Toxicity from Immune checkpoint inhibitors
What have we learnt?

Caroline Robert, MD, PhD
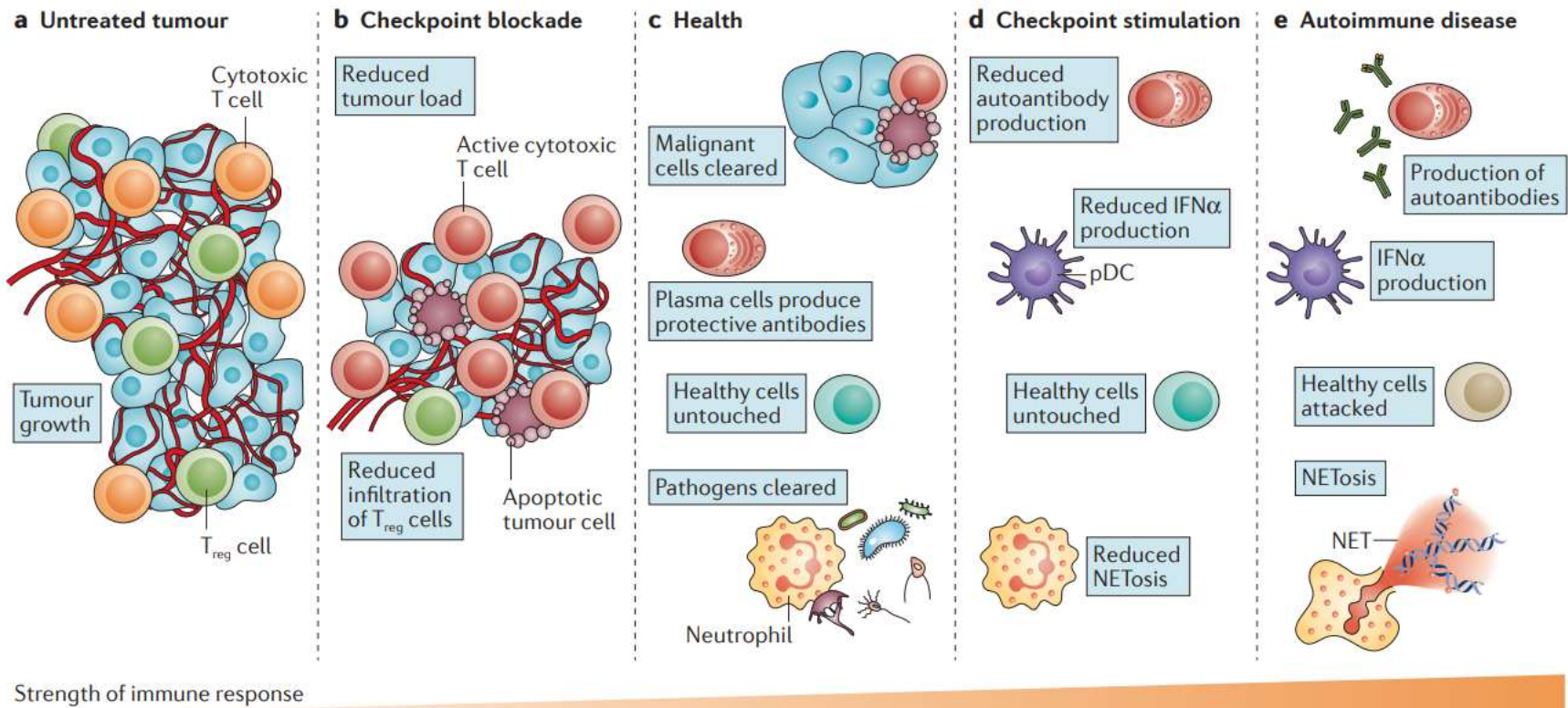
Gustave Roussy and Paris-Saclay University

France

disclosures

C Robert is consultant for BMS, MSD, Novartis, Roche, Pierre Fabre, Novartis, Sanofi, Biothera, CureVac

From cancer to auto-immune disease

What could we expect when blocking mechanisms critically involved in self-tolerance?

- **Inactivation of CTLA4 or PD1 induces lympho-proliferative syndromes and autoimmunity in humans and murine model of lupus respectively**

- **Polymorphisms of CTLA4 and PD-1 associated with autoimmunity**
  - CTLA4 rheumatoid arthritis, auto-immune endocrinopathies, Type 1 diabetes, Addison disease, Celiac disease
  - PD1 linked to Systemic lupus erythematosus, rheumatoid arthritis, Type 1 diabetes, ankylosing spondylitis

- **Autoimmune diseases are treated with agonists of CTLA4 and PD1**
  - CTLA4-FC (abatacept): authorized for RA, psoriasic arthritis and JIA , evaluated in SSc, Sjögren Sd, SLE
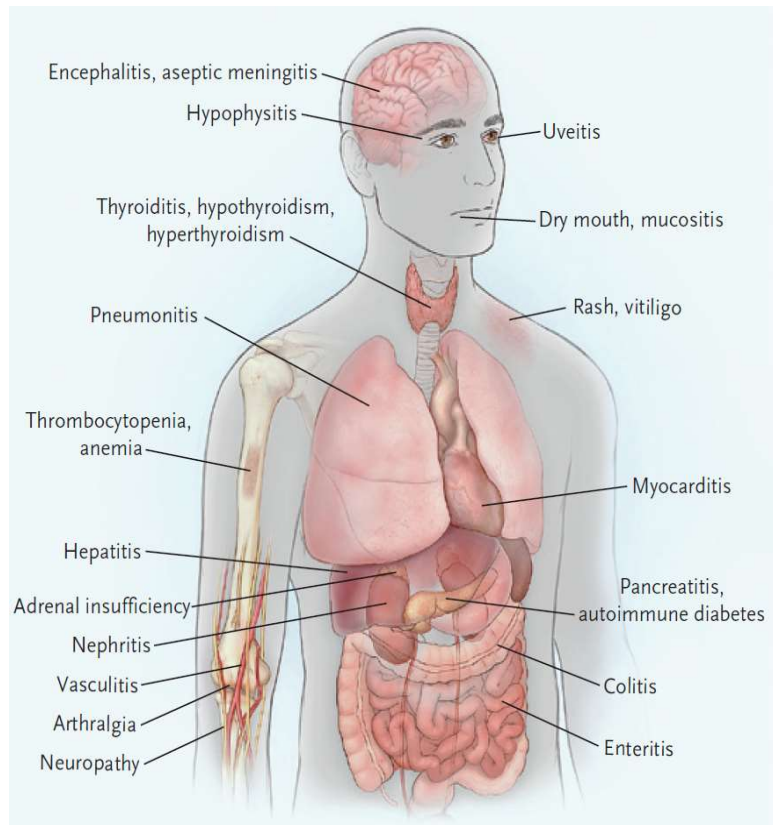 - PD1- CD3 bispecific antibody : efficacy in mice EAE

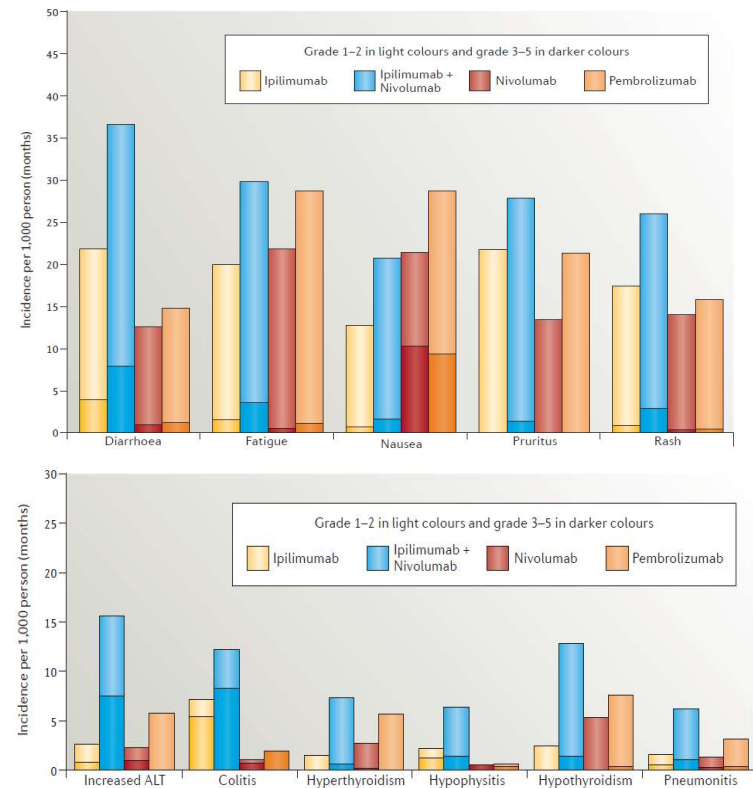*Schubert et al Nat Med 2014; Nishimura et al. Immunity 1999*

What have we learnt?
What are the questions?

