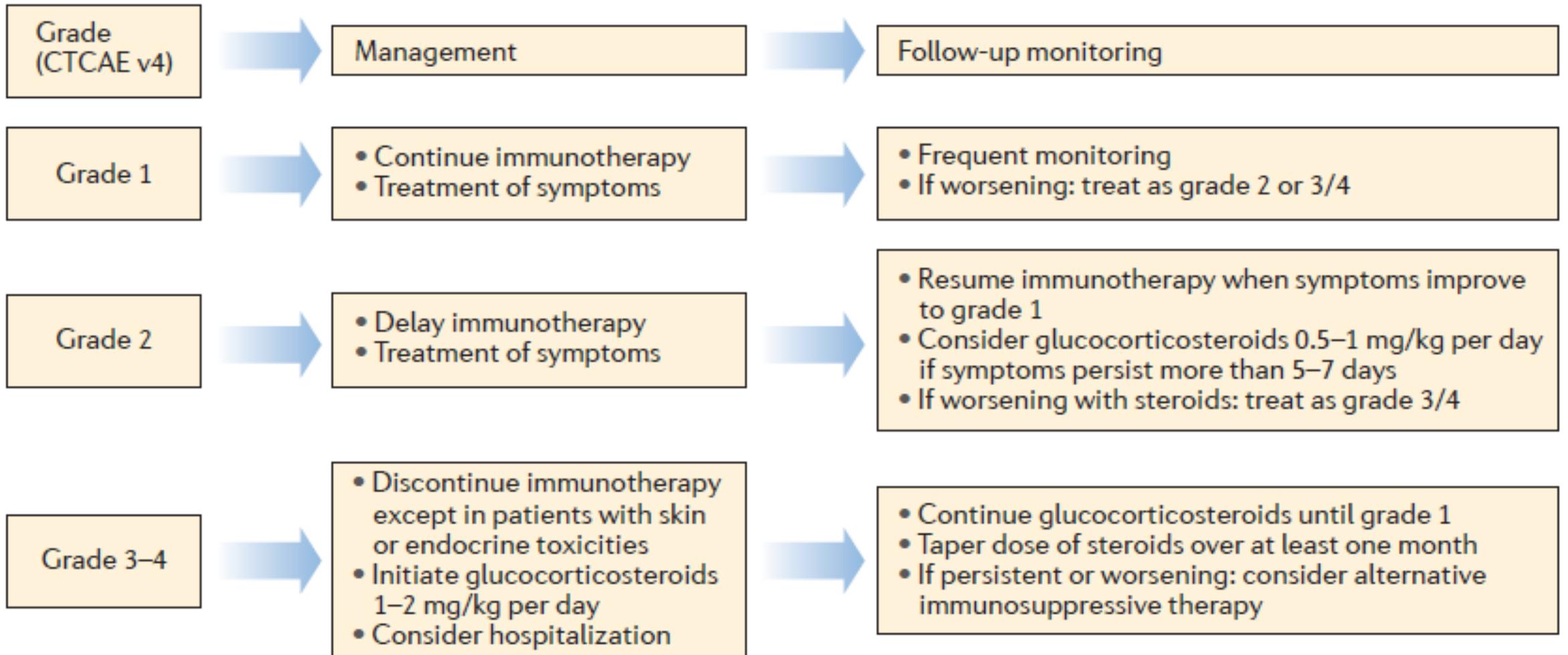
- New
- Diverse
- Rare
- Manageable



# irAE can be good news



# Severity and Treatment



# BSMO Immunomanager



Joint pathology



Colitis



Skin toxicity



Hepatic toxicity



Nephrotoxicity



Neurologic toxicity



Pneumonitis



Endocrine toxicity



Muscle pathology



## Immune Checkpoint Inhibition in combination with TKI

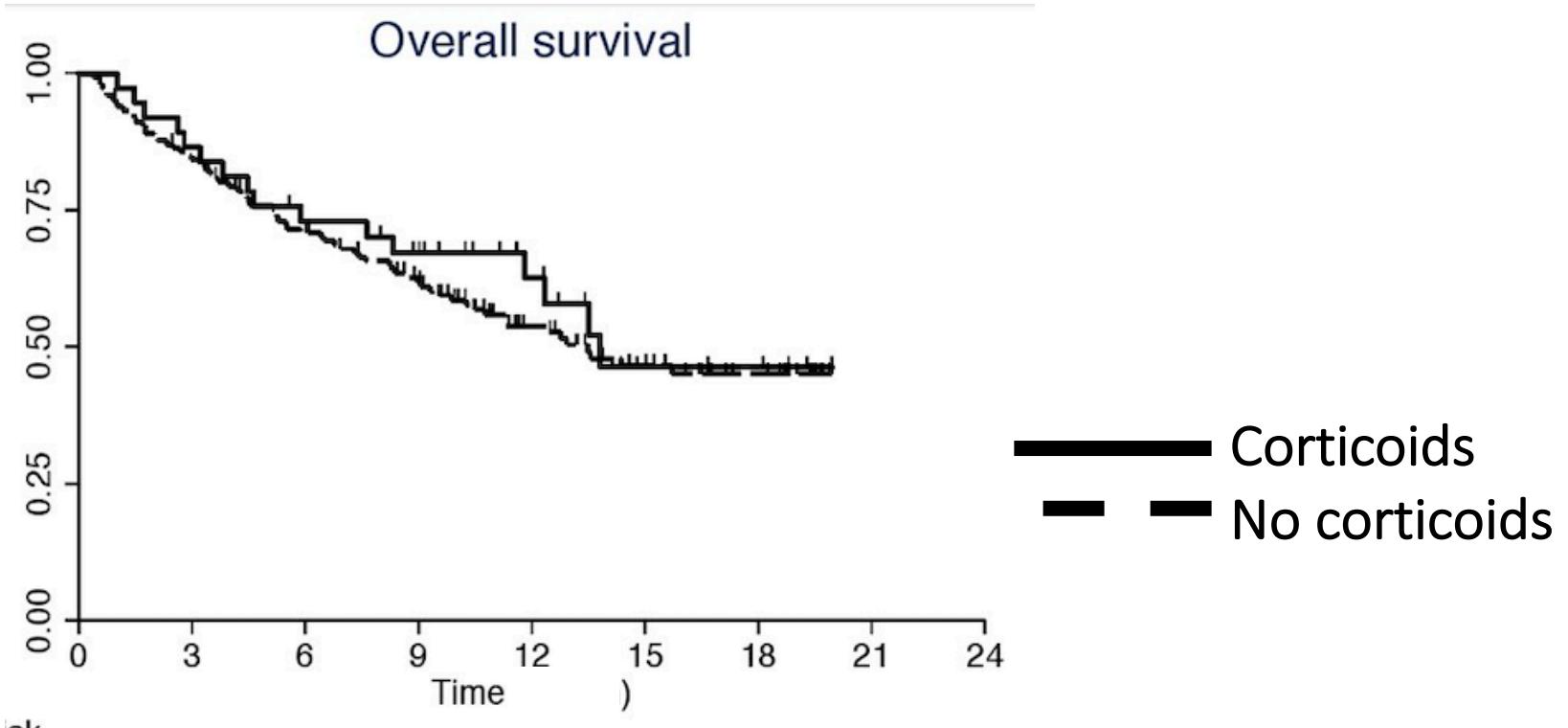


Axitinib + anti-PD-(L)1



<https://www.bsmo.be/immunomanager/irae/>

# What is the effect of corticoids given for irAE on the anti-tumor response?



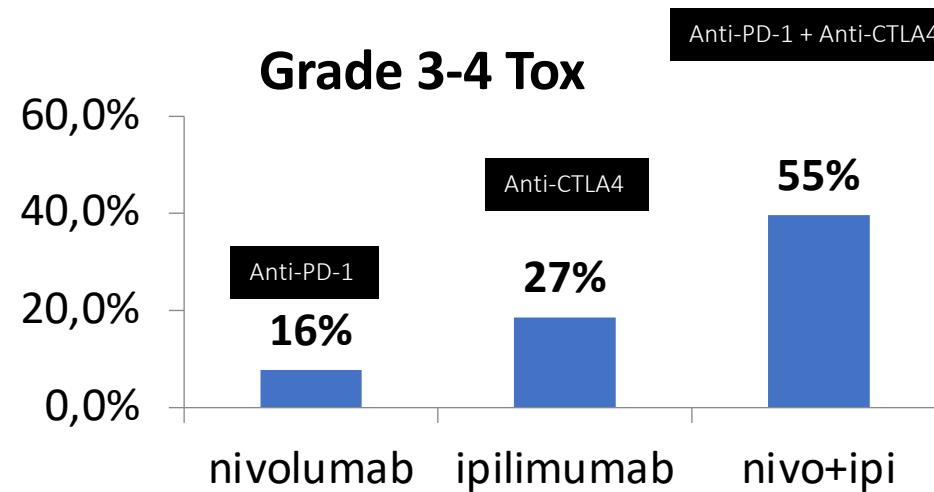
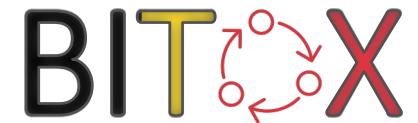
The effect of other immunosuppressants on cancer evolution such as TNF blockers, Leflunomide, Vedolizumab, MMF,... is rather unclear...

## *IPI/NIVO/TOCILIZUMAB phase II*

- A total of 41 patients, melanoma st IV
  - **Response rate by RECIST is 58%: higher than Checkmate-511 (47%)**
    - 1/5 stable pts having progressed at a median follow up of 6 months;
    - 3 pts have died so far, all related to progression
  - Grade 3-4-5 treatment-related irAE rate: 17%
    - which is **lower than expected** based on Checkmate-511 at 34%
  - 6 pts of 41 have stopped therapy due to grades-2-3-4 irAEs so far = 14%
    - 3 had G3/4 colitis
