



Immune checkpoint-induced arthritis

Tocilizumab vs Corticosteroids

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Conflicts of interests

- Research: Grant from Fresenius
- Lecturing: None
- Consulting: None

AP-HP.Université Paris-Saclay Hospitals and Paris-Saclay University

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Inserm

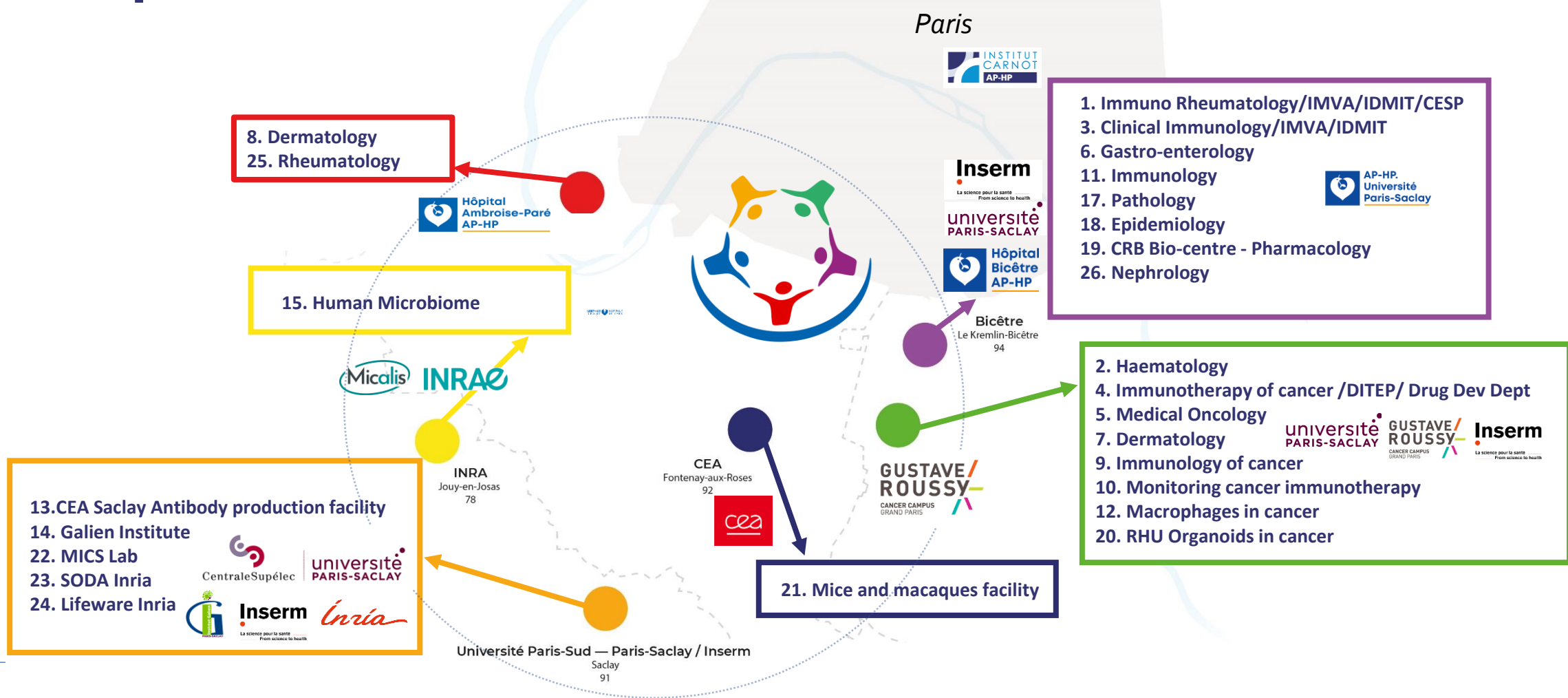
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