- Incidence, severity and timing of irAE

- What are the mechanisms of irAE?

- Are irAE associated with response to ICI?

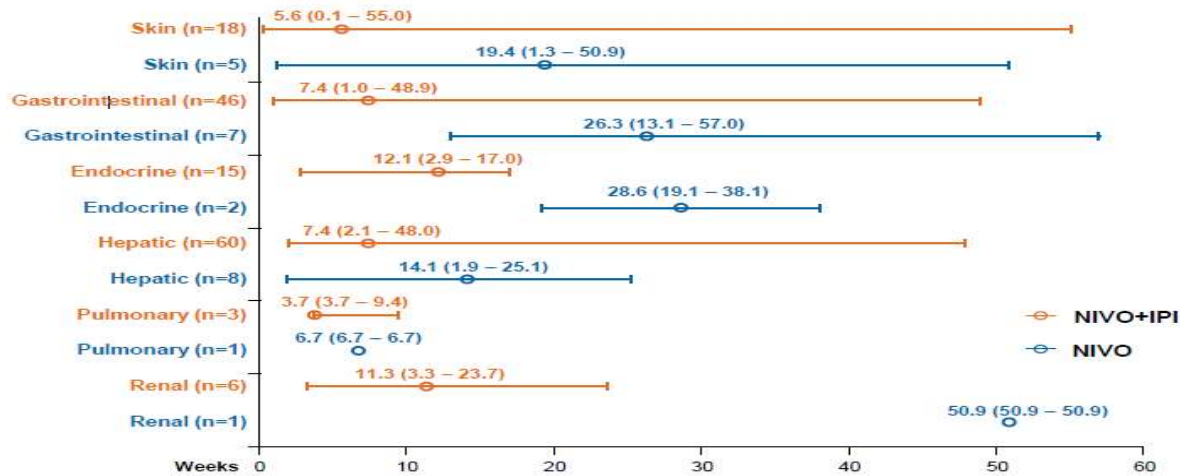- Can we predict irAE?

- How to manage irAE?

Wide spectrum of AE

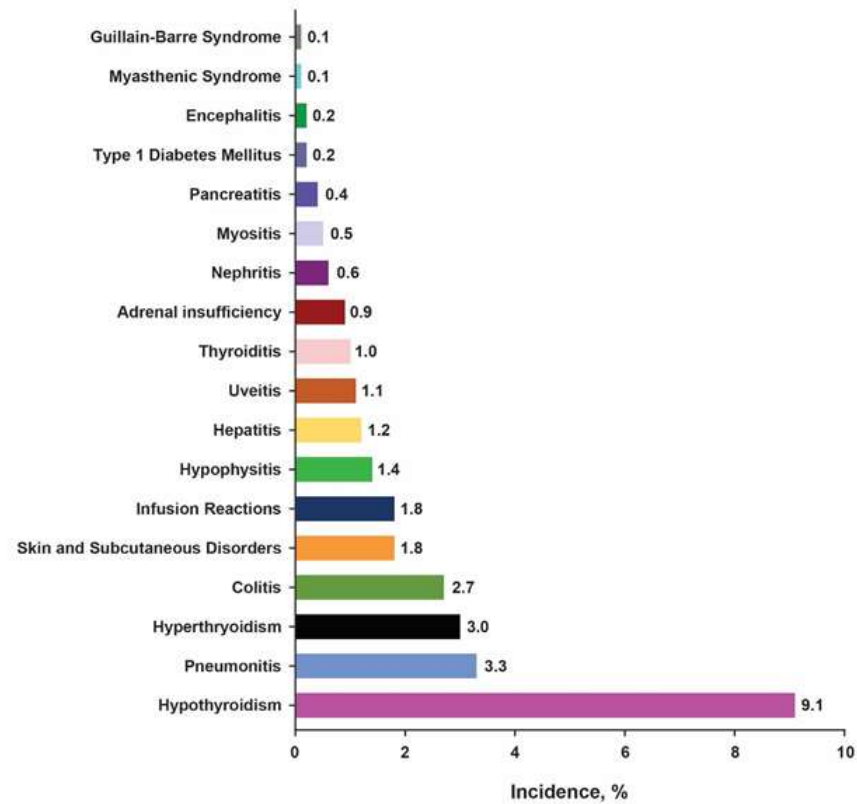

Postow et al N Eng J Med 2018

Boutros et al, Nat Clin Pract Oncol 2016

Time to onset of irAE with nivolumab +/- ipilimumab
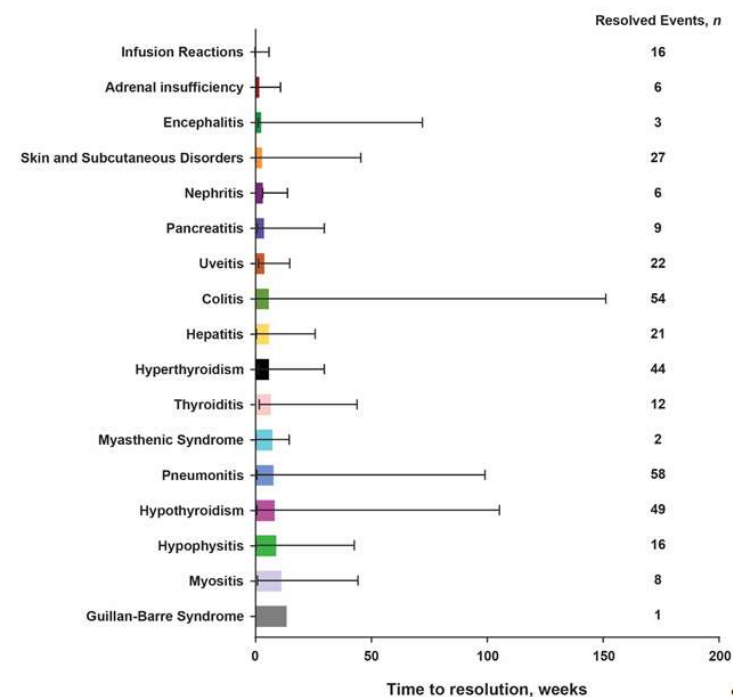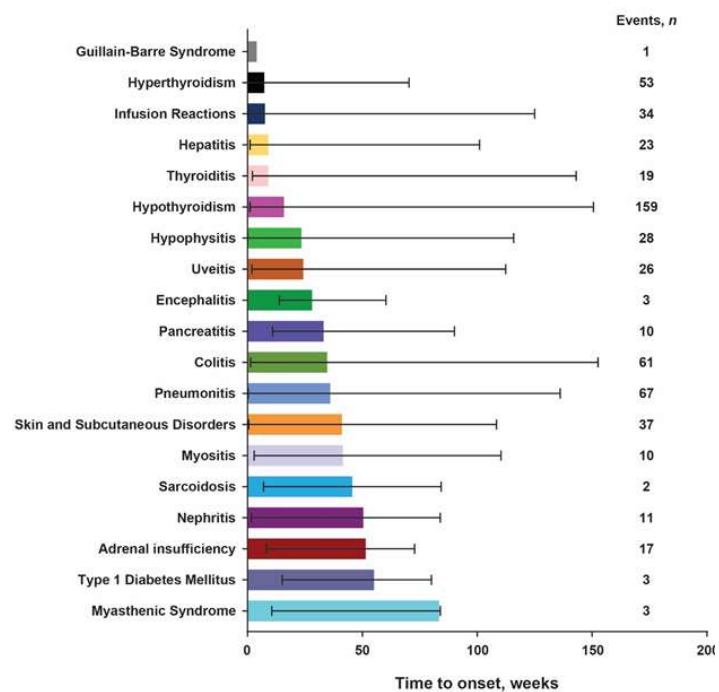

Larkin et al ECC 2015

Incidence of any-grade irAE occurring in at least one patient (N = 1567 treated with pembrolizumab)