- use tocilizumab in case of steroid refractory irAE

# The more combinations, the more toxicity?

We need to be prepared and create a network with up-to-date physicians



Larkin J et al. N Engl J Med 2015;373:23–34.

# Combination anti-CTLA4 + anti-PD(L)1

- Cave **hypophysitis/colitis**
- Minor suspicion of irAE: explore (lab tests, natural evolution)
- Toxicity tends to be **more severe** compared to monotherapy anti-PD1
  - FU on your patient (phone consult in between)
- **Combine only if required:** implicate patient in risk assessment
  - Melanoma: brain mets
- If irAE: **stop both ICI**
  - restart monotherapy only after resolution of irAE and no immunosuppression
  - Perform imaging before restart (if complete response: wait)
- **Dose dependency:** melanoma: discuss ipi 1mg vs 3mg

# Higher dose = more irAE?

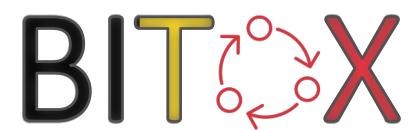
- Probably not for anti-PD(L)1
- For anti-CTLA4:
  - Melanoma: ipi 3mg/nivo 1mg: G3/4: **59%** (Wolchok et al, 2017)
  - Prostate Cancer: ipi 3mg/nivo 1mg: G3/4: **53%** (Sharma et al, 2021)
  - Renal Cell Carcinoma: ipi 1mg/nivo 3mg: G3/4: **46%** (Motzer et al, 2018)
  - Melanoma: ipi 1mg/nivo 3mg: G3/4 **34%** (Checkmate 511)
  - ColonCA MSI high: ipi 1mg (q6w)/nivo 3mg: G3/4: **19%** (Checkmate 214)