INRAE

cea

26 partners

CARE 2 Partners



ICI-inflammatory arthritis

- Clinical presentation

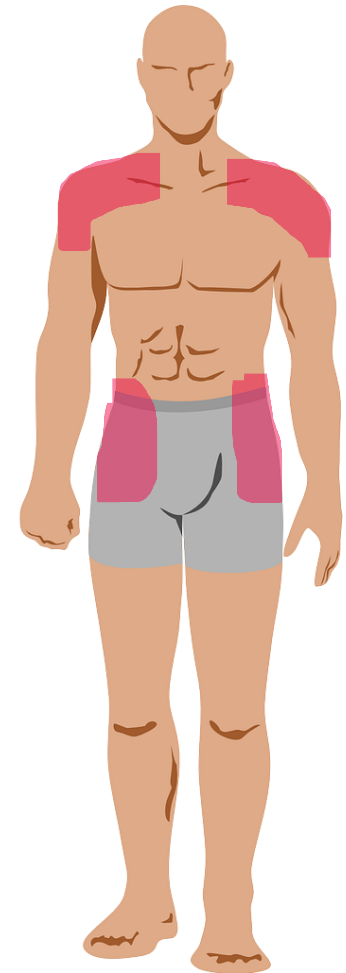
- Mono, Oligo polyarthritis
- Tenosynovitis

- Only 13 to 16% are acute
- 87% are chronic even with ICI discontinuation



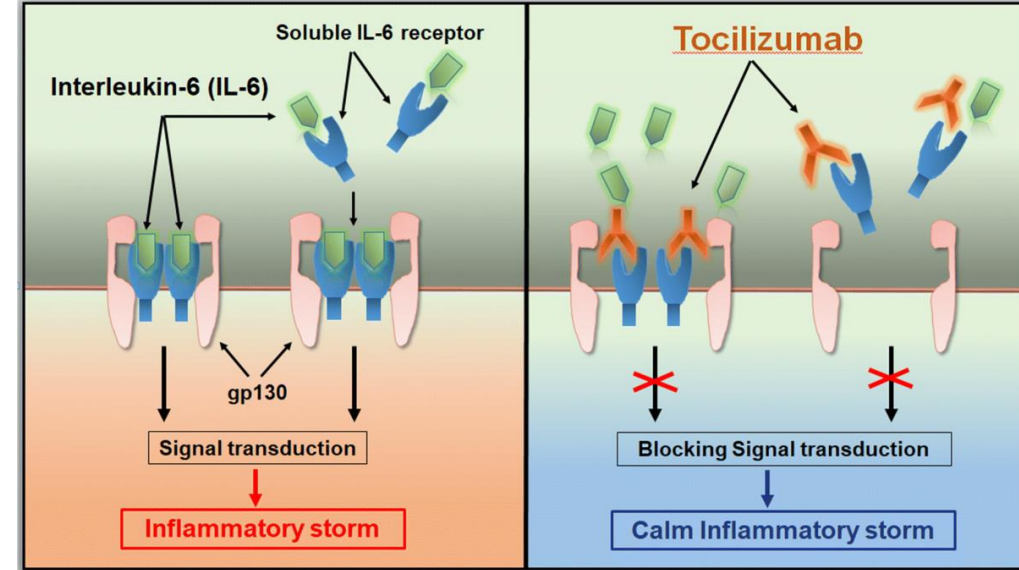
ICI-Polymyalgia Rheumatica

- Scapular and pelvis involvement
 - Can occur without CRP
 - Can only be a PET CT finding.
 - Often associated with arthritis
- Less persistence than arthritis