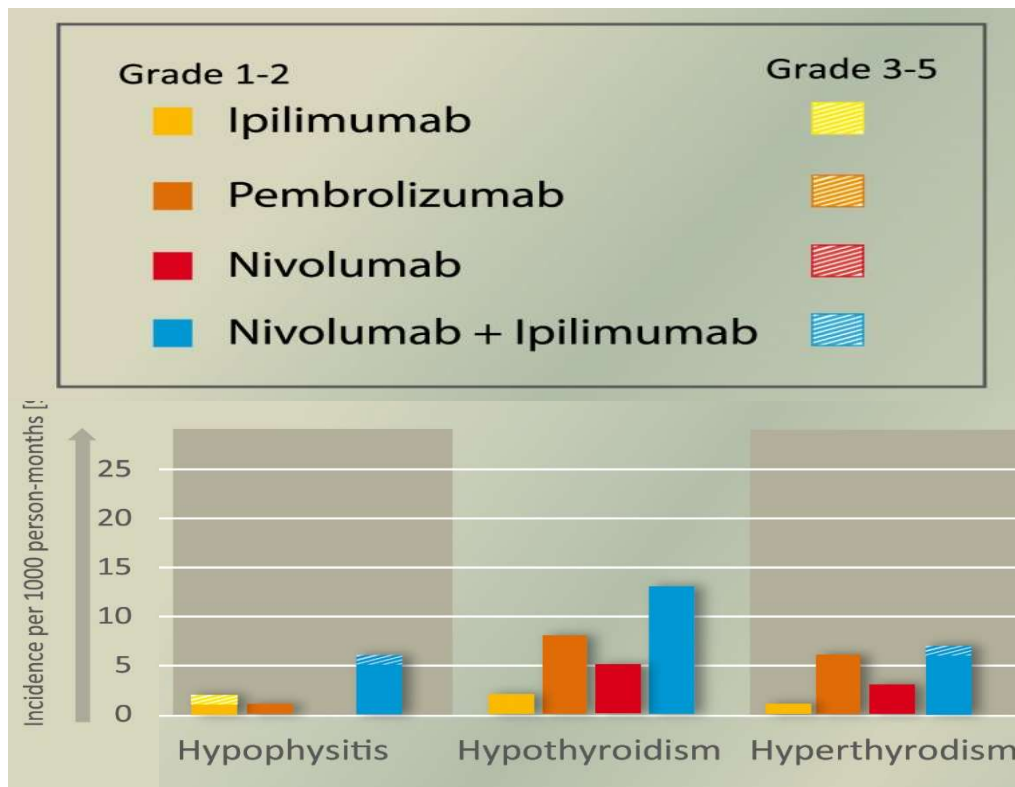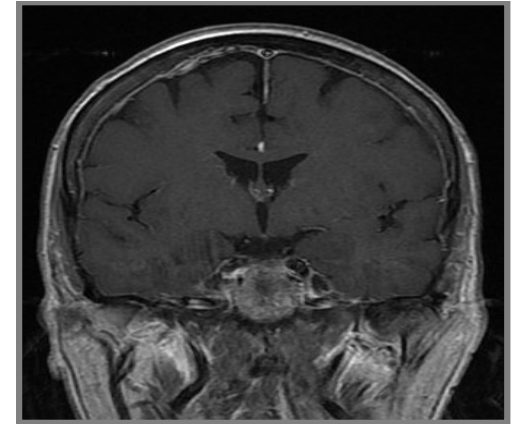| irAE	Incidence, %
Guillain-Barre Syndrome	0.1
Myasthenic Syndrome	0.1
Encephalitis	0.2
Type 1 Diabetes Mellitus	0.2
Pancreatitis	0.4
Myositis	0.5
Nephritis	0.6
Adrenal insufficiency	0.9
Thyroiditis	1.0
Uveitis	1.1
Hepatitis	1.2
Hypophysitis	1.4
Infusion Reactions	1.8
Skin and Subcutaneous Disorders	1.8
Colitis	2.7
Hyperthryoidism	3.0
Pneumonitis	3.3
Hypothyroidism	9.1

Robert et al In press

Median (range) time to onset and resolution of any-grade irAE
(*N* = 1567 treated with pembrolizumab)

Robert et al In press

Endocrine AE
can be permanent

Grade 1-2 | Grade 3-5
- Ipilimumab
- Pembrolizumab
- Nivolumab
- Nivolumab + Ipilimumab

Incidence per 1000 person-months
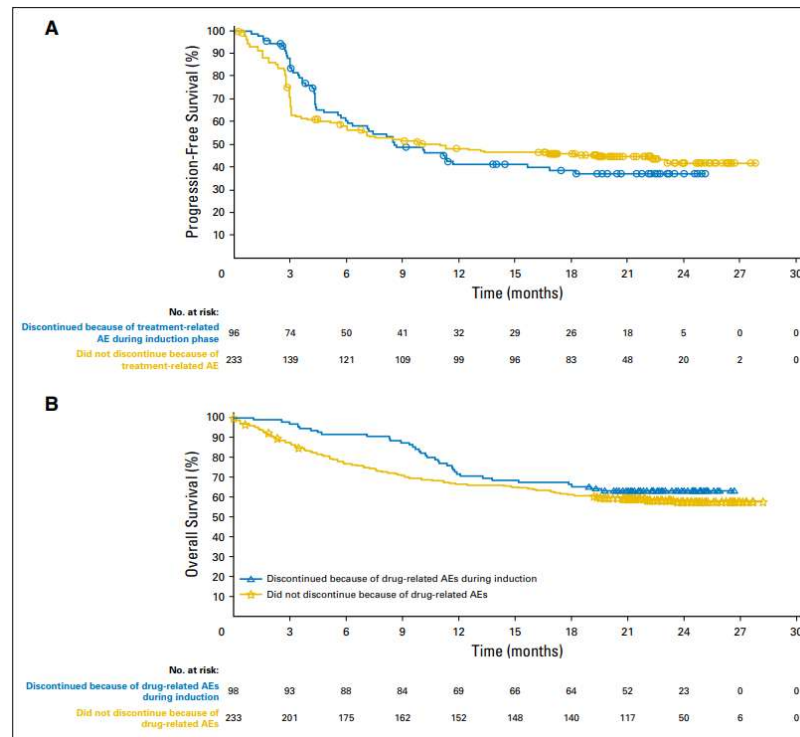
Hypophysitis | Hypothyroidism | Hyperthyrodism

- Dysthyroidisms more frequent with anti-PD-1 than CTLA-4
- Hypophysitis induces pan or partial hypopituitaris, more frequent with anti-CTLA-4

Boutros et al NCPO
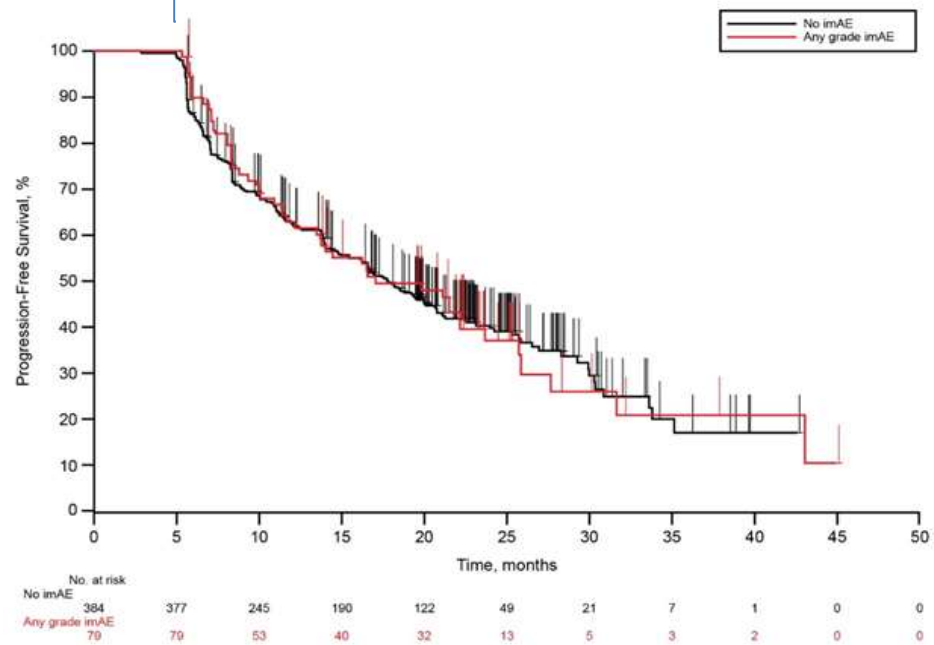
irAE and clinical outcome?