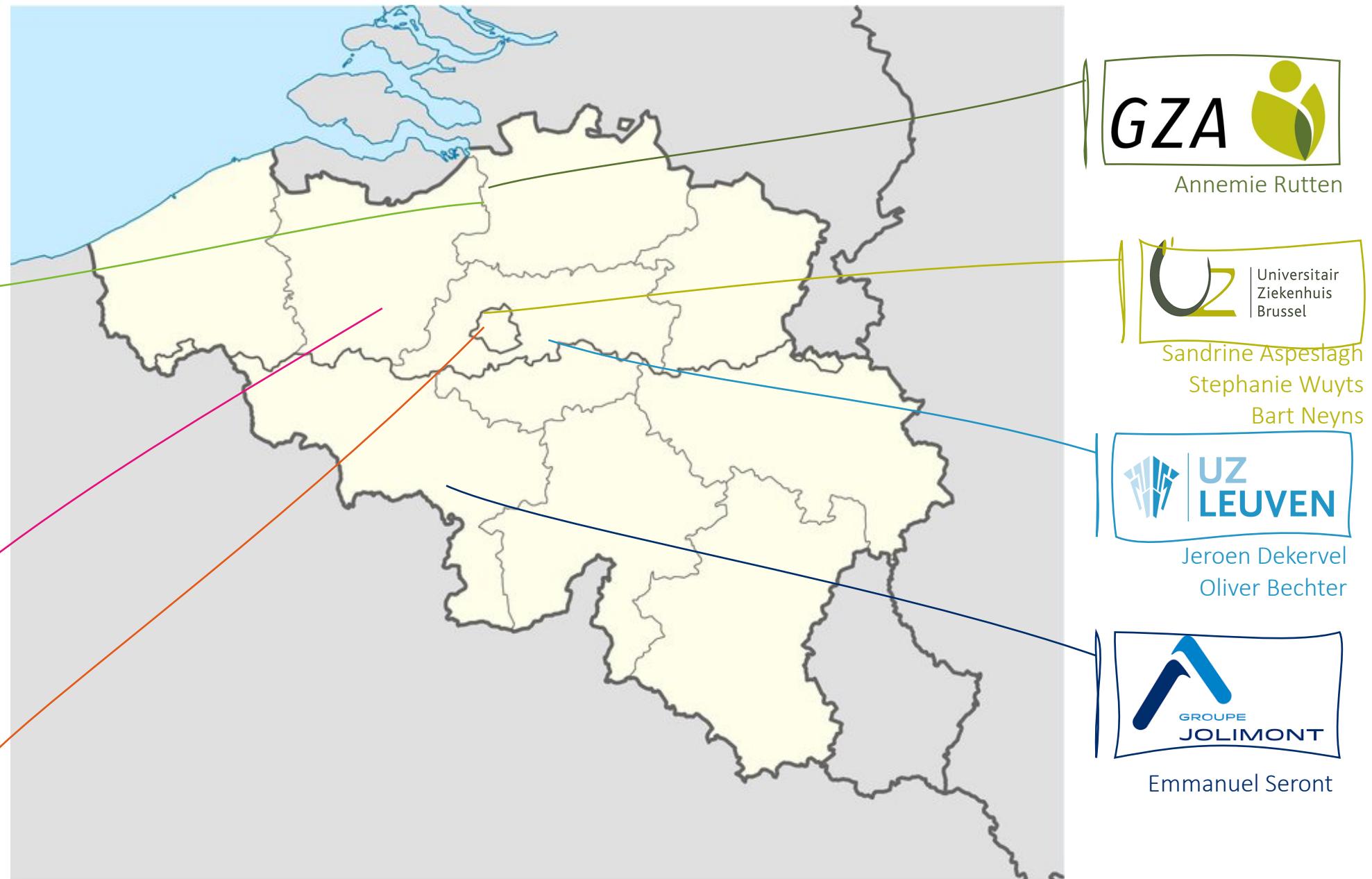
# Combination anti-VEGF + ICI

- If required stop both ICI and anti-VEGF
- Restart TKI if **quick resolution** of symptoms
- If no resolution with 72h, discuss hospitalisation to explore
- **Dose adaptation** of TKI if necessary
- Restart IO after resolution of irAE and no immunosuppression
- Perform imaging before restart of IO (if complete response: wait)

# Can we predict irAE?

- Neoadjuvant vs metastatic setting with high tumor burden (Verheijden R et al, ESMO open 2020)
- Pre-existing autoimmune disease (Danlos FX et al, EJC 2017; Saul TRIAL, Loriot Y et al, EJC 2020)
- Kinetics of anti-TPO antibodies (Music M et al, F1000 research 2020)
- CRP (Lauwyck et al, Melanoma Research 2021)
- Microbiome (Dubin et al, Nature Communications, 2016; Andrews et al 2021, NI)
- Baseline TNFa (Weber J et al, 2021, ESMO)
- Baseline antibiotics (Jing et al 2022, JITC)



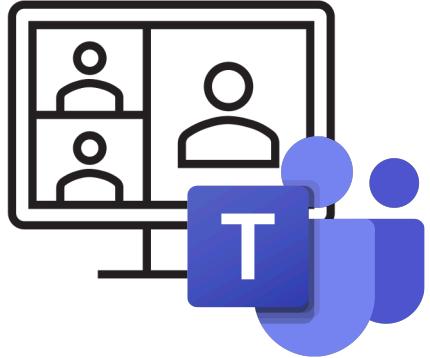


# Background

↑ use of immunotherapy (IT) → ↑ immune-related adverse events (irAEs)

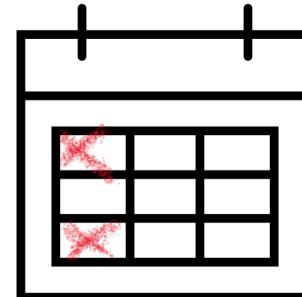
-  common exclusion of patients with auto-immune (AI) diseases or organ transplants from **clinical trials**
-  lack of **long-term data** on irAE management
-  **impact** of immunosuppressant use on oncological outcome is unclear
-  irAEs can affect any organ system making **multidisciplinary collaboration** essential