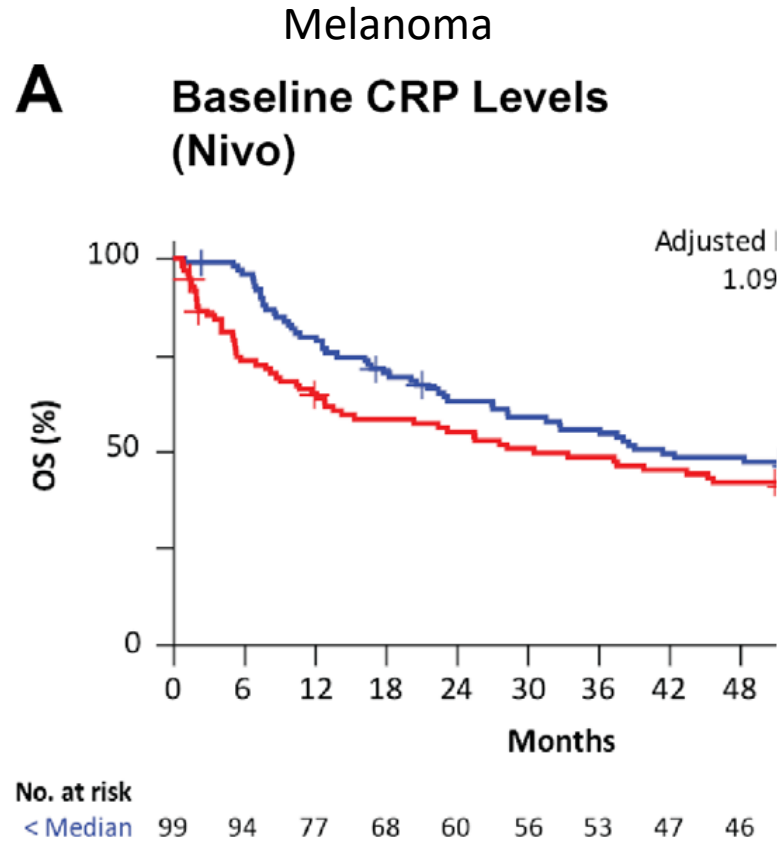


Why tocilizumab?

- Widely used for the treatment of RA.
- Has been used off label for the treatment of irAE even other than arthritis with good efficacy and tolerance
- Widely used for the management of CAR-T cell toxicity without loosing efficacy