No difference in clinical outcomes for patients who discontinued because of AE and patients who did not discontinue

Schadendorf et al J Clin Oncol 2017

Kaplan-Meier plot of PFS in patients with or without irAEs who were receiving pembrolizumab before week 21

Landmark analysis to decreased the guarantee-time bias

Robert et al In press

Vitiligo with anti-PD1 or anti-PDL1

Vitiligo and clinical response to pembrolizumab

Patient	CR	PR	SD	PD	p*
Vitiligo (N=17)	3 (18)	9 (53)	3 (18)	2 (12)	0.002
Non vitiligo (N=50)	4 (8)	10 (20)	1 (2)	35 (70)	
Total (N=67)	7 (10)	19 (28)	4 (6)	36 (54)	

*Complete/partial response versus stable/ progressive disease/progression progression in patients disease/progression in patients with and without vitiligo, exact fisher test
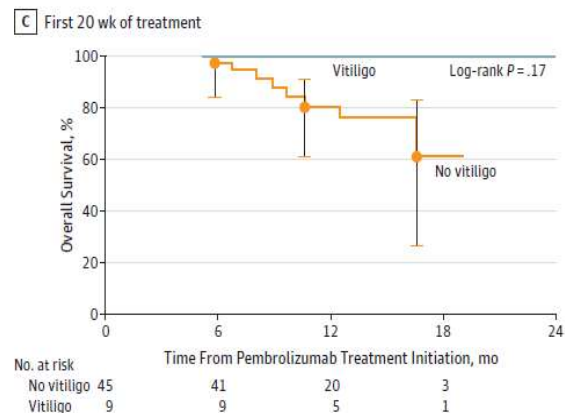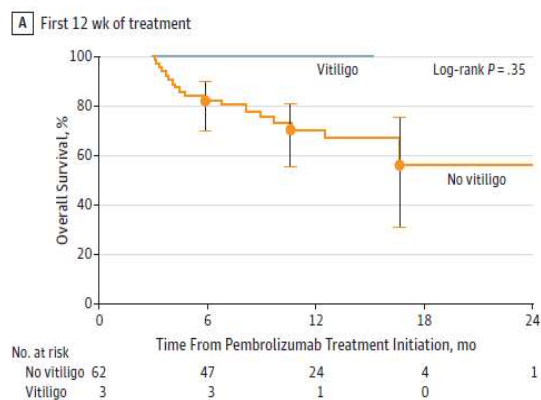

Hua et al JAMA Dermatol 2016

Incidence of AE and relapse free survival with pembrolizumab

Immune-Related Adverse Event Status and Treatment Arm	Recurrence-Free Survival, HR (95% CI)[a]	P Value[a,b]
Any irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.62 (0.49-0.78)	.03
Pembrolizumab after irAE onset	0.37 (0.24-0.57)	
Endocrine irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.60 (0.48-0.75)	.03
Pembrolizumab after irAE onset	0.34 (0.20-0.57)	
Vitiligo		
Placebo	1	
Pembrolizumab without/before irAE	0.57 (0.46-0.70)	.15
Pembrolizumab after irAE onset	0.13 (0.02-0.95)	
Any severe (grade 3-4) irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.55 (0.44-0.68)	.43
Pembrolizumab after irAE onset	0.78 (0.32-0.91)	

Eggermont et al JAMA Oncol 2020

Possible Mechanisms Underlying Immune-Related Adverse Events
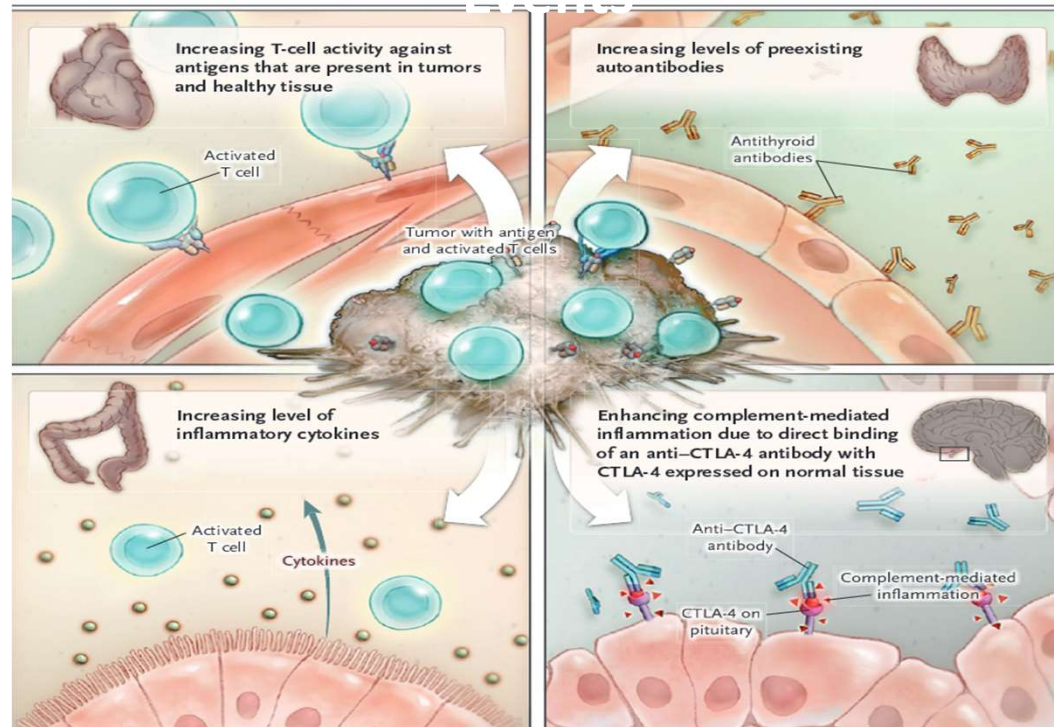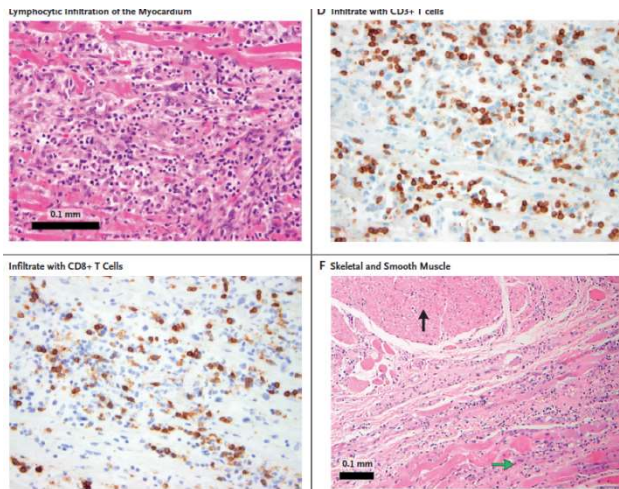

Postow et al. NEJM 2018

Mechanism of irAE

Fulminans myocarditis with ICI

- 2 melanoma patients ipi/nivo
- Selective clonal T-cell population in the myocardium and skeletal muscles