# Methods



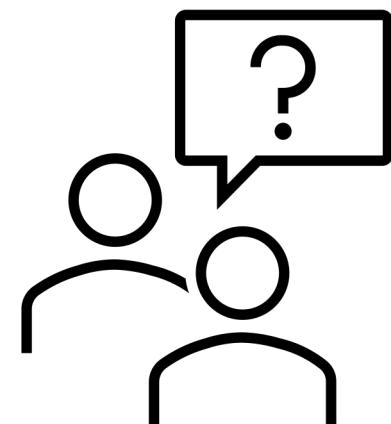
biweekly virtual meeting between oncologists and organ specialists  
accessible to all Belgian hospitals

every 1<sup>st</sup> and 3<sup>rd</sup> Monday of the month  
4-5 pm



# Methods

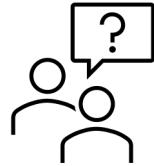
toxicity of  
immunotherapy



dysimmunity



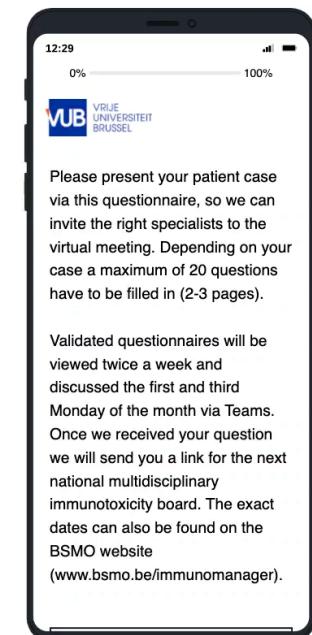
# Methods



diagnosis  
management  
prevention of irAEs

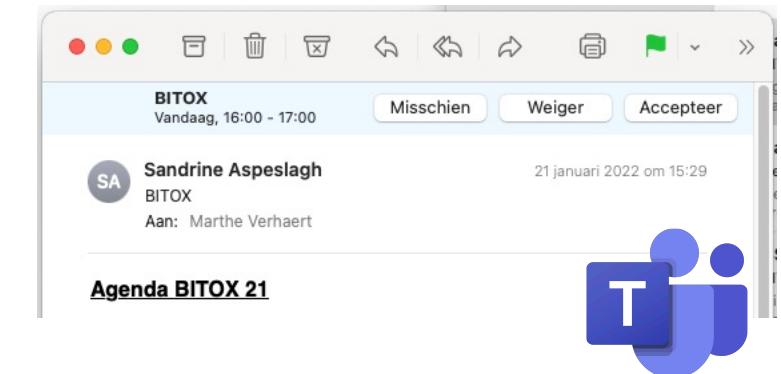


← → C ⌂ [bsmo.be/immunomanager/start/](https://bsmo.be/immunomanager/start/) ⌂ ⌂

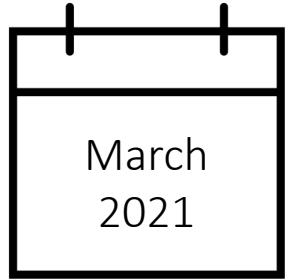


## Aim:

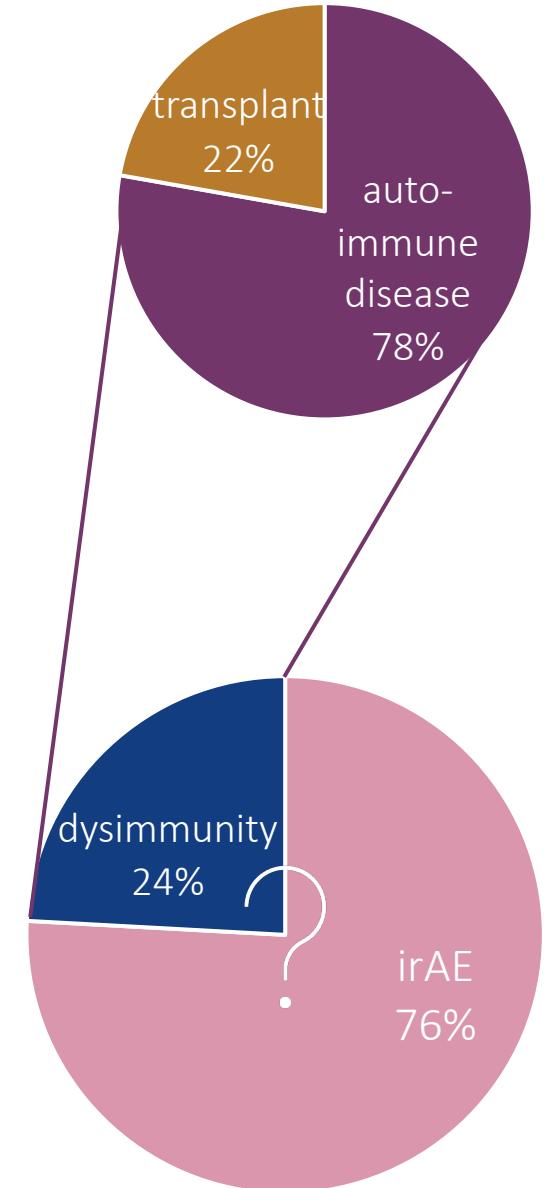
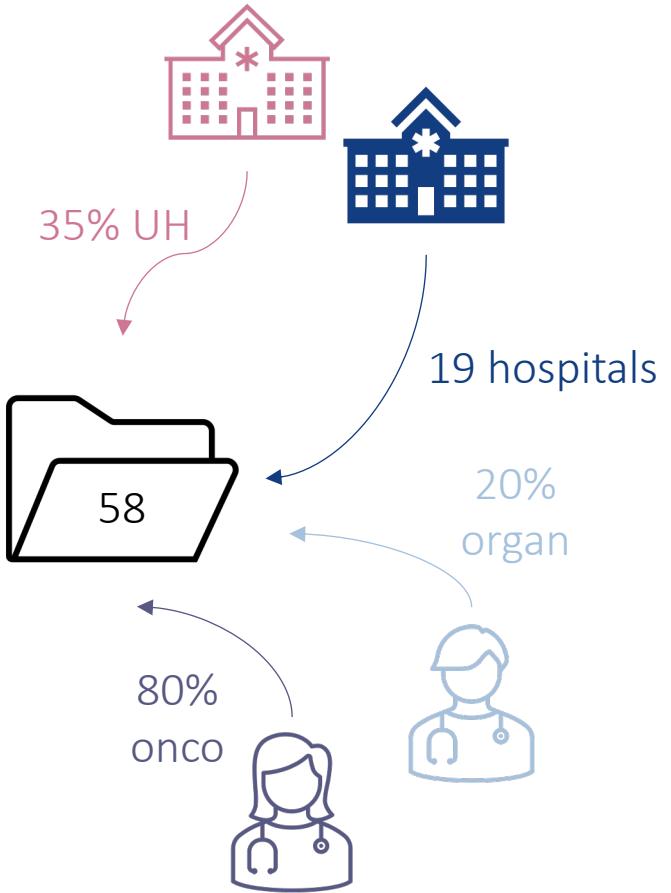
- share experiences
- standardize approach for irAEs
- find clinically relevant research questions