CRP is associated with lower response rate to ICI

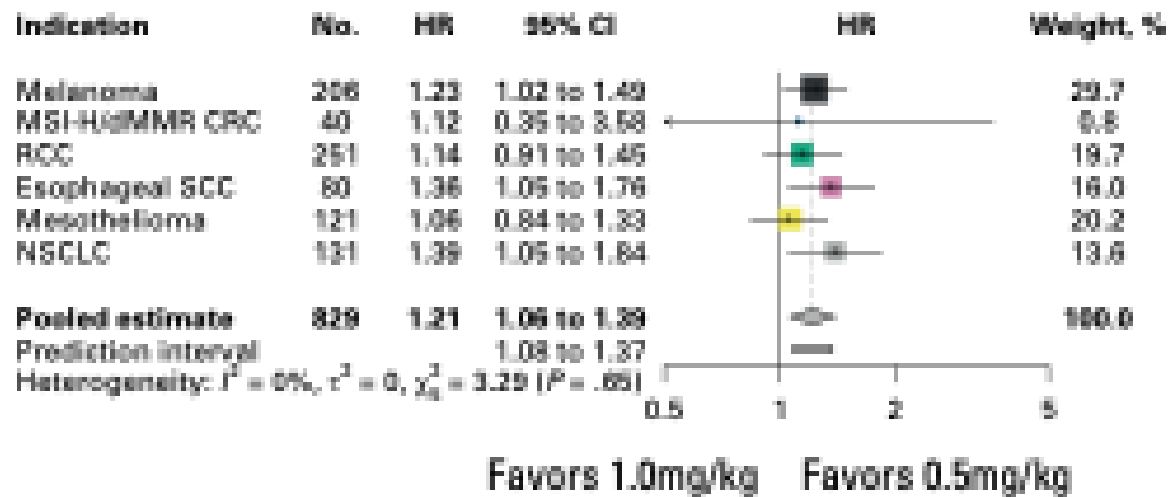


Median CRP 5,5

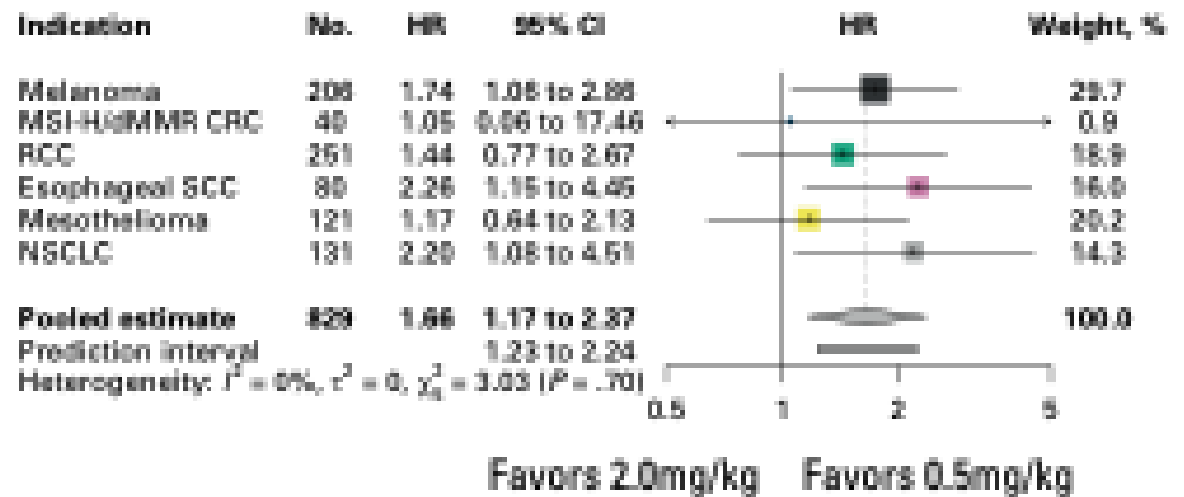
- Target IL-6 could be an interesting way to improve response to ICI therapy.

A high peak dose is less favorable than a high cumulative dose for cancer survival