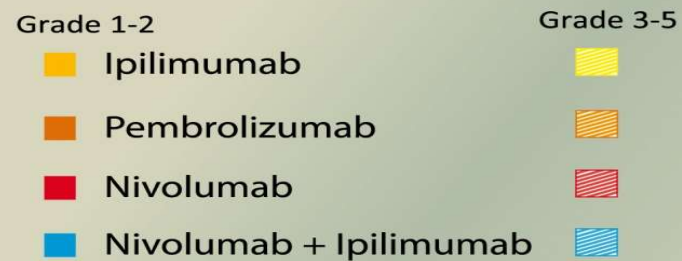## Fulminans encephalitis with anti-PD1

- 1 melanoma patient
- Fatal meningoencephalitis 18 months after initiation of pembrolizumab
- Oligoclonal memory CD4+ T cells infiltration
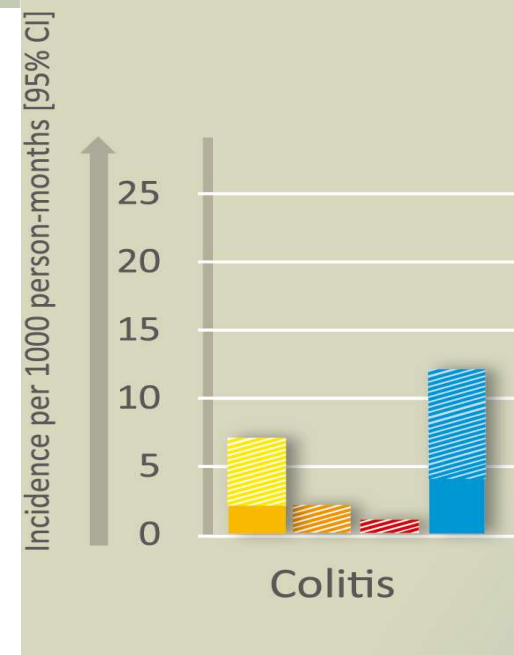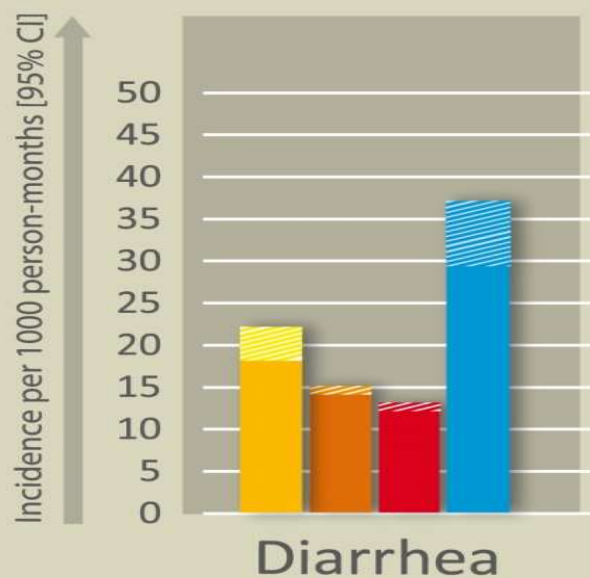- Presence of EBV-specific T cells
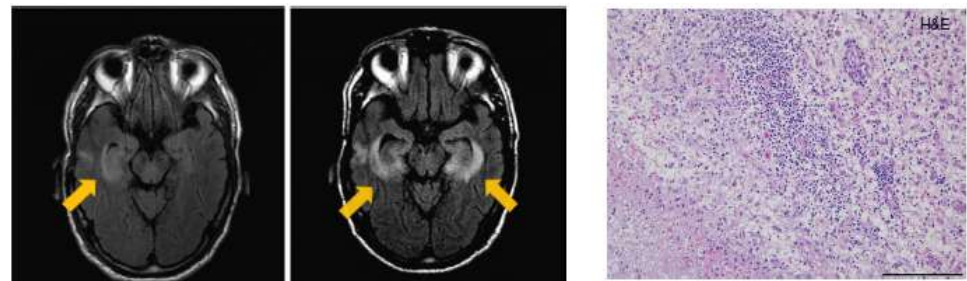
Johnson et al NEJM 2016; Johnson et al Nat Med 2019
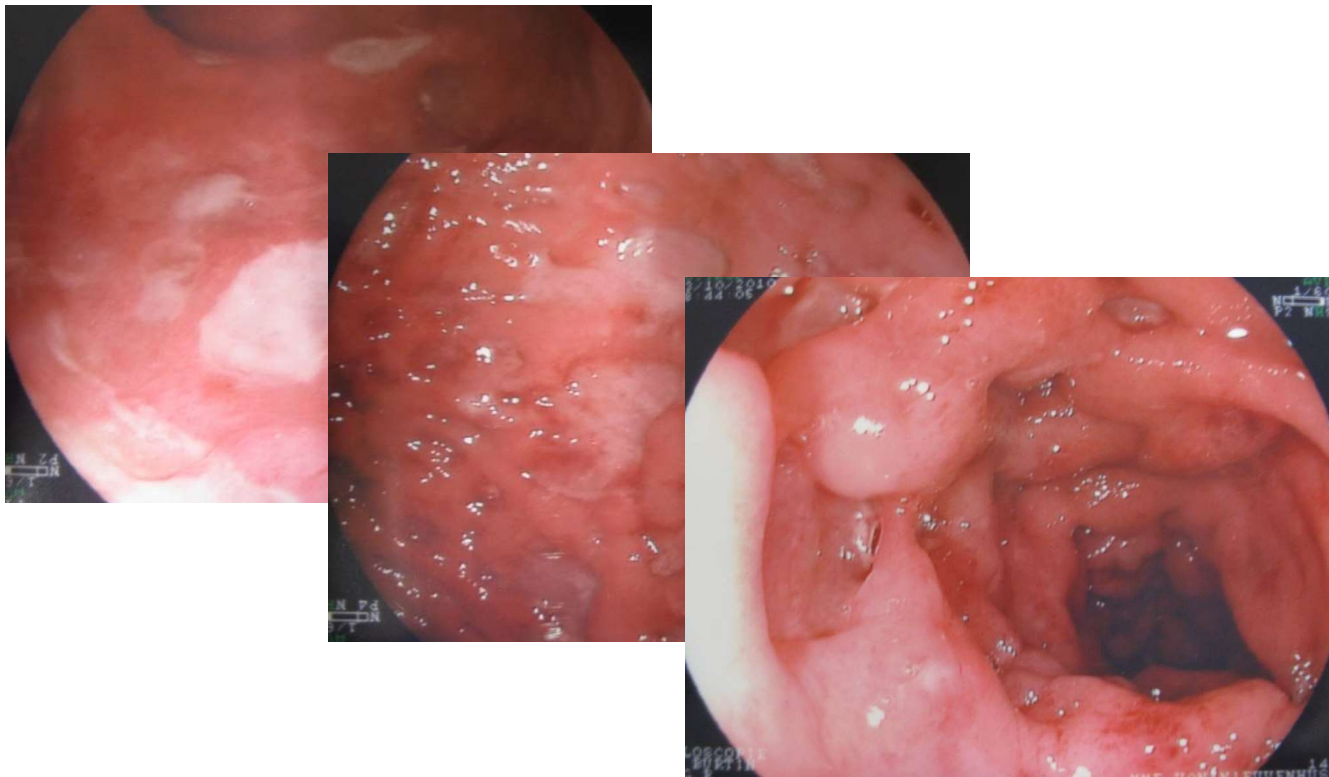
Prediction of toxicity?

Diarhhea/colitis

Boutros et al NCPO

Gut microbiota and anti-CTLA-4-induced colitis

Marthey L,… Carbonnel F JCC 2016

Microbiota and immune-mediated colitis

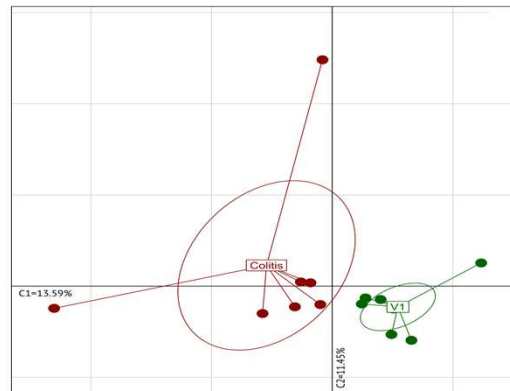➤ Ipilimumab-mediated colitis is associated with microbial dysbiosis

Patricia Lepage

Nathalie Chaput

Franck Carbonnel

paired samples
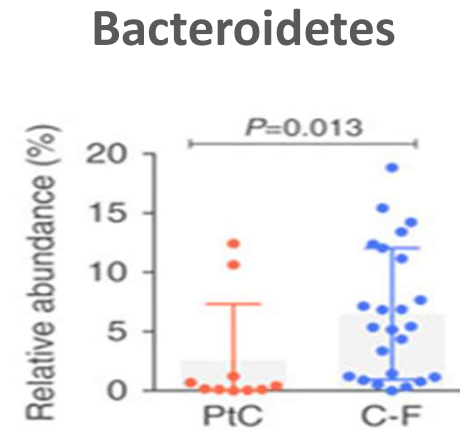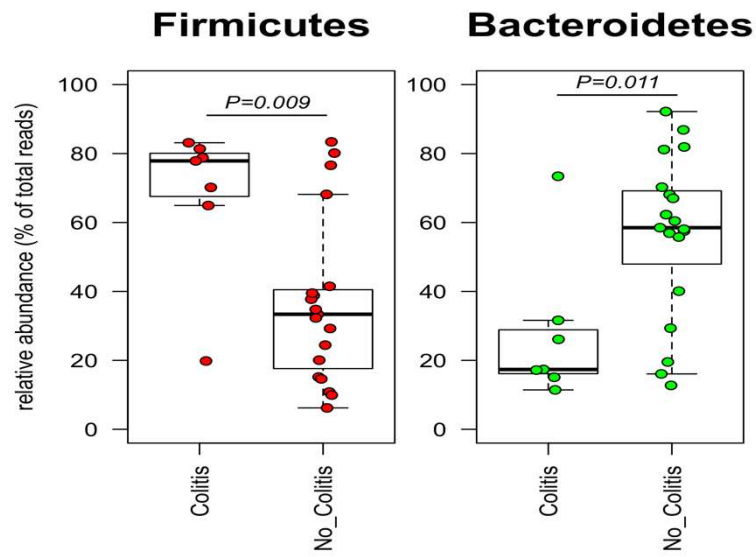*Genus distribution*
monte-carlo p=0.0059
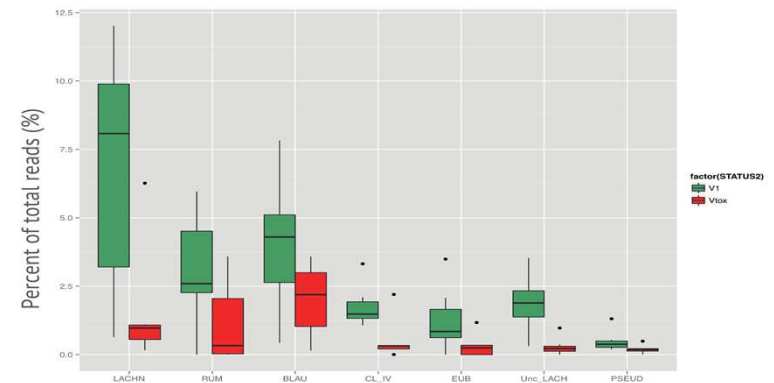
Colitis associated with decreased Firmicutes proportion
and
decreased diversity

Chaput et al Ann Oncol 2017

Microbiota as a colitis predictor?