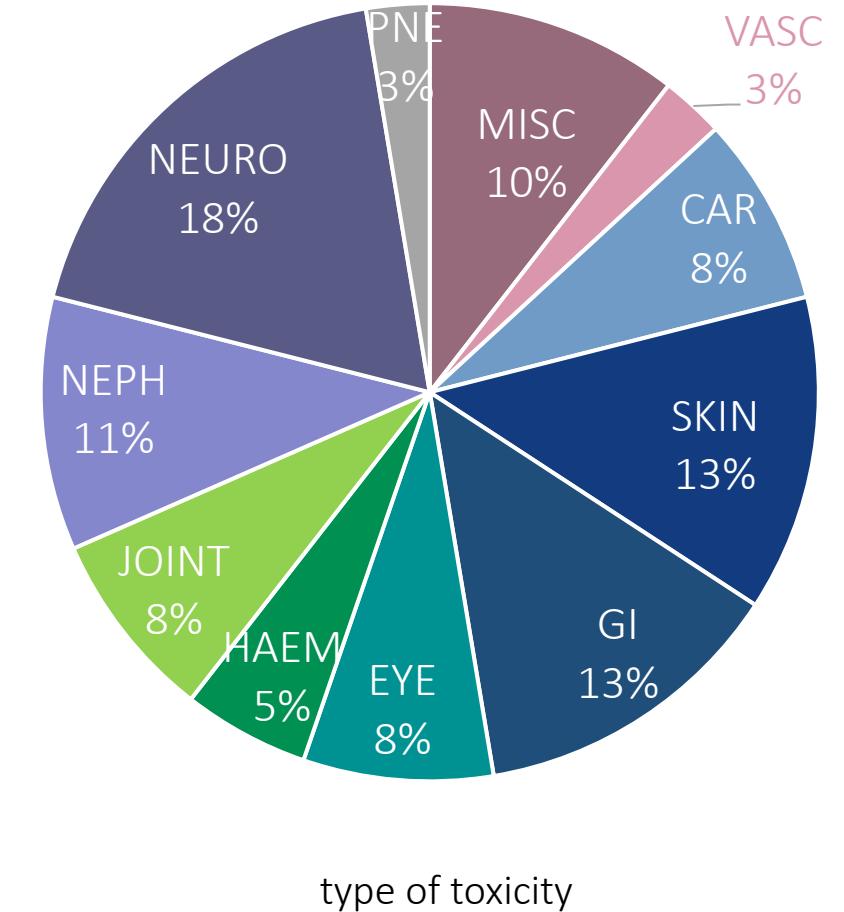
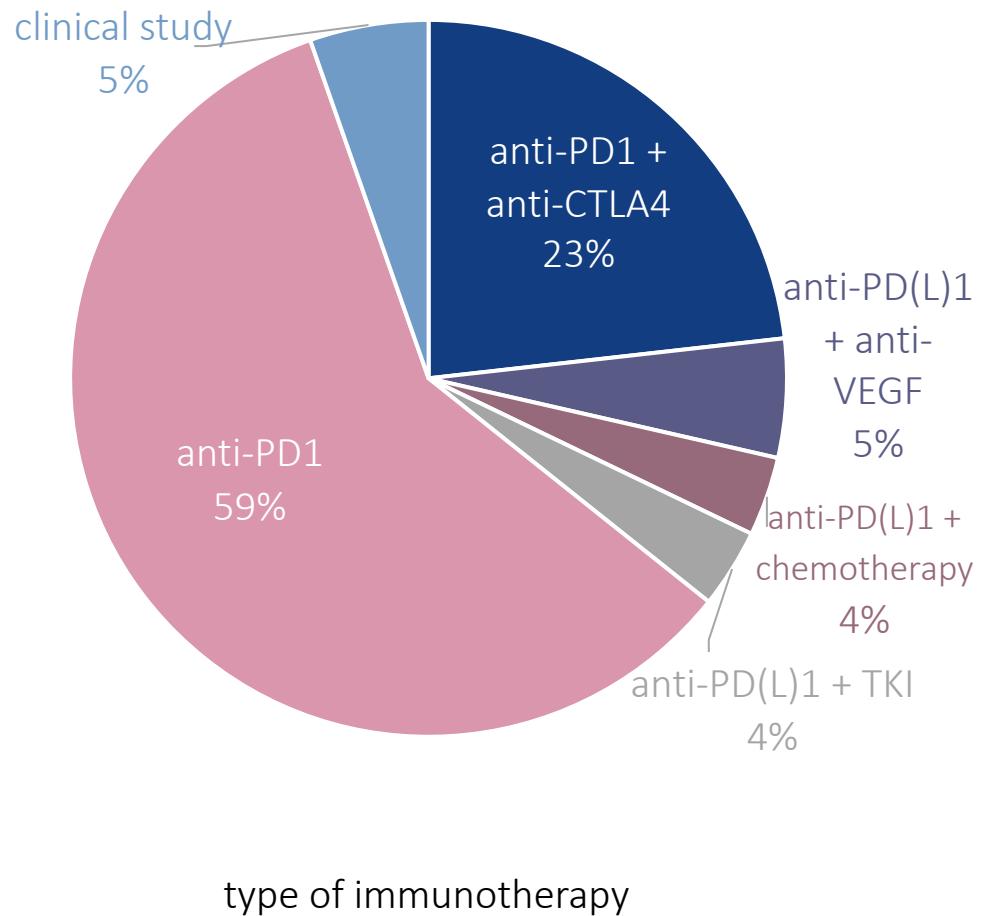
# Results