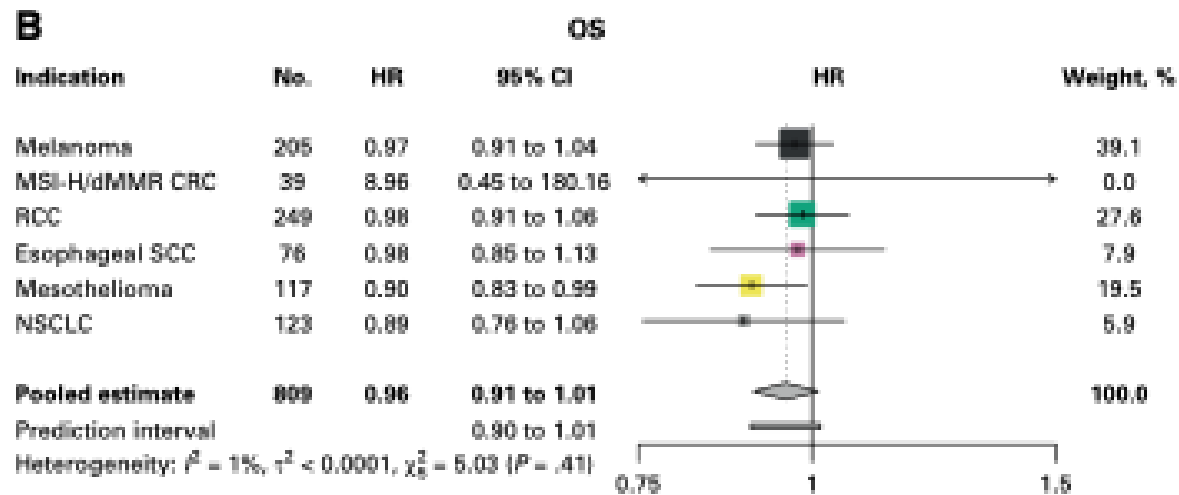
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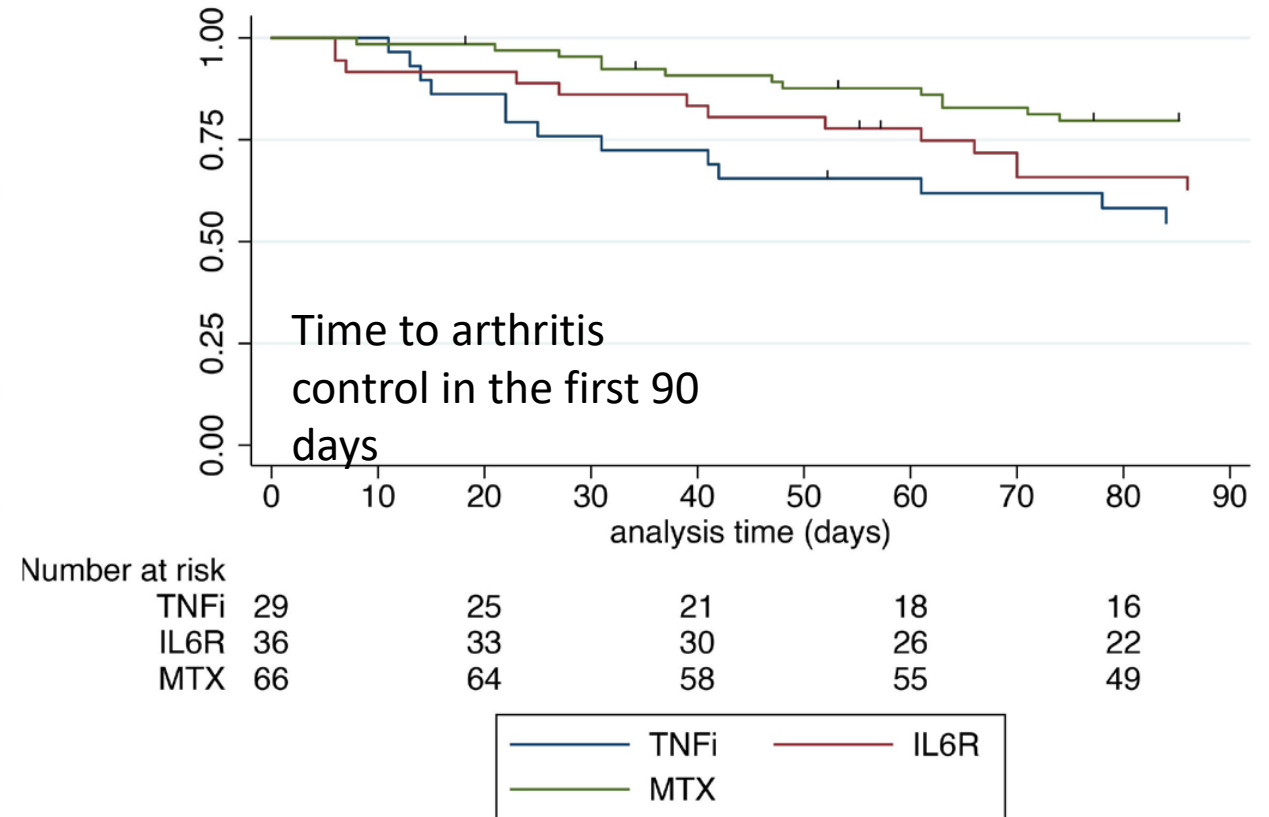
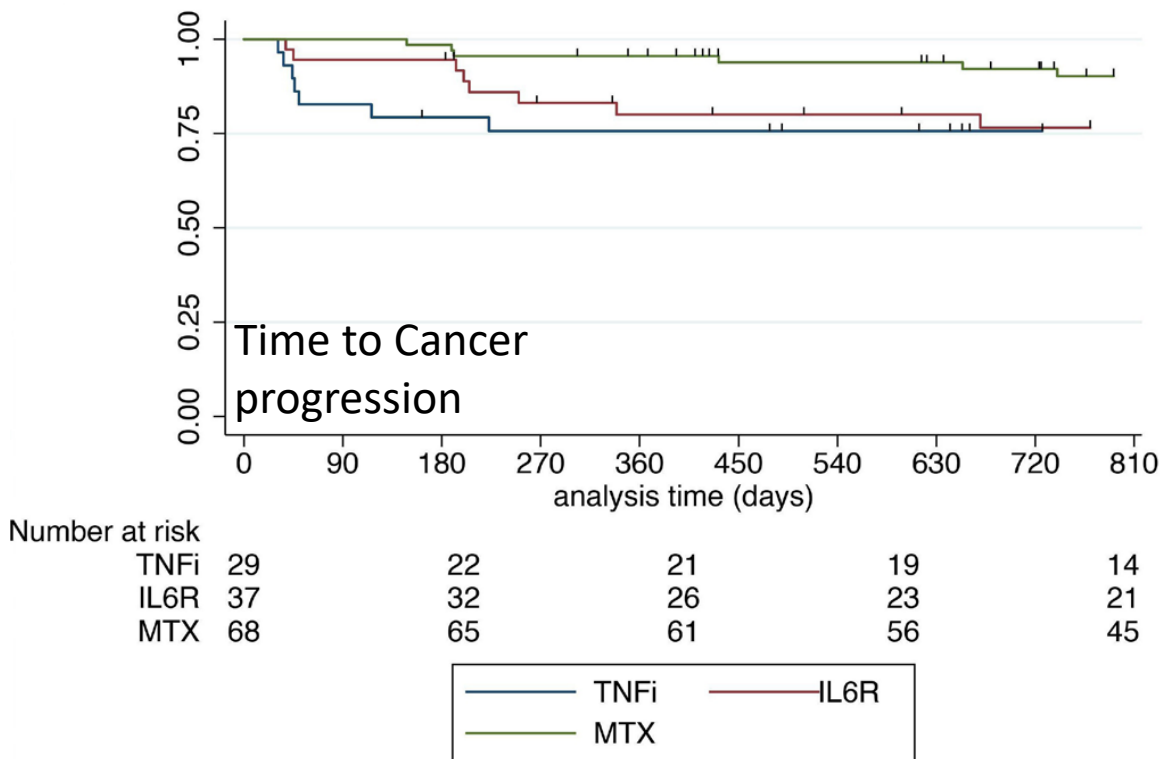