> High proportions of Bacteroidetes at baseline are associated with colitis protection

Chaput et al Ann Oncol 2017; Dubin et al Nat Com 2016

Patients with pre-existing auto-immune disease

History of autoimmune disease (AID) and kinetics of autoantibodies associated with irAE

- Patients with preexisting AID exacerbate their AID when treated with ICI (40 to 50%) or present with an irAE (30 to 40%) (Brahmer et al. JCO 2010; Menzies et al. Ann Oncol 2017 ; *Gutzmer at al EJC 2017; Abdel Wahab et al Ann Intern Med 2018)*

- early increase (≤4 wk) in serum thyroglobulin and thyroid autoantibodies associated with thyroid irAE   (Kurimoto et al Cancer Science 2020 and De Moel et al Cancer Immunol Res 2020)

- Early blood rise in auto-antibodies to nuclear and smooth muscle antigens is predictive of prolonged survival and autoimmunity in NSCLC treated with PD-1 (Giannicola et al Mol Clin oncol 2019)

- Increase of anti-GNAL and anti-ITM2B autoantibodies associated with hypophysitis and anti-CD74 autoantibody with pneumonitis (Tahir et al PNAS 2019)

Patient developing an acute anti-HU encephalopathy after one avelumab infusion
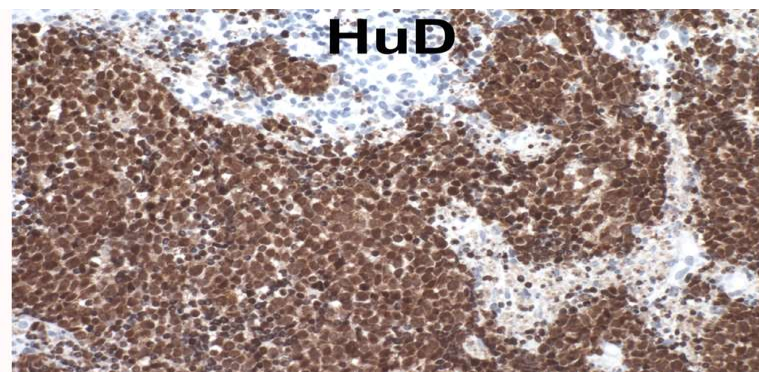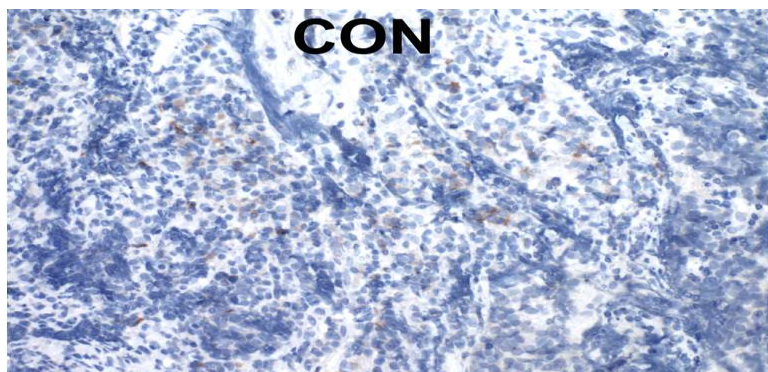
anti-HU AAB before ICI, increase after ICI

in a patient developing an acute anti-HU encephalopathy after one avelumab infusion

| Sérum		Sérum	
Anti-YO	Négatif	Anti-YO	Négatif
Anti-HU	Positif	Anti-HU	Positif
scan 55 UA pour un seuil à 5.		scan 75 UA pour un seuil à 5	
Anti-RI	Négatif	Anti-RI	Négatif
Anti-amphiphysine	Négatif	Anti-amphiphysine	Négatif
Anti-CV2	Négatif	Anti-CV2	Négatif
Anti-Sox1	Négatif	Anti-Sox1	Négatif
Anti-GAD	Négatif	Anti-GAD	Négatif
Anti-Ma1	Négatif	Anti-Ma1	Négatif
Anti-Ma2	Négatif	Anti-Ma2	Négatif
Anti-Zic4	Négatif	Anti-Zic4	Négatif

meet.google.com/jvb-vrzw-cvy

anti-HU AAB before ICI, increase after ICI
and HuD expression on Merkel cell carcinoma
in a patient developing an acute anti-HU encephalopathy after one avelumab infusion

Sérum		Sérum	
Anti-YO	Négatif	Anti-YO	Négatif
Anti-HU	Positif	Anti-HU	Positif
scan 55 UA pour un seuil à 5.		scan 75 UA pour un seuil à 5	
Anti-RI	Négatif	Anti-RI	Négatif
Anti-amphiphysine	Négatif	Anti-amphiphysine	Négatif
Anti-CV2	Négatif	Anti-CV2	Négatif
Anti-Sox1	Négatif	Anti-Sox1	Négatif
Anti-GAD	Négatif	Anti-GAD	Négatif
Anti-Ma1	Négatif	Anti-Ma1	Négatif
Anti-Ma2	Négatif	Anti-Ma2	Négatif
Anti-Zic4	Négatif	Anti-Zic4	Négatif

CON   HuD

# Auto-Antibodies and irAE : large scale analysis

- Presence of antibodies and irAE (Gowen et al, J Transl Med 2018)
  - Human Proteome microarray for 19,000 unique human proteins covering more than 75% of the proteome on serum from 75 metastatic melanoma pts
  - Distinct pre-treatment serum antibody profiles associated with severe irAEs and ability to discriminate between toxicity groups with >90% accuracy, sensitivity, and specificity.
  - Pathway analyses showed enrichment of antibody targeting immunity/autoimmunity, including TNFα signaling, toll-like receptor signaling and microRNA biogenesis
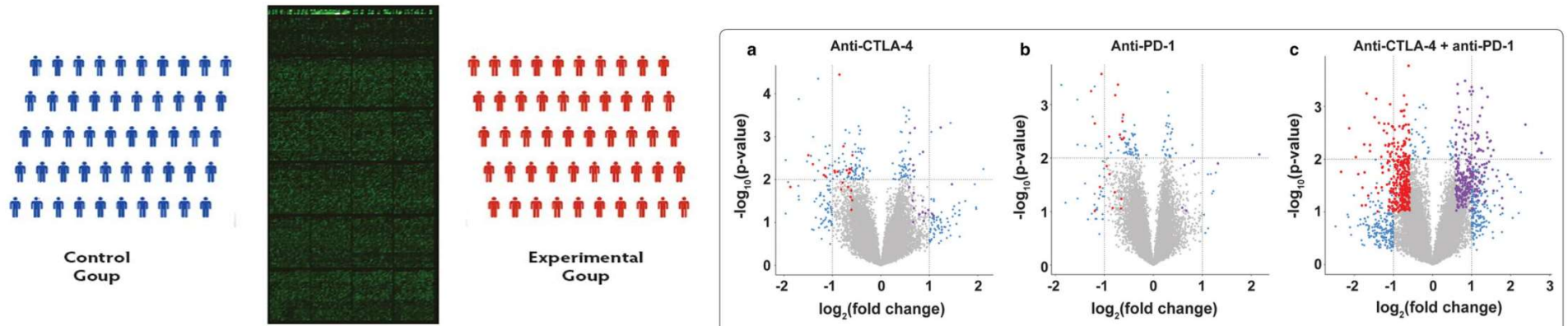
Seromics-based irAE biomarker discovery

Some AAB
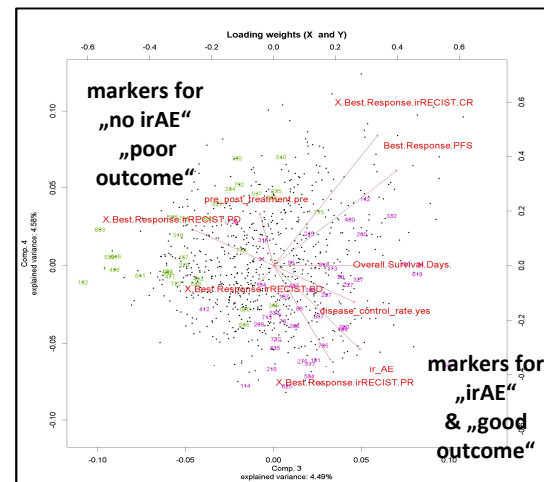## associated with distinct irAE, or differentially associated with outcome and irAE

Luminex AutoAb profiling from 333 CPI treated stage IV melanoma patients in from 5 european centers
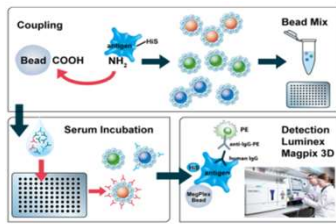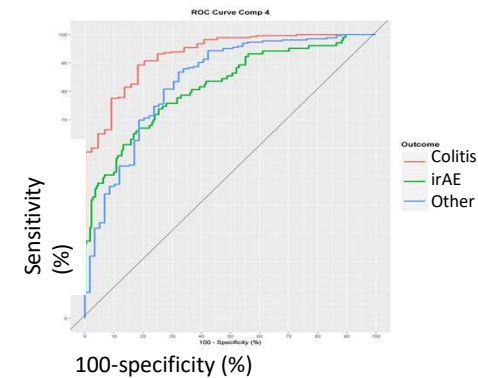