22 meetings



# Results



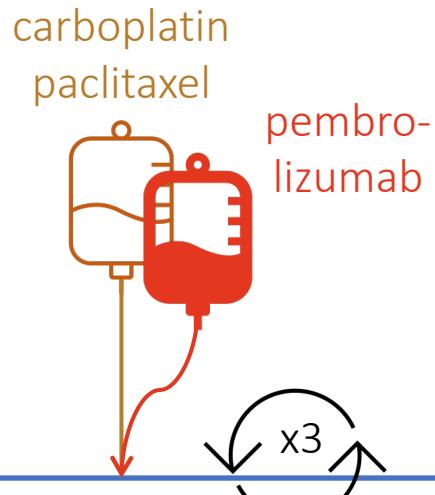
# Results

- longitudinal follow-up
- rediscussion
- updates



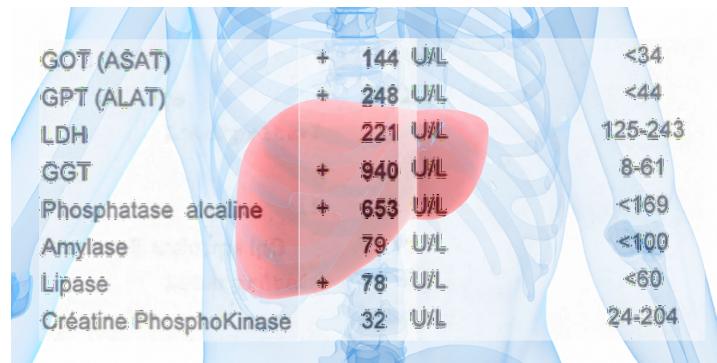
# Example 1

°1946



grade 2 hepatitis

normalisation of AST/ALT  
gGT remains at 800 U/L



BITOX  
rechallenge?