B



- Steroids for irAE
- Data from 6 clinical trials

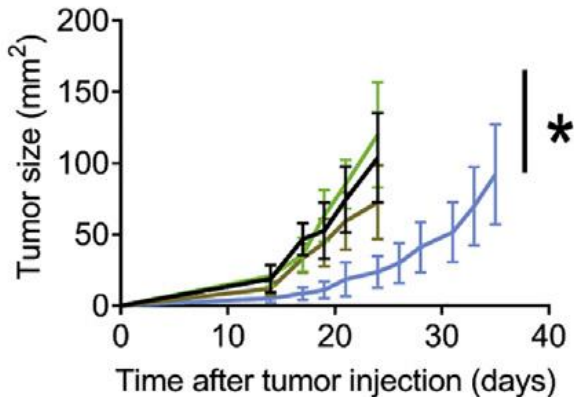
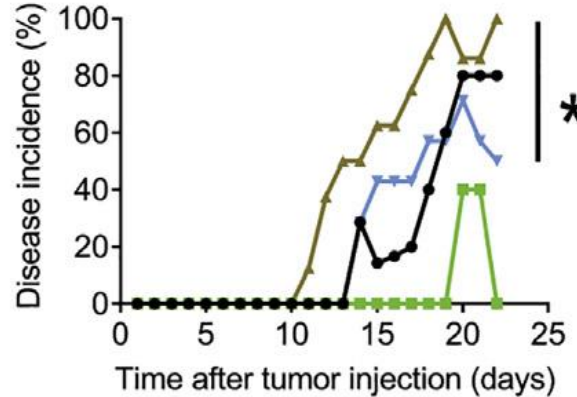
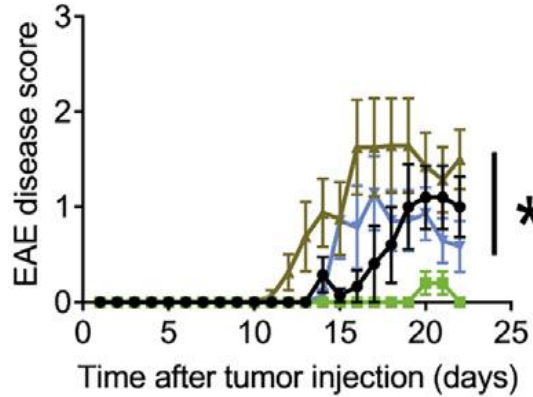
MTX vs TNF vs IL6R a retrospective study



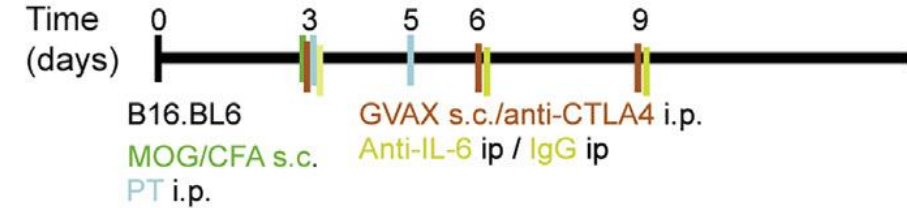
- Shorter time to cancer progression in the TNFi vs MTX
- Shorter time to arthritis control
- Higher max corticosteroids dose in the bDMARDs groups

The decoupling effect of tocilizumab : Helps ICI efficacy while controlling autoimmunity

— C57BL/6_B16.BL6 + EAE + IgG
— C57BL/6_B16.BL6 + EAE + anti-IL-6
— C57BL/6_B16.BL6 + EAE + anti-CTLA-4_GVAX + IgG
— C57BL/6_B16.BL6 + EAE + anti-CTLA-4_GVAX + anti-IL-6 | *



G



- Anti IL-6 controls EAE without affecting anti tumor efficacy

Tocilizumab prevents relapse during ICI rechallenge

	Without TCZ prophylaxis		With TCZ prophylaxis	
	n = 5	%	n = 11	%
Patients with >1 rechallenge	2	40	1	9
Median interval between end of initial ICI and rechallenge	70	95% CI 56-84	22.5	95% CI 20-295
Rechallenge for PD	2	40	4	36
Tumor type				
Lung	2	67	5	50
Melanoma	1	33	4	40
Colorectal	0	0	1	10
Rechallenge compared with initial ICI therapy				
Similar ICI	3	60	10	91
Nivolumab to ipilimumab/nivolumab	0	0	1	9
Nivolumab to pembrolizumab/chemotherapy	1	20	0	0
Nivolumab to nivolumab/relatlimab	1	20	0	0
rh-irAE evolution				
Requiring steroids >0.1 mg/kg for arthritis	1	20	0	0
Relapse rh-irAE ≥G2	2	40	2	18
Other irAEs				
Colitis ≥G2	1	20	5	45
CRS G1	0	0	1	9
Pneumonitis	1	20	0	0

- IV treatment with tocilizumab 8mg/kg /2weeks
- Effective to prevent rheumatologic relapse but not colitis
- Longer ICI treatment with TCZ (206 vs 113 days)

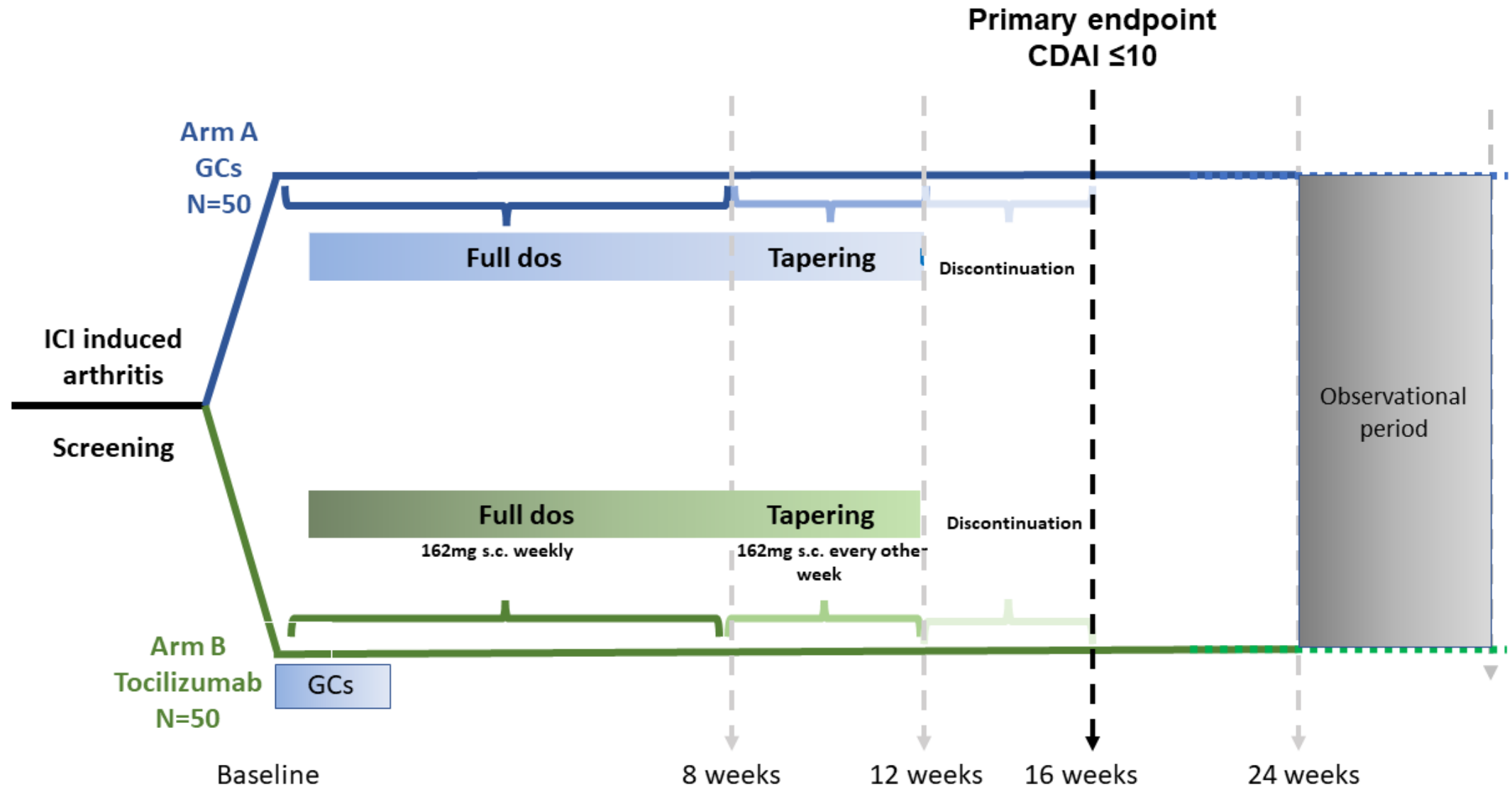
Tocilizumab + IPI+ Nivo Melanoma

- Latest data
- 10 patients with 162mg weekly for 6w then /2weeks 6 weeks
- 40% G3/4 irAE median 4.9 weeks
 - Liver (20%)
 - Colitis (10%)
- ORR 70% vs 56% for Toci every 2 weeks
- ORR 75% with patients with high LDH.

CITAR: Checkpoint Inhibitor Treatment of ARthritis

- Phase 2
- Randomized
- Open
- Superiority
- Multicentric (Sweden, France (Bicêtre, Bordeaux, Brest, Strasbourg) Germany, the Netherland)
- First line
 - 106 patients 53 in each arm

Design of the CITAR study



Inclusion criteria

- Any cancer treated with ICI mono or combo
- A least 2 swollen joints and CDAI>10
 - Tender joints, Swollen joints, patient and physician VAS
- Patients with less than 7 days of steroids
 - Patients should be screened before steroid treatment

Exclusion criteria

- Prior inflammatory rheumatic disease
- Concomitant life-threatening irAE requiring steroids
- Steroids for oncologic manifestation that cannot be stopped
- Other immunosuppressive therapy
- History of diverticulitis
- Neutropenia < 1000

Endpoints

- Primary
 - % of patient CDAI<10 at week 16.
- Secondary
 - % of patient CDAI<10 at week 16 with 0 mg steroids
- PFS and OS at week 24
- Total number of missed ICI treatments

Ancillary analysis

- Design with treatment stop allows
 - Prediction of chronicity
- Prediction of response to Tocilizumab
- Sc RNA seq
 - PBMC
 - synovial fluid
 - Synovial biopsy (optional)

Take-home Messages

- IL-6 is an interesting target for rheumatologic irAE.
- Hypothesis
 - Might uncouple anti-tumor response and efficacy on irAE.
- Substantial improvement in anti-tumor response remains to be demonstrated in melanoma
- Randomized trial are required to establish benefit.

CITAR Trial

- 2 swollen joints
- Inclusion before steroid initiation
- IGR ligne directe 2 25 22 Clea Bardon