832 antigens

1:100 serum dilution

PLS Regression Analysis of AAB association with irAE and **better** clinical outcome
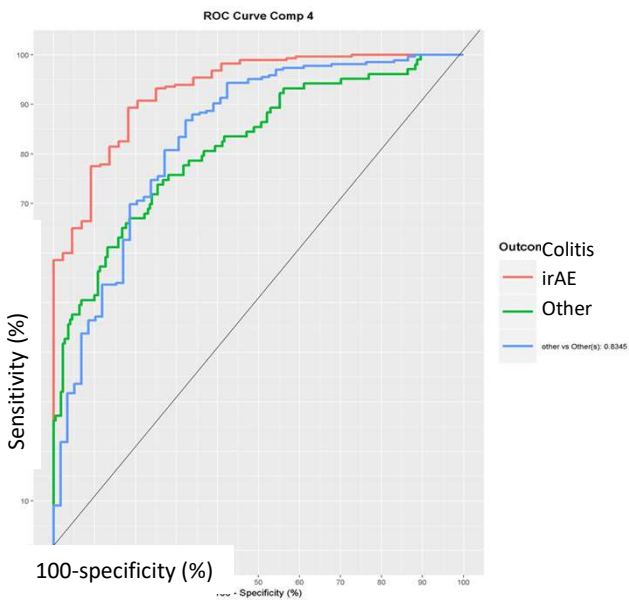

markers for „no irAE" „poor outcome"

markers for „irAE" & „good outcome"

Antigen	Ipi or Ipi/Nivo		Pembro	All
	Colitis	irAE	irAE	DCR, PFS or OS
MITF	⬇	⬇		
PIAS3	⬇	⬇		
MAGED2	⬆	⬆		
SUMO2	⬆			
GRP				
MIF			⬆	⬇
GPTIN				
MAGEB4	⬇	⬇		⬆
FGFR1		⬆		⬇
KRT7		⬇	⬇	

Good PLS-DA performance of a panel of AAB
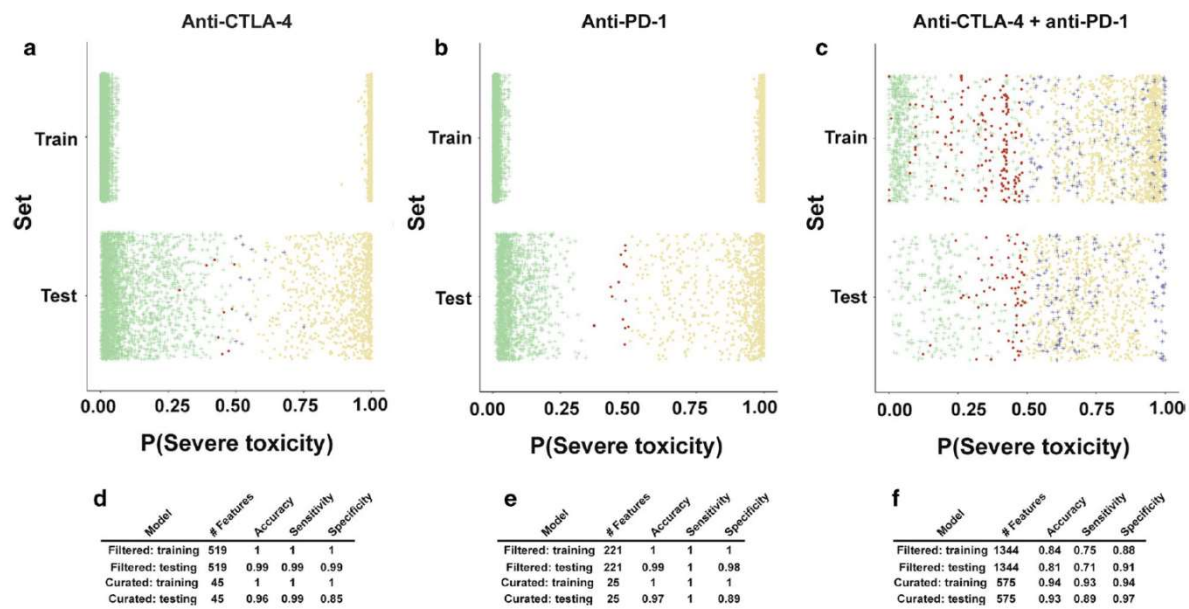

Hassel et al ASCO 2020

Toward a predictive AAB signature for irAE and maybe for response?

PLS-DA performance of panel

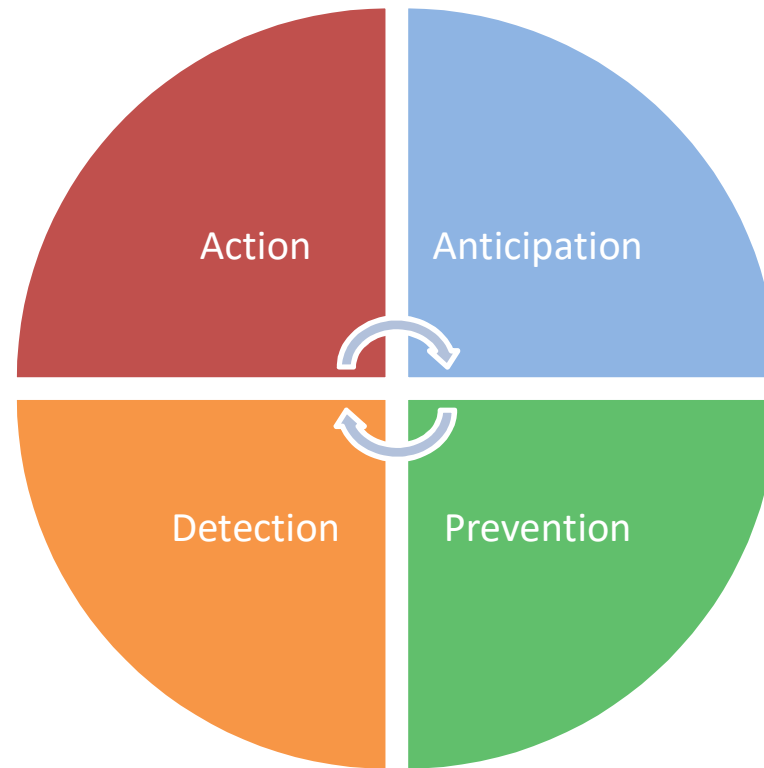Hassel et al ASCO 2020

Gowen et al J Transl Med 2018

Management

Anticipate
Anticipating by starting on a strong and adjusted check-up

|		Baseline	Every cycle
General	Complete CBC Serum electrolytes, creatininemia Liver tests	x	x
	Haemostasis CK tests Lipase CRP	x	
Endocrine	TSH, T4, T3; cortisolemia 8 H	x	Every 2 cycles
	Cortisolemia/ACTH 8h FSH, LH, oestradiol/testosterone IGF1, Prolactine Ab anti-îlots β, anti-insulin, anti-GAD	for IO-IO combination or adjuvant or neoadjuvant setting	
Urine	Urine dipstick	x	
Infectious	Virology: HIV, HCV, HBV serologies Quantiferon tuberculosis (a)	x	
Cardiac	ECG BNP and troponin	x	During the first 3 months
Respiratory	Thoracic CT imaging	x	