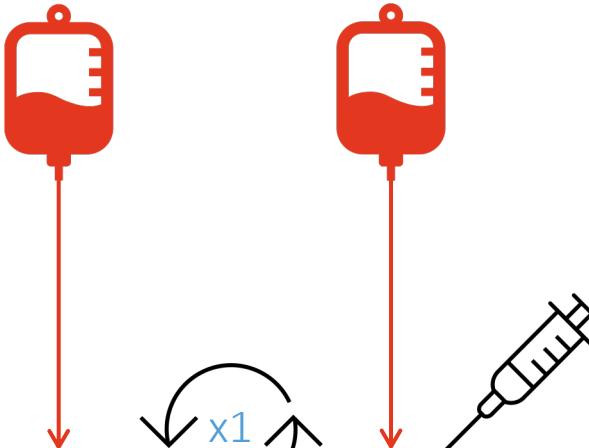
# Example 2

°1951 CKD  
DMII  
AHT  
HCT  
RA



stop MTX and anti-TNF

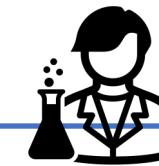
nivolumab



nivolumab



malaise  
fatigue  
wrists better



start salazopyrine  
start plaquenil

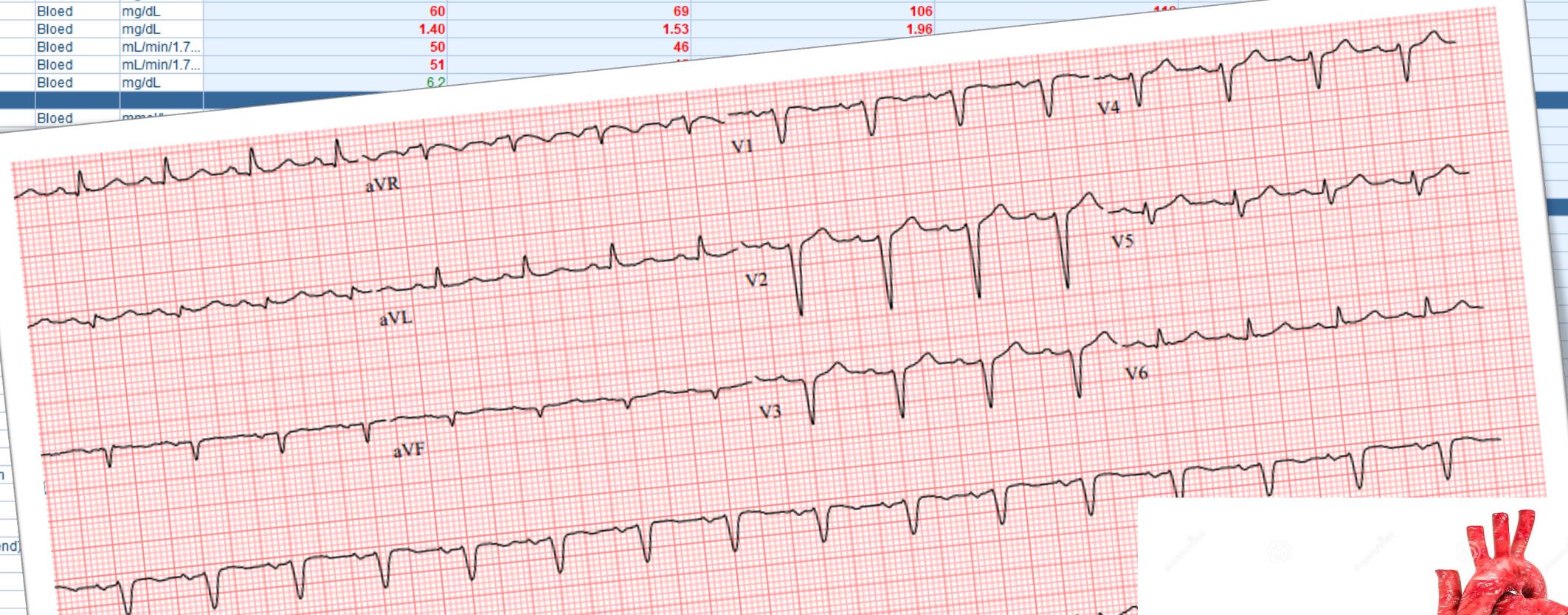
ssMM

Breslow 1,3 mm, Clark III

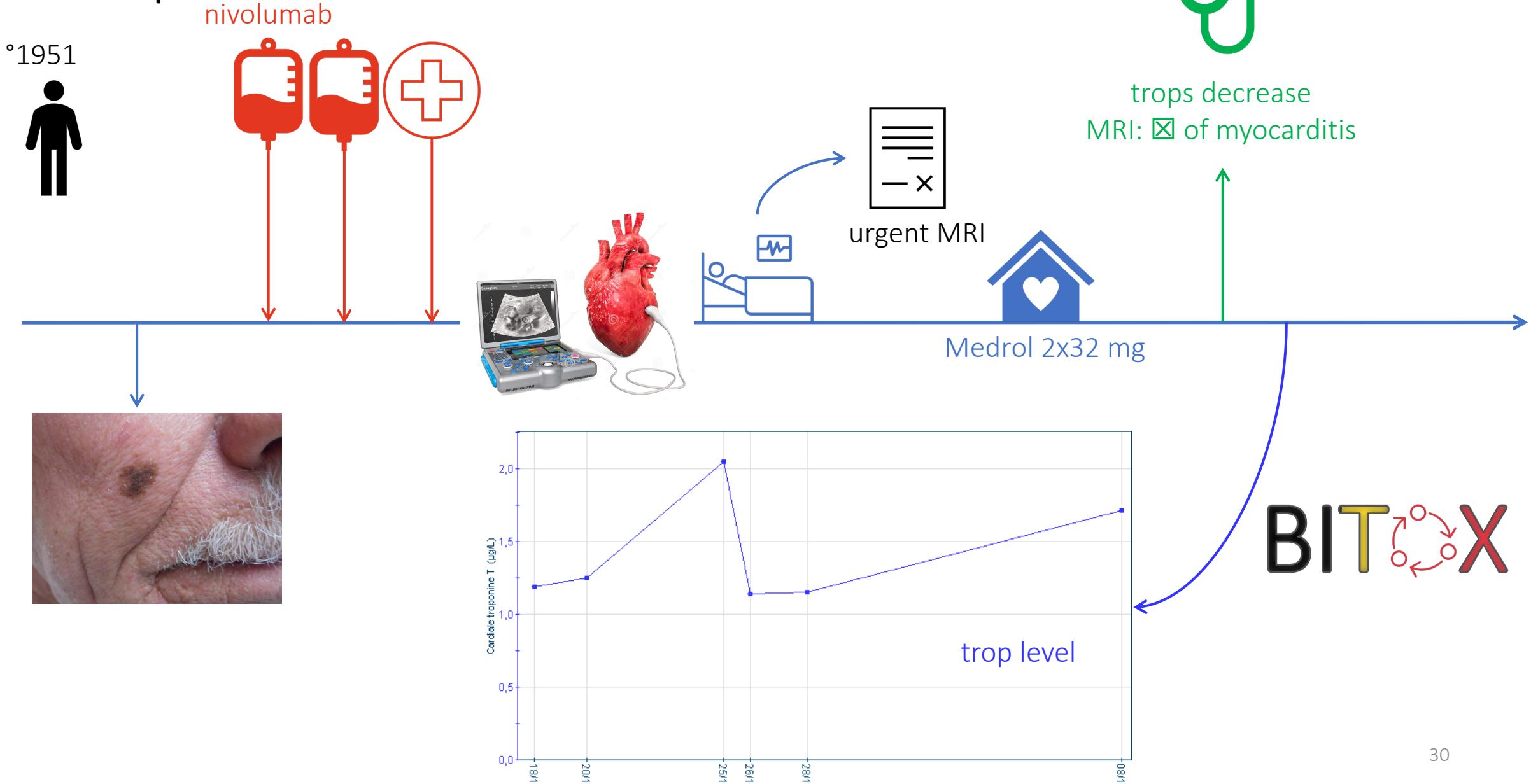
in transit mets

BRAFwt

			20/10/2021 09:41	18/10/2021	12/10/2021	11/10/2021	27/09/2021	13/09/2021
Klinische Chemie Bloed - CSV	Bloed	mg/dL						
Glucose	Bloed	mg/dL		114				144
Ureum	Bloed	mg/dL		60			70	1.82
Creatinine (IDMS-norm)	Bloed	mg/dL		1.40			58	38
eGFR (MDRD-IDMS)	Bloed	mL/min/1.7...		50			46	37
eGFR (CKD-EPI-IDMS)	Bloed	mL/min/1.7...		51				
Urinezuur	Bloed	mg/dL		6.2				
Ionogram								
Natrium	Bloed	mmol/L						
Kalium								135
Chloride							4.0	98
Bicarbonaat							21	20
Anion gap								
Fosfor							0.91	
Calcium							2.27	
Magnesium							0.77	
IJzer								
Transferrine							77	
Transferrinesaturatie							41	
Proteinen totaal (plasma)							28.2	
Albumine							22	
CRP (inflammatoir)							183	
Creatine kinasen							10	
Lactaat dehydrogenasen							6	
Aspartaat aminotransferasen							101	
Alanine aminotransferasen							48	
Alkalische fosfatases							30	
Gamma-glutamyltransferasen								
Lipasen								
Cholesterol								
HDL-cholesterol								
Non-HDL-cholesterol (berekend)								
LDL-cholesterol								
Triglyceriden								
Bilirubine: totaal								
Bilirubine: direct								
Cardiale troponine T								

