BARCELONA 2024 ESMO congress

Survivors of advanced melanoma: Management and support

Managing long-term treatment sequelae

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DECLARATION OF INTERESTS

Charlée NARDIN

- Compensation for consulting, board, presentation and speaker role: BMS, MSD, Novartis, Pierre Fabre.
- Traveling accommodation for attending conferences: BMS, MSD, Novartis, Pierre Fabre.
- Local principal investigator (institutional payment): MSD, Novartis, Pierre Fabre, Regeneron.
- Advisory role (non-remunerated activities): Pierre Fabre.

Introduction

Why should we talk about long-term treatment sequelae?

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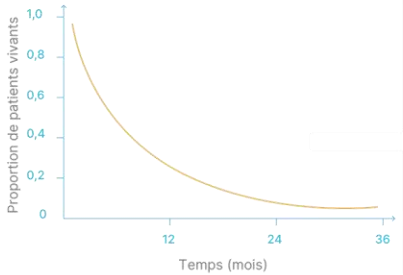
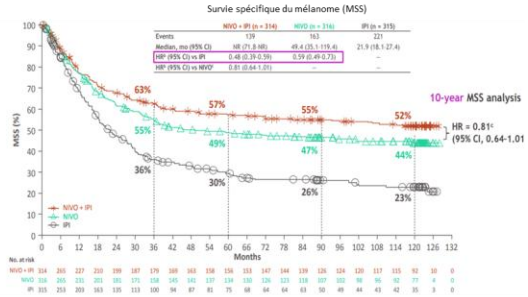
patients with advanced melanoma have an increased survival
(median OS 6 months → 6 years reported with immune checkpoint inhibitors (ICIs))

Avant 2015, médiane de survie 6 mois



Après 2015, médiane de survie à > 6 ans



Larkin et al. ESMO 2019 Abs LBA68

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More patients are treated
(systemic treatments used from stage IV to early stage IIB/IIC)

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Is the treatment well tolerated ?

Does the patient feel well?

Does he work ?

Physically Psychologically ?

How about his quality of life?

What about his family ?

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Introduction

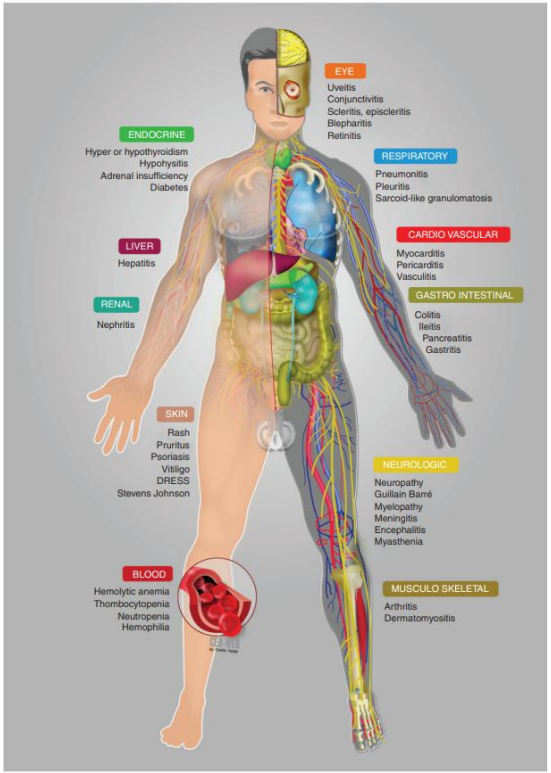
What are the long-term treatment sequelae?

Long-term sequelae: persistent symptoms from previous diseases, injuries, or trauma

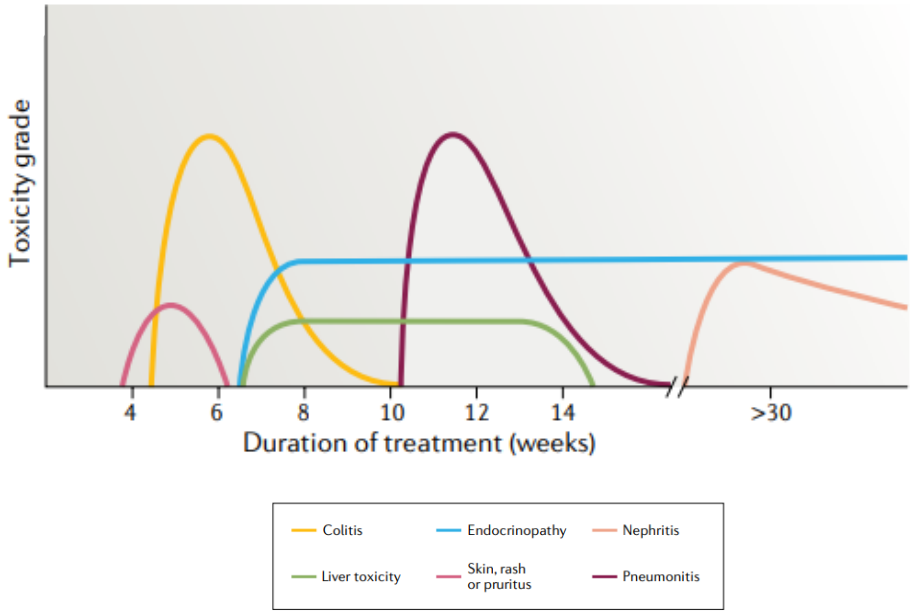
→ Long-term sequelae of melanoma, local and systemic treatments

15-43% of chronic or delayed adverse events reported with immune checkpoint inhibitors

1- Immune-related adverse events (irAEs)



Champiat et al., Annals Oncology 2016



Martins et al., Nat Rev Clin Oncol 2016

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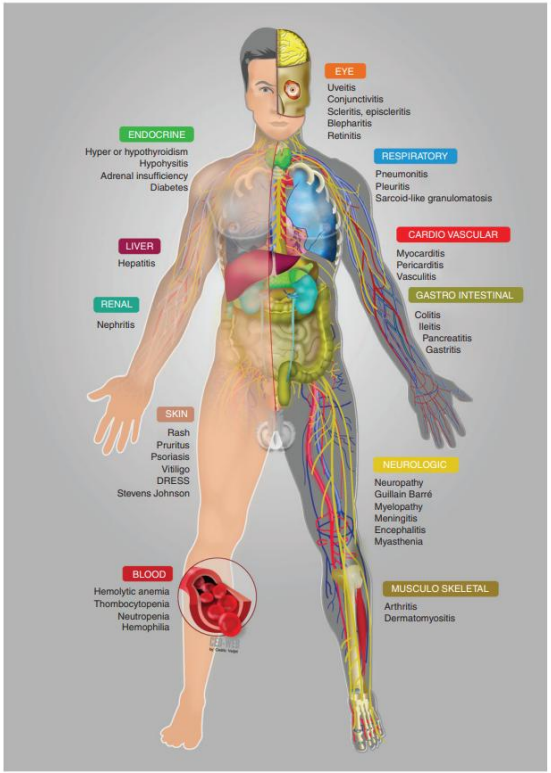
1- Immune-related adverse events (irAEs)



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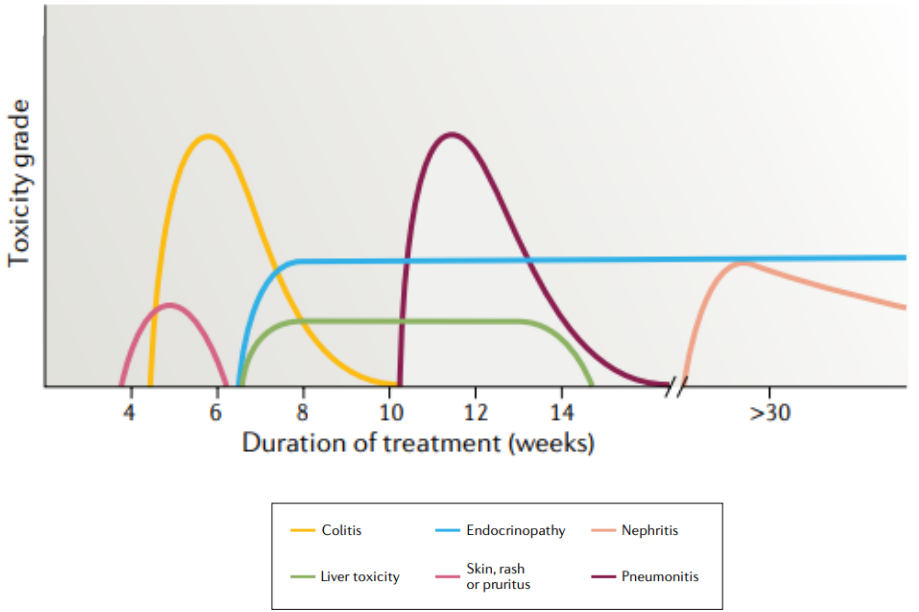
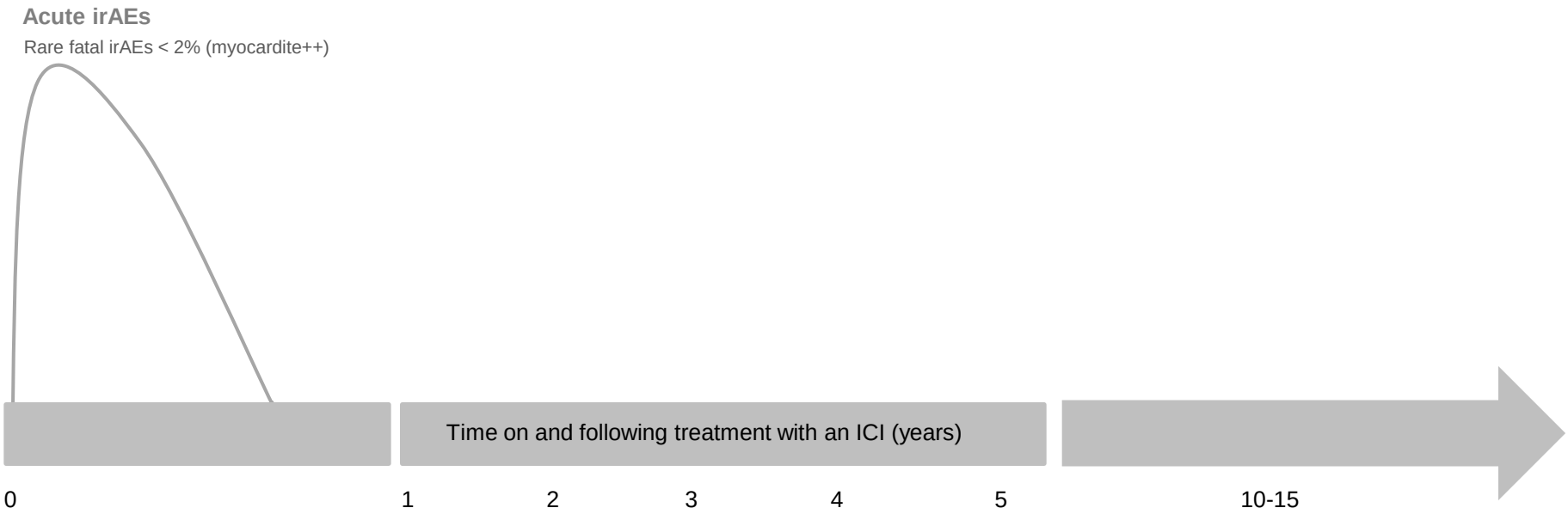


Martins et al., Nat Rev Clin Oncol 2016

And after?

Time course of immune-related adverse events



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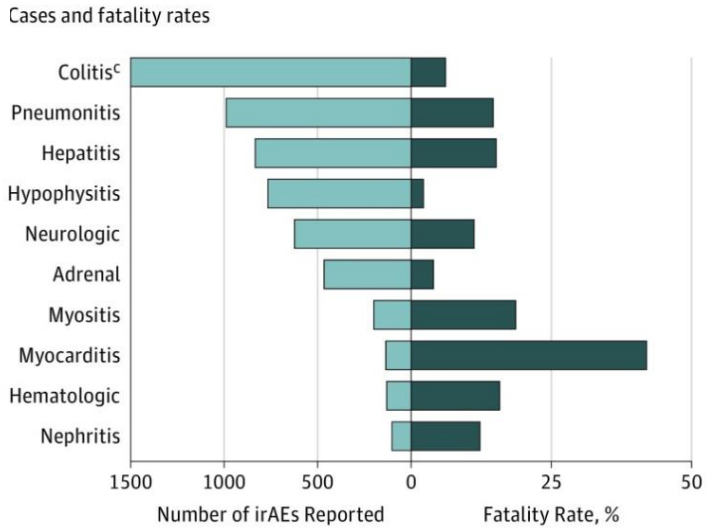
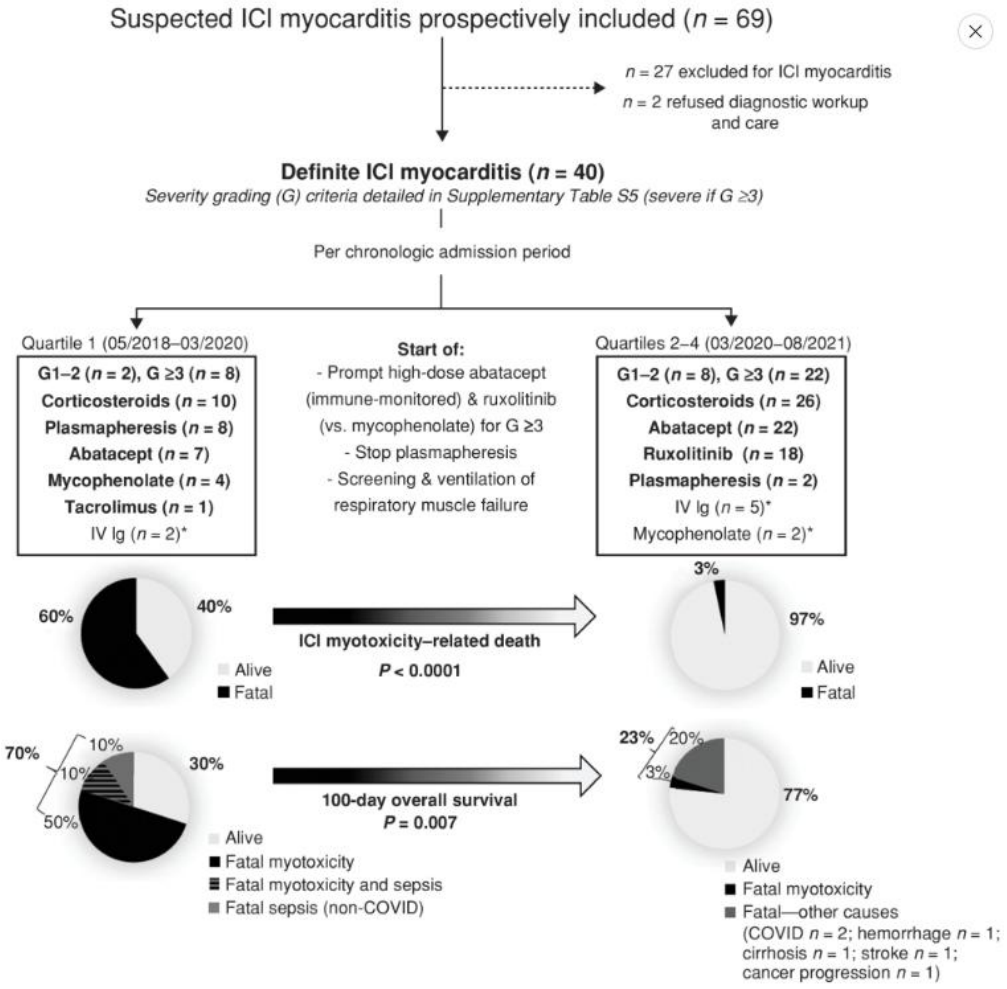
Fatal irAEs [1,2]

- Up to 2% in clinical trials, **0.4 with anti-PD1 1.2 % with IPI NIVO** in a Meta-analysis
- Early event (median of 15 days)
- **40% of myocarditis** > myositis , pneumonitis, hepatitis, nephritis and neurologic and hematologic irAEs with incidence ranging from 10 to 17%



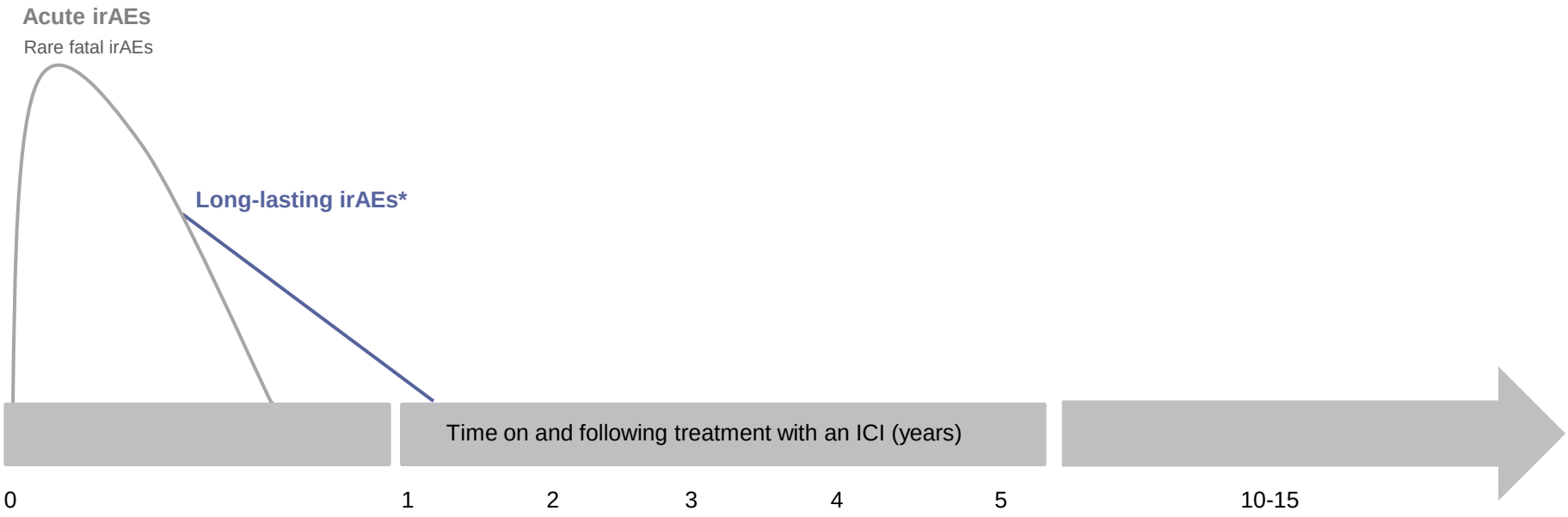
1, Wang et al. JAMA Oncol 2018
2, Naidoo et al., J Immunother Cancer 2023
3, Barron et al., J Immunother Cancer 2023



*Started before admission in our unit and transferred for poor evolution on these drugs [5/7 for intravenous (IV) Ig and 2/2 for mycophenolate]. They were stopped upon admission in our unit.

Salem et al. Cancer Discovery 2023

Time course of immune-related adverse events



* Long-lasting irAEs were frequently reported as irAE lasting more than 6 months

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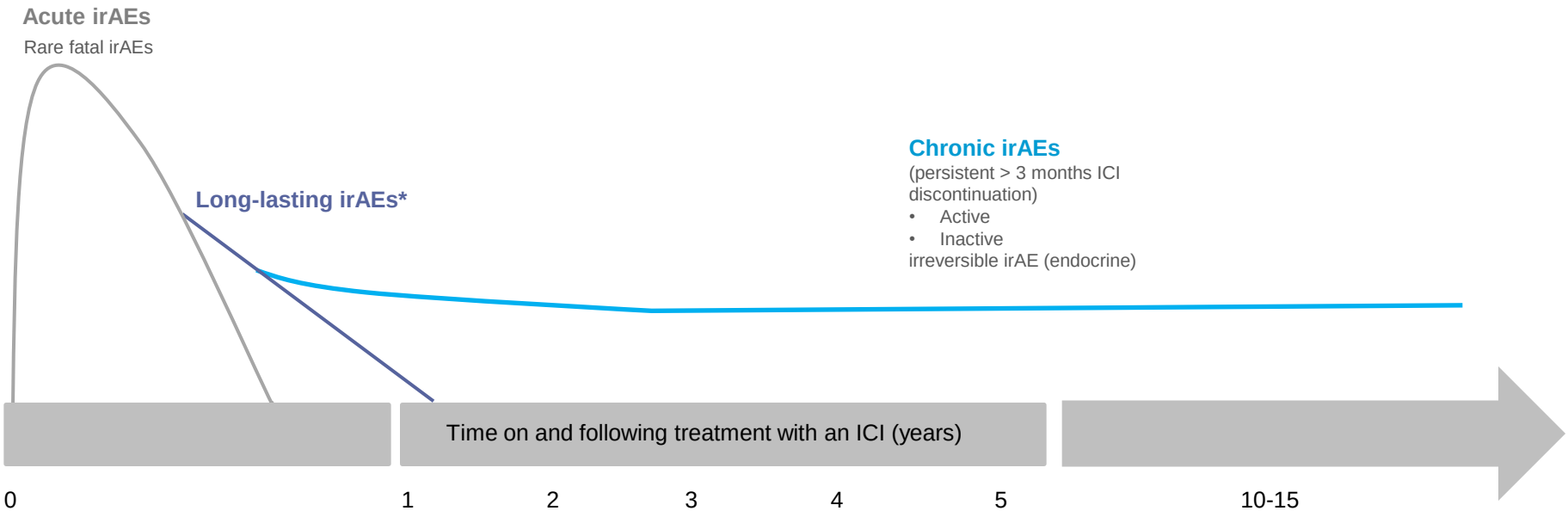
Time course of immune-related adverse events



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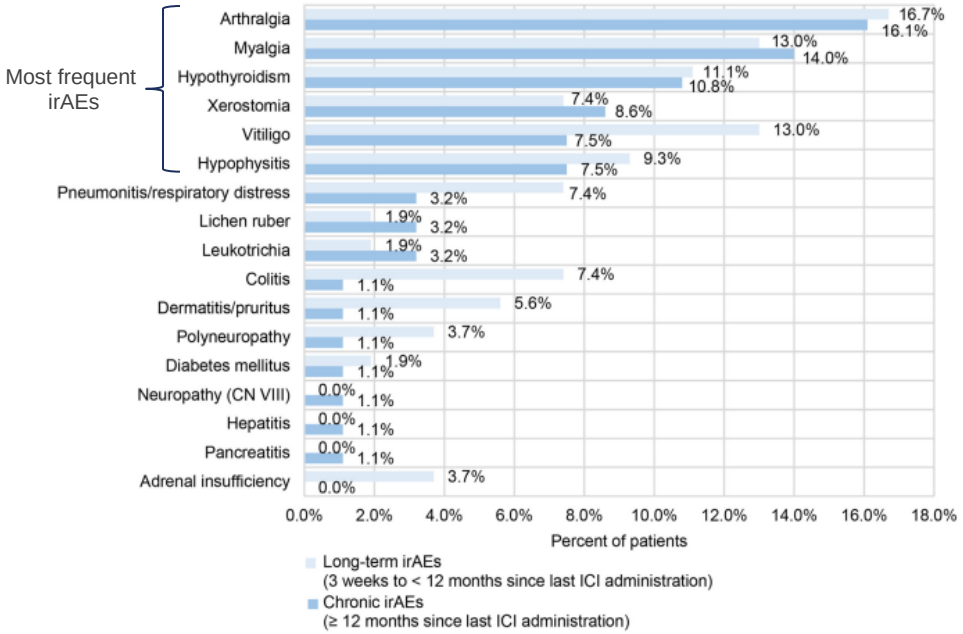
Chronic irAEs

irAE **persistent > 3 months ICI discontinuation** (time to clearance of ICI)



+ Hematological, ocular, and renal chronic irAEs [2]

The multicentre, cross-sectional study included 200 patients with cancer (97% of melanoma patients) ≥ 3months after ICI cessation (ICI-patients)

Persistent irAEs[1]

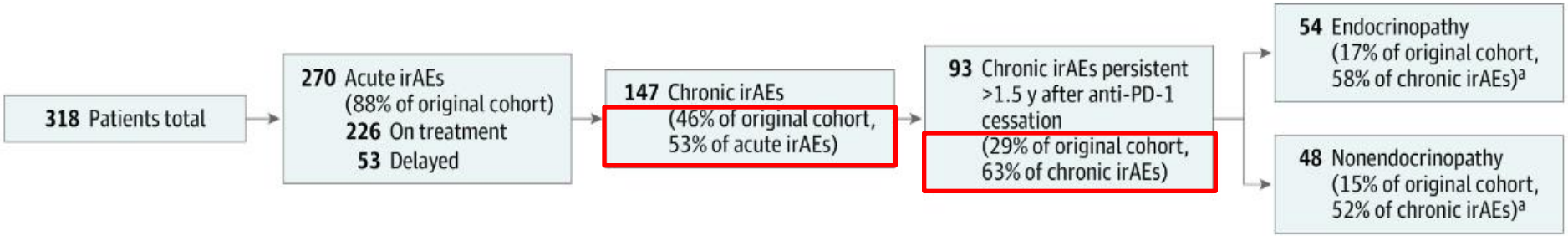
- 51% ≥ 3 months after treatment discontinuation
- 35% >12 months after treatment discontinuation

→ Chronic irAE are frequent
→ Mostly non visceral organs

1, Schulz et al., Eur J Cancer 2022
2,Barron et al., JITC 2023

Chronic irAEs

Event in the adjuvant setting: patients treated with adjuvant anti-PD1 for stage III melanoma[1,2]



Incidence	Patients with chronic toxic effects, No. (%)
Any chronic irAE, No.	147
Grade ≥2	74 (50.3)
Grades 3-5	6 (4.1)
Toxicity requiring steroids	56 (38.1)
Toxicity requiring steroids (grade 2)	29 (19.7)
Toxicity requiring steroids (grades 3-5)	2 (1.4)
Symptomatic	100 (68.0)
Symptomatic endocrinopathy	20 (13.6)
Resolved	52 (35.4)
Persisted	95 (64.6)

→ Mild/moderate chronic irAEs (96%)
→ Active irAEs requiring treatment

1, Patrinely et al. JAMA Oncol 2021
2, Goodman et al. JAMA Network 2023

Chronic endocrine irAEs

Complications

Acute (15 to 40%) → chronic (irreversible)

Reversibility not systematically studied

- **Hypothyroidism** 10%-20% (anti-PD1 and IPI NIVO) most common, +/- previous thyrotoxicosis after 6 weeks

- Hypophysitis 5-10% (++ with **IPI** because due to anti-CTLA-4 antibodies) after 3 months

- Diabetes <1% (acute) (anti-PD(L)1+)

- Adrenal insufficiency: 1-8% (mono, combotherapy) few days to >12 months

Treatment

Same as acute irAE

- Hormonal replacement therapy

- ICI can be pursued

- steroids are ineffective

Haneen et al., Annals Oncol 2022; Johnson et al., Nat Rev Clin Oncol 2022

Chronic rheumatological irAEs

Complications

Acute: 5-10% → 50% chronic[1]

- **inflammatory arthritis**
- **polymyalgia rheumatica**

Large and medium joints

But no HLA, seronegative (like in rheumatoid arthritis)

Treatment of long-term AE

- NSAIDs
- Steroids : low-dose

Usually not sufficiently severe to justify high-dose steroids and ICI discontinuation

Suboptimal response to steroids

- Disease-modifying antirheumatic drugs (DMARDs): Methotrexate, mycophenolate mofetil, TNF inhibitor, IL6 inhibitor
- ICI discontinuation if needed

1 Haanen et al. Ann Oncol 2022
2 Owen et al Annals of Oncology 2021
3 Braaten, et al. Ann Rheum Dis 2020

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Chronic cutaneous irAEs

Complications

Vitiligo/vitiligo-like depigmentation seen in **melanoma patients**

-Frequency 25% after a median follow-up of 14 months [1] more frequent in long-term responders

-Grade 1 +
-Chronic even after ICI discontinuation [2]
underreported

More frequent than other dermatologic irAE (bullous pemphigoid, lichen planus, psoriasis…)

Treatment

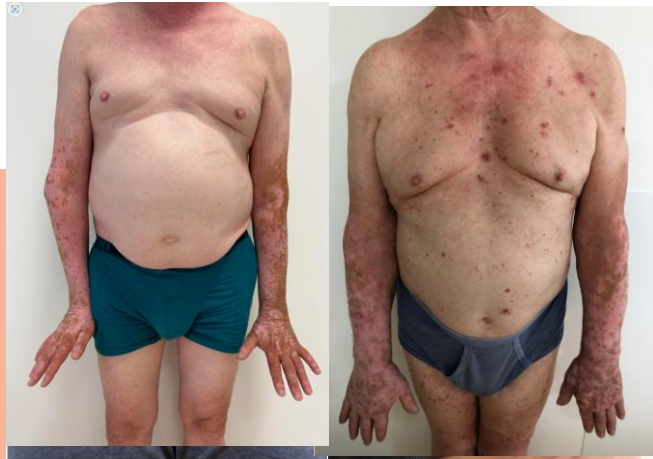
- Usually not treated

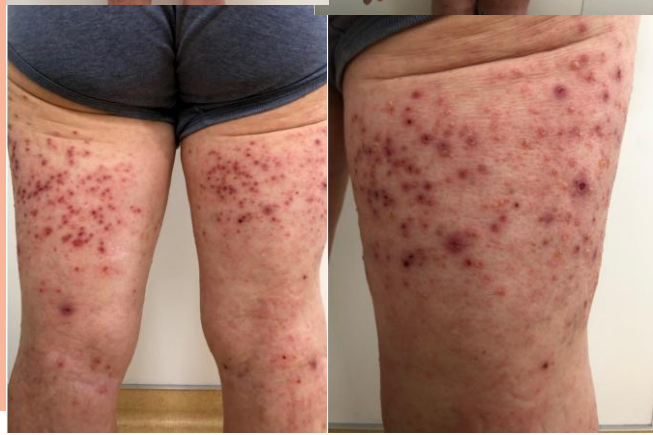
- but it changes (possibility of treatment with topical steroids, tacrolimus ointments)

topical JAK inhibitors?

- ICI continued

Vitiligo
on photo-exposed areas





Bullous pemphigoid

Hua et al., JAMA Dermatol 2016, Schulz et al., Eur J Cancer 2022, Nardin et al., J Am Acad Dermatol 2022

Chronic xerostomia

Complications

Mostly **xerostomia** and, less frequently, dry eyes [1]

In studies Sjrogren (SjD) syndrome 0.3–2.5%
Sicca syndrome (up to 24%) more frequently with IPI NIVO

8% of chronic xerostomia [2] → **salivary secretion remains suppressed** with a high impact on quality of life

Labial salivary gland biopsy (distinct pattern with ICIs compared to idiopathic SjD)
Negative anti-Ro/SS-A antibody

Treatment

- symptomatic treatment,
- subjective improvements observed with the use of saliva stimulants and/or steroids
- **No efficient treatment**

1, Haanen et al,. Ann Oncol 2022
2, Schulz et al., Eur J Cancer 2022

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Long-term neurological irAEs

Complications[1,2]

Acute 1-5%

time to onset varies from 6 to 13 weeks

- Acute: central, peripheral nervous system and 50% neuromuscular disorders

- **Chronic** : **peripheral sensory neuropathy (2% with anti-PD1)** > myastenia gravis evolves in a stereotypal chronic syndrome, **Guillain Barré syndrome sequelae**

Risk of long-term sequelae (11/15 in one series)[3] may be related more to the initial damage incurred rather than persistent inflammation.

Treatment

- Steroids, intravenous immunoglobulin, etc.

- withdrawal of ICI

1,Johnson et al., Nat Rev Clin Oncol 2022
2, Haanen et al., Annals Oncology 2022
3. Patrinelv et al..JAMA Oncol 2021

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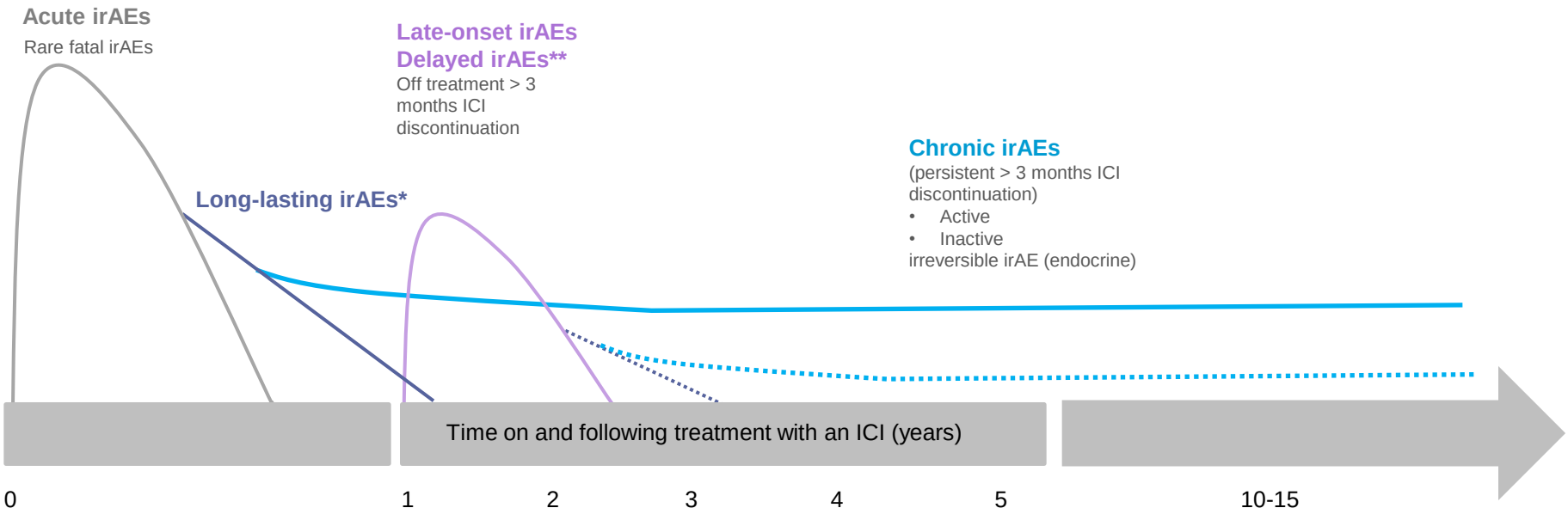
Time course of immune-related adverse events



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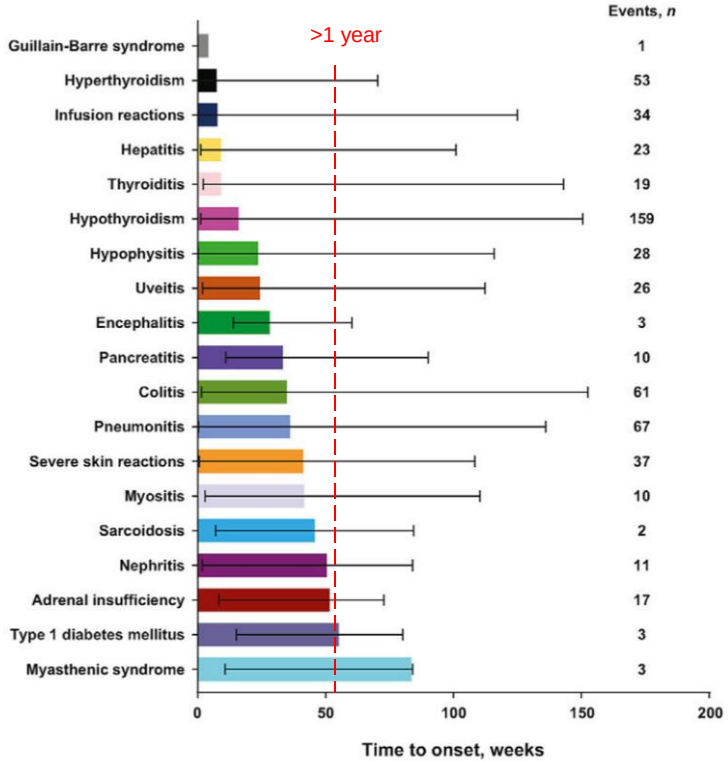
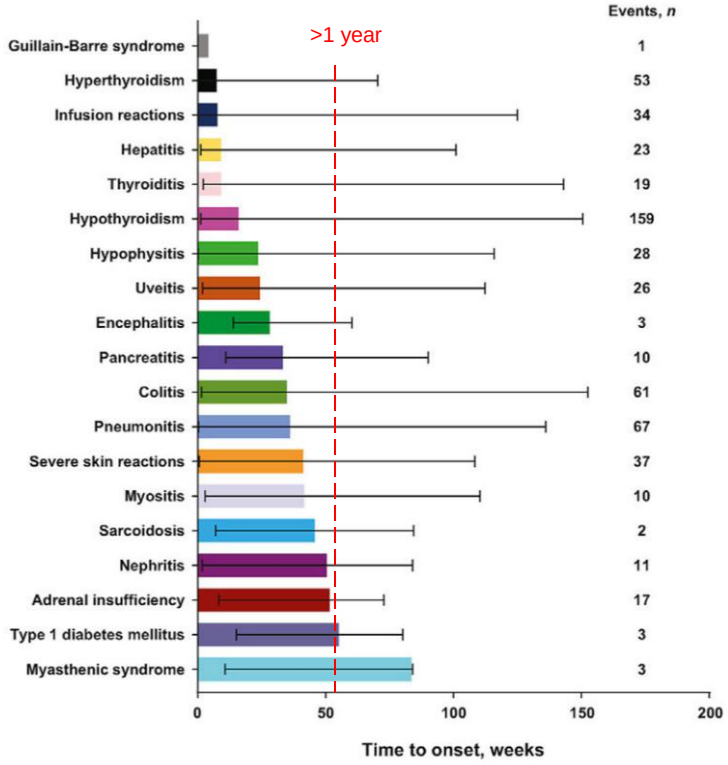
« Late-onset » irAE with prolonged treatment



Robert et al. Eur J Cancer 2021

irAE

« Late-onset » irAE with prolonged treatment



Robert et al. Eur J Cancer 2021

<u>Patients treated ≥ 2 years of anti-PD1 (long responders)</u> (n=119) (under treatment or not) in the prospective French real-life cohort (MELBASE)

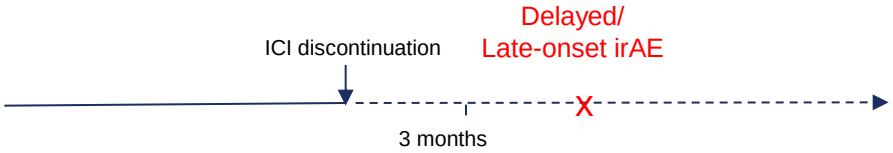
Median follow up : 41.7 months (range, 25.2-57.5)

- **"Late-onset"AEs (n=140), occurred in 51 (43%) patients** [2]
- **Mostly Grades 1/2 AEs (97%)** and 4 grade 3/4 AEs in 4 patients (3%) [3]
- Factors associated with late-onset AEs:
  - Early-onset AEs (OR, 3.64 95%CI,1.28-11.85 ; P = 0.02)
  - Duration of anti-PD1 may increased the risk [4]

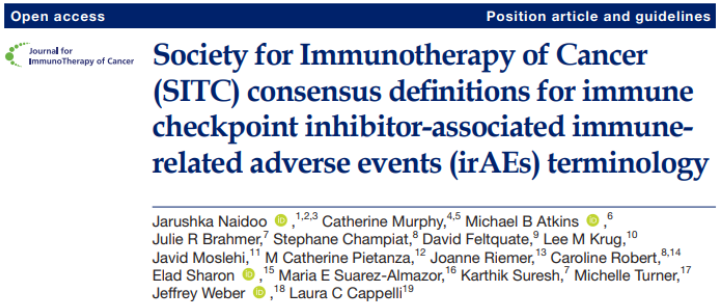
→ Frequent irAE under prolonged ICI treatment

1, Nardin et al., J Am Acad Dermatol 2020; 2, Shulz et al., Eur J Cancer 2022;
3, Nigro et al., Eur J Cancer 2021; 4, Eun et l. Sci Rep 2019

Delayed/Late-onset irAE



- Delayed/late-onset irAE after treatment : **recently defined as occuring > 100 days (3 months) after treatment discontinuation** [1]


Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events (irAEs) terminology

Jarushka Naidoo [1,2,3] Catherine Murphy,[4,5] Michael B Atkins [6] Julie R Brahmer,[7] Stephane Champiat,[8] David Feltquate,[9] Lee M Krug,[10] Javid Moslehi,[11] M Catherine Pietanza,[12] Joanne Riemer,[13] Caroline Robert,[8,14] Elad Sharon [15] Maria E Suarez-Almazor,[16] Karthik Suresh,[7] Michelle Turner,[17] Jeffrey Weber [18] Laura C Cappelli[19]

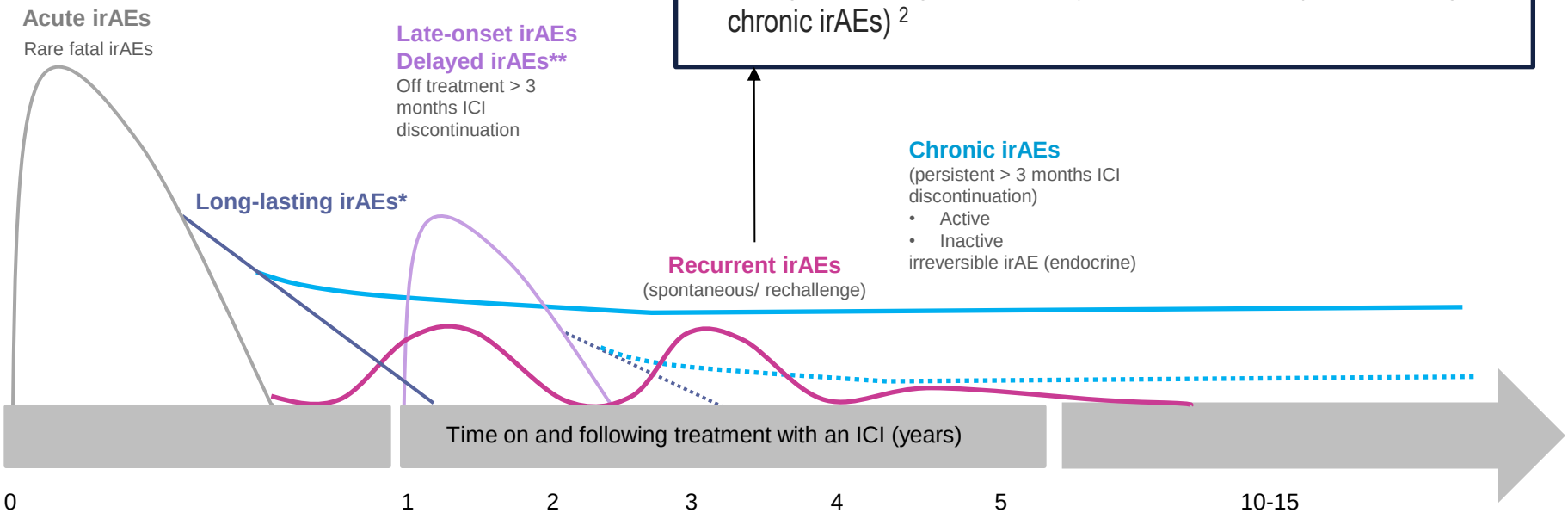
- Voluntary reports of delayed treatment-related Aes were few in number **4 and 6%** in the adjuvant trial Checkmate 238 (Nivo versus IPI in resected stage III/IV melanoma) [2]

→ Delayed/late-onset irAEs are uncommon

1, Naidoo et al., J Immunother Cancer 2023
2, Ascierto et al., Lancet Oncol 2022

Time course of immune-related adverse events

Re-emergent or recurrent irAE [1] **:** 10-40% recurrent irAE during rechallenge, which may become chronic (≈ 9% among chronic irAEs) [2]



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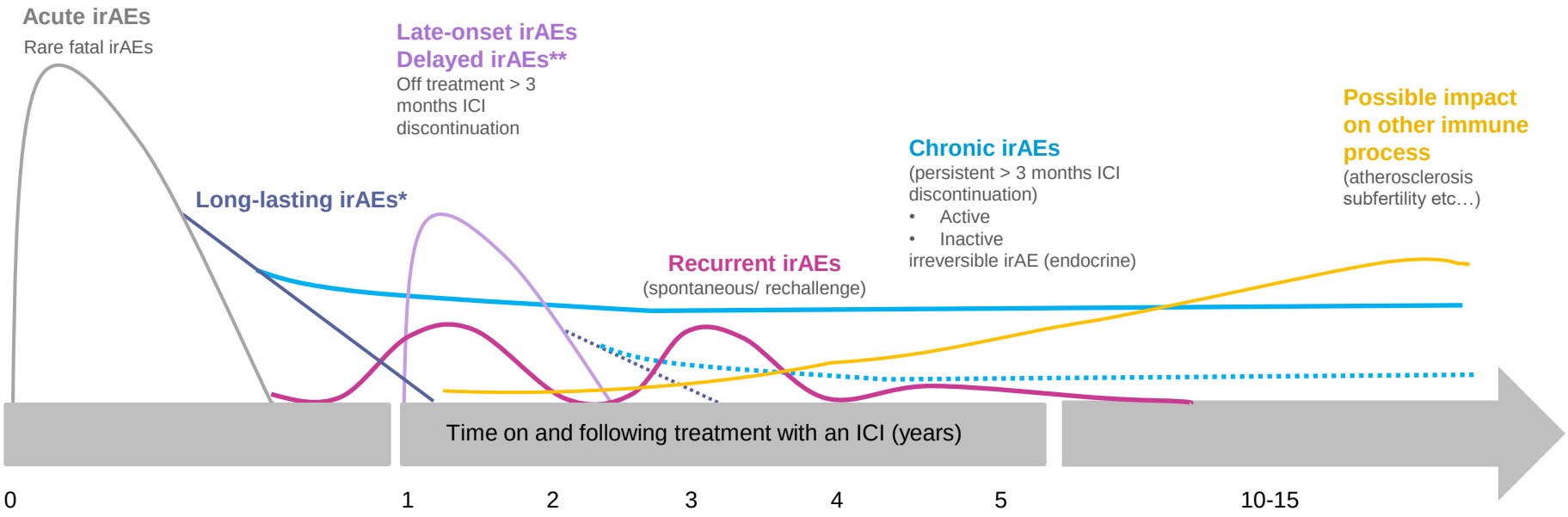

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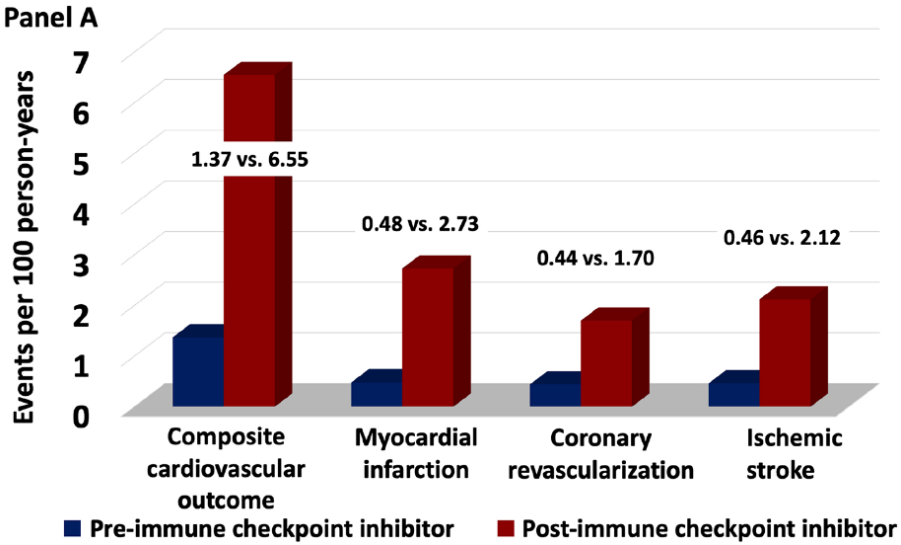
Long-term cardiovascular sequelae of ICI

Increased cardiovascular risk with ICI

- **Increased aortic plaque volume** three times higher [1]
- **Cardiovascular events** three times higher after ICI initiation [1]
- a 10.3% incidence of cardiovascular events after a median follow-up of 13 months [2]

→ shift in the plaque inflammatory cell composition (increased CD3/CD68 ratio [3], CD8 T cell) suggesting **atherosclerosis formation driven by a T cell-mediated plaque inflammation** [3,4]



Drobni et al. Circulation 2020

1, Drobni et al.,, Circulation 2020
2, Laenens et al.,, J Clin Oncol 2022
3, Suero-Abreu et al., JACC CardioOncol 2022
4, Poels et al., JACC CardioOncol 2020

Long-term fertility sequelae of ICI

Scarce data BUT most patients likely remain fertile after treatment HOWEVER, fertility may be impaired :

- After ICI:
  - Direct effect :
    - ➢ epididimo-orchitis, impaired spermatogenesis [1,2,3]
    - ➢ murine ovarian immune cell infiltration-depletion of ovarian follicles after ICI → possible impact on ovarian function (ovulation) [4]
  - Indirect effect :
    - ➢ hypogonadism - hypopituitarism (hypophysitis : 3,2, 0,4%, 6,4% after IPI, anti-PD1 and IPI NIVO)[5]
- Delaying the project of having a child after cancer diagnosis can affect fertility

→ There is a need for prospective studies.

1,Garutti et al., ESMO open 2021; 2,Scovell et al., JAMA Oncol 2020; 3, Salzmann et al., Eur J Cancer 2021; 4, Winship et al., Nat Cancer 2022; 5, Barroso-Sousa et al., JAMA Oncol. 2018; 6, Poulet et al., Birth Defects Res. B Dev. Reprod. Toxicol. 2016; 7, Suijkerbuijk et al., Nat Cancer 2024

Long-term irAEs background related

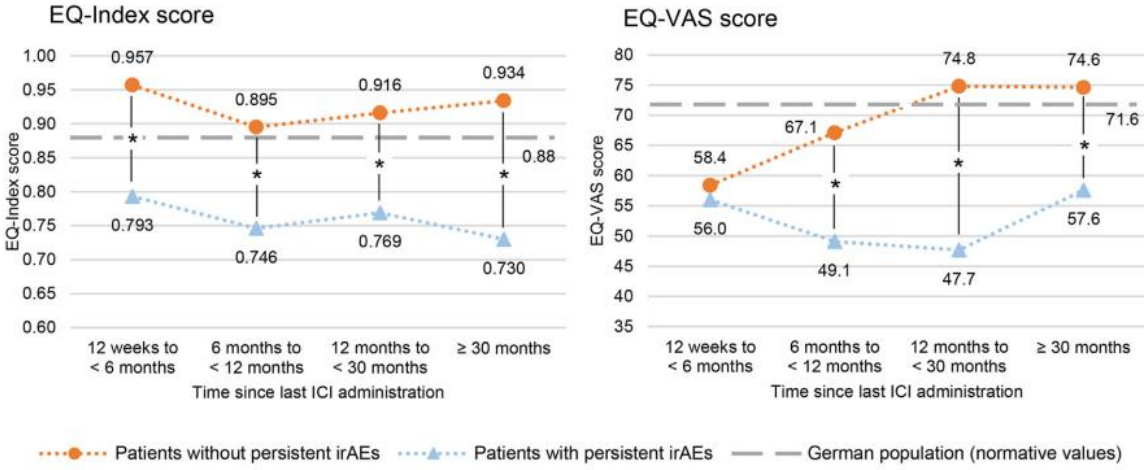
- **Flare-up of auto-immune disease** : 25% [2]
- **Allograft rejection of solid organ transplant** : up to 50% [3,4]

1, Naidoo et al., J Immunother Cancer 2023
2, Barron et al., J Immunother Cancer 2023
3, Johnson et al., Nature Reviews Clinical Oncology2022
4, Kumar et al., Oncologist. 2020

Consequences of irAE sequelae

Quality of life of patient with chronic irAE

- Multicentre cross-sectional study (ICI-cohort (n=200) of 96% melanoma patients ≥12 weeks of ICI discontinuation) in Germany



- **Reduced health-related quality of life if long-term/chronic irAEs** , confirmed in multivariate analysis
- Patients with chronic irAEs felt inadequately informed about side-effects compared to patients without chronic irAEs ($p < 0.001$)

→ Alteration in quality of life

Schulz et al., Eur J Cancer 2022

Consequences of irAE sequelae

Changes in treatments

- Treatment compliance or interruption
    - Tt discontinuation reported in up to 60%
    - Tt discontinuation due to toxicity if auto-immune disease, the elderly and in the adjuvant setting

- Use of immunosuppressors (varies according the situation)

  6% of complications of immunosuppressors (steroids, mycophenolate mofetil,….) for chronic irAEs:
    - ➢ Infections
    - ➢ diabetes
    - ➢ fractures

1,Barron et al., J Immunother Cancer 2023

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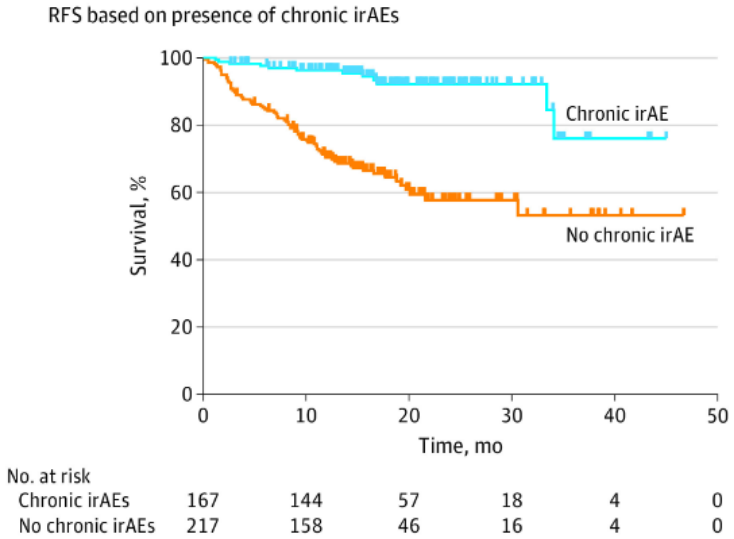
Consequences of irAE sequelae

Better outcome but what impact of immunosuppressors?

- Parallel between irAE and tumor response and survival with ICI



Patrinely et al., JAMA Oncol 2021

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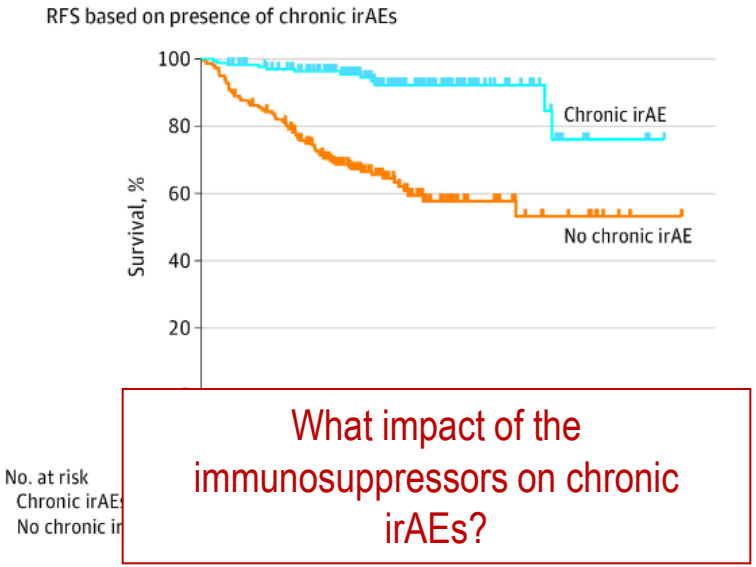
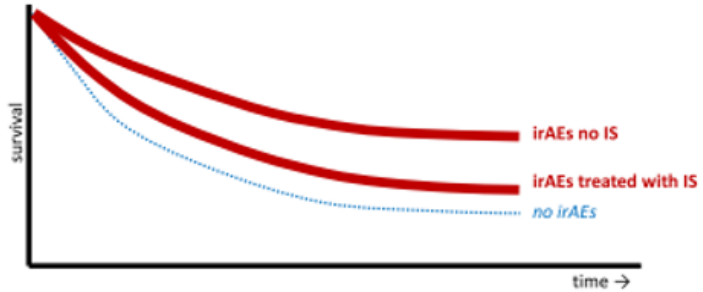


What impact of the immunosuppressors on chronic irAEs?

Patrinely et al., JAMA Oncol 2021

- Survival benefits in patients with higher-grade irAEs potentially compromised by their immunosuppressors