S Champiat courtesy

General management strategies for irAEs
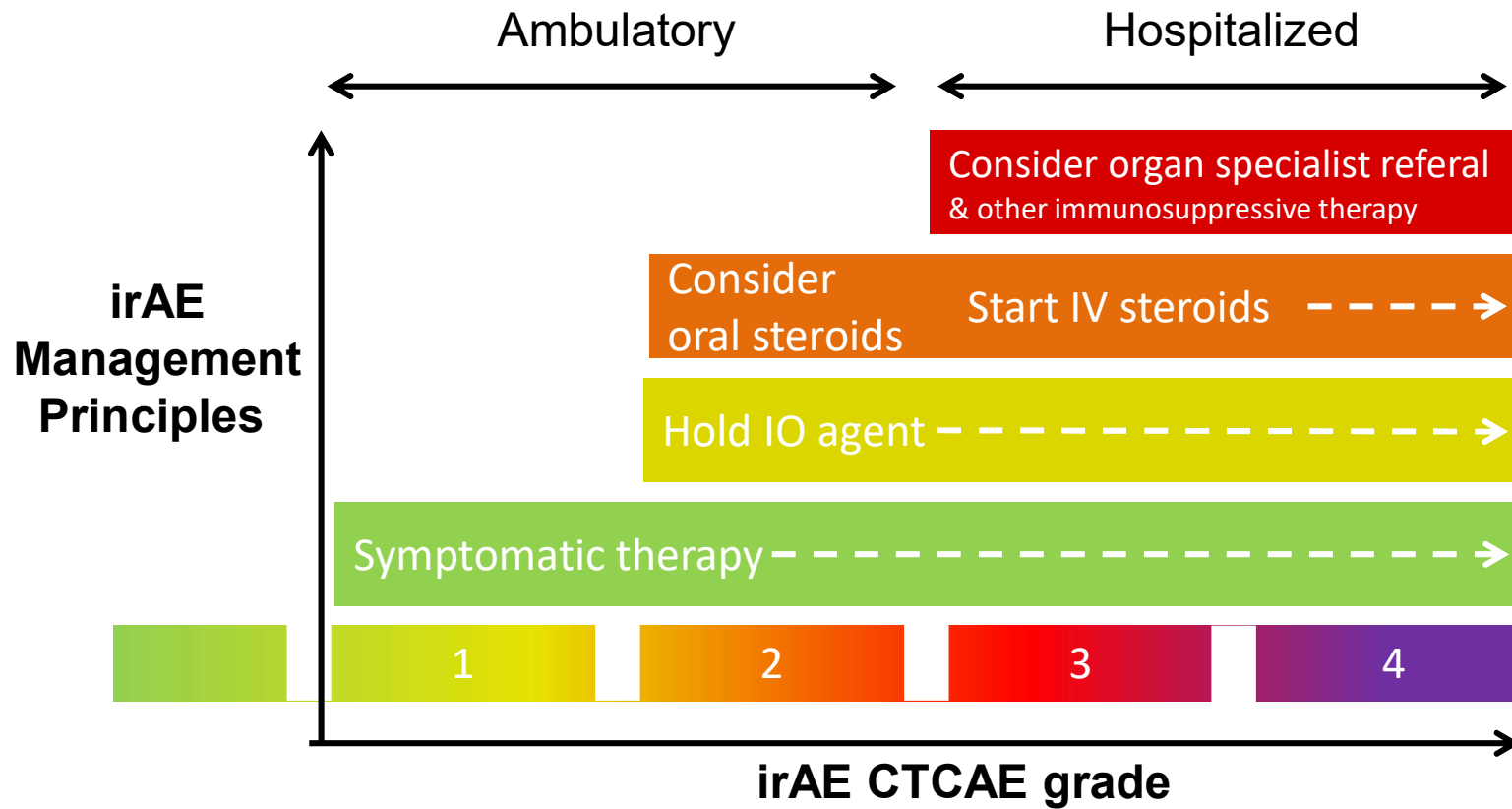
S Champiat courtesy
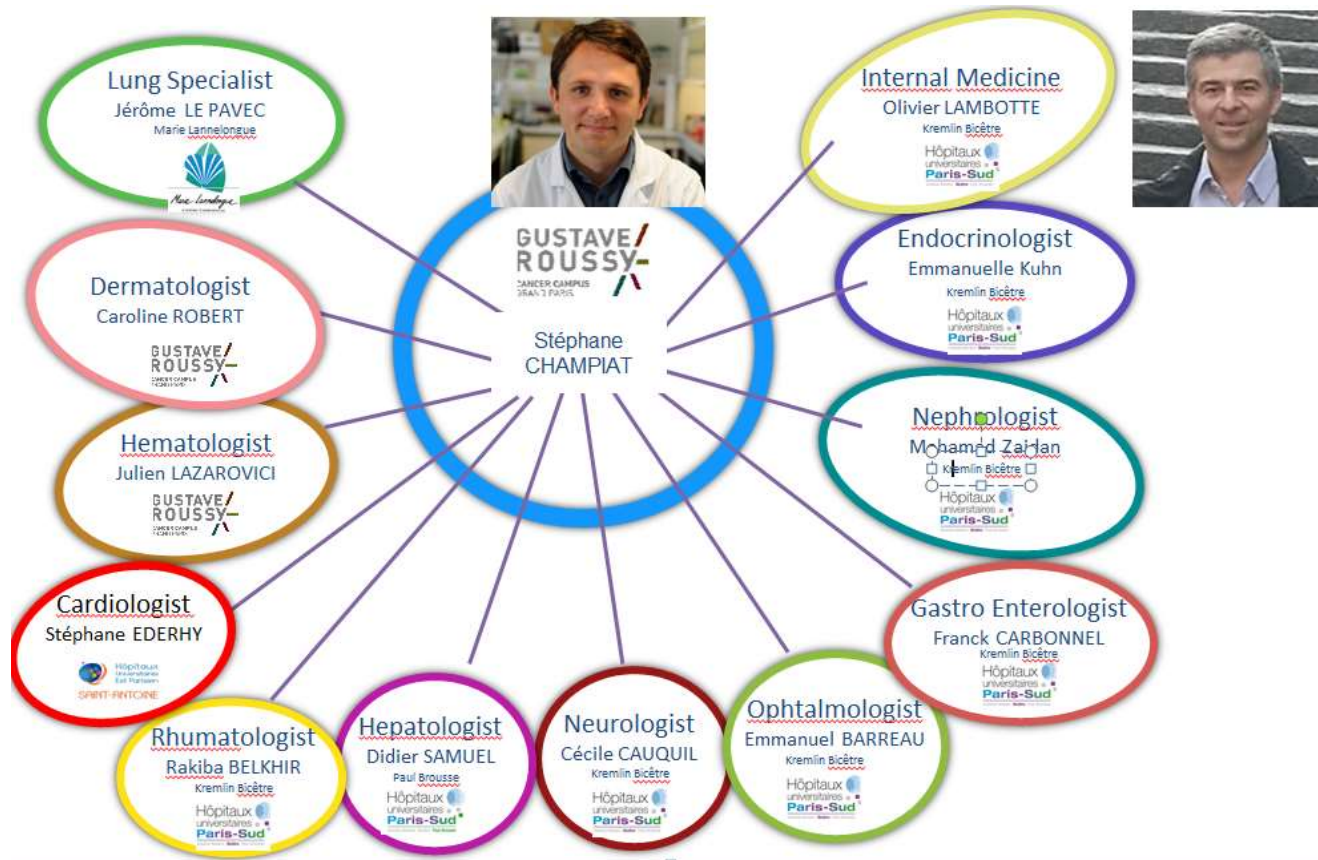
Pathology can help for the management

- **Different types of hepatitis with anti-CTLA-4 and PD1**

- **Steroids indication relies on pathological features + expert opinion**

De Martin et al , J Hepatol 2018
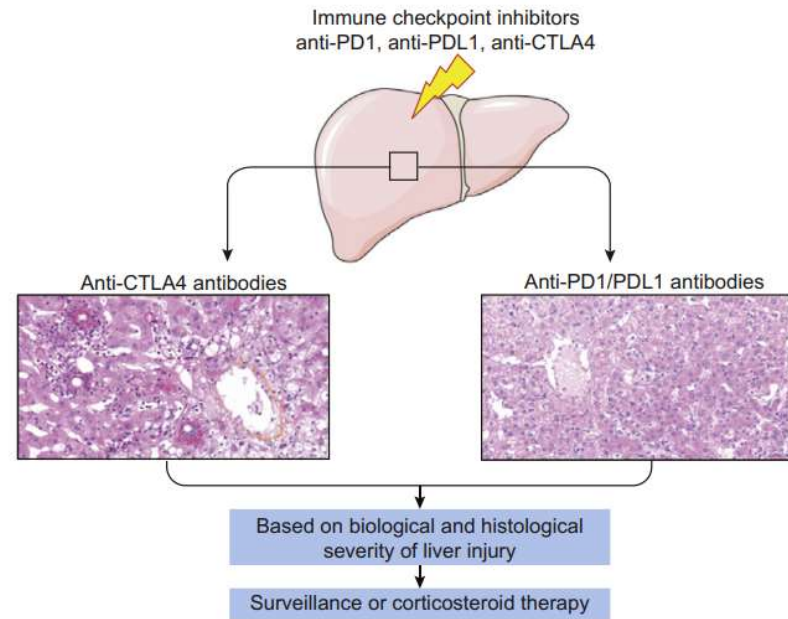
Conclusions

- **Ir AE are frequent and can be severe**
- **Anticipation:** It is critical to **inform** the patients of the risk of toxicity before initiating the treatment, especially in the adjuvant setting
- **Prevention** : Patients with pre-existing auto-immune disease are at risk of exacerbating their AID and of developing an irAE but preemptive systemic steroid not validated
- It is critical to **detect** the potential severe AE early.
- The toxicity is usually **manageable**, with validated algorithms but algorithms have to be challenged and improved
- The predictive impact of toxicity on response to ICI is still controversial
- Mechanisms still unresolved, probably multifactorial
    - Genetic background, autoimmune background, shared epitopes, chronic infection, role of microbiota..

A network of specialists at GR

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