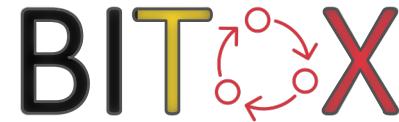
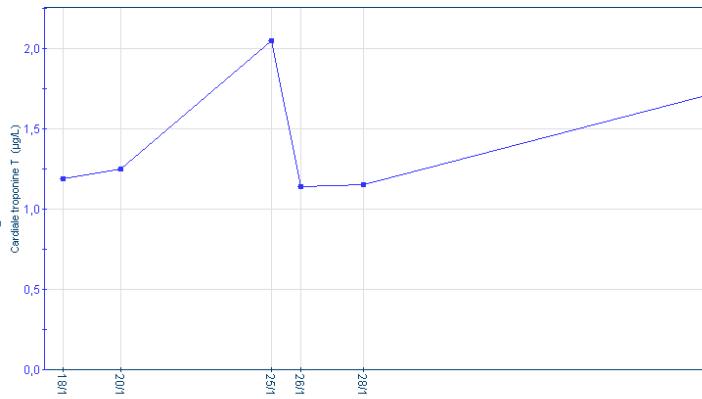
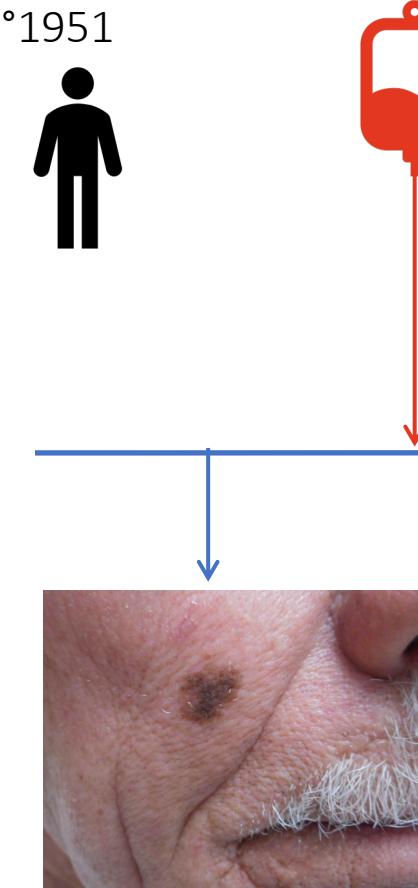


# Example: case 2

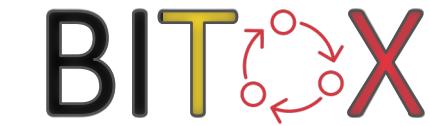
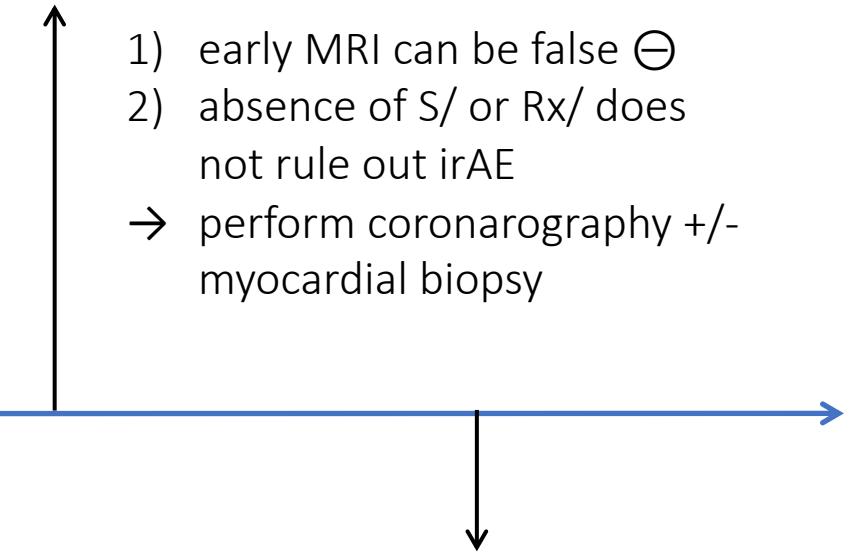


# Example: case 2

nivolumab



- 1) early MRI can be false  $\ominus$
- 2) absence of S/ or Rx/ does not rule out irAE
- perform coronary angiography +/- myocardial biopsy



rechallenge anti-PD1 after CABG

# Looking ahead

collaboration with FAMHP



- reach **more** oncologists and organ specialists
- expand our team of **regulars**
- update **BSMO immunomanager** according to recently published guidelines



Home » Immunomanager » Belgian Multidisciplinary Immunotoxicity Board (BITOX)

## Belgian Multidisciplinary Immunotoxicity Board (BITOX)



The screenshot shows the BITOX website's navigation menu. It includes a main header with three buttons: "Agenda" (white background), "How to present a case" (light gray background), and "People" (white background). Below this are three rows of toxicity categories, each with an icon and a link:

- Joint pathology →
- Colitis →
- Skin toxicity →

- Hepatic toxicity →
- Nephrotoxicity →
- Neurologic toxicity →

- Pneumonitis →
- Endocrine toxicity →
- Muscle pathology →



retrospective trial about **patients with dysimmunity** treated with ICI (dr. M. Verhaert)



register of **renal transplant patients** treated with ICI (dr. T. Van Meerhaeghe)



**BIRD**  
BELGIAN INFLAMMATORY  
BOWEL DISEASE RESEARCH  
AND DEVELOPMENT

Delphi round

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## GET IN TOUCH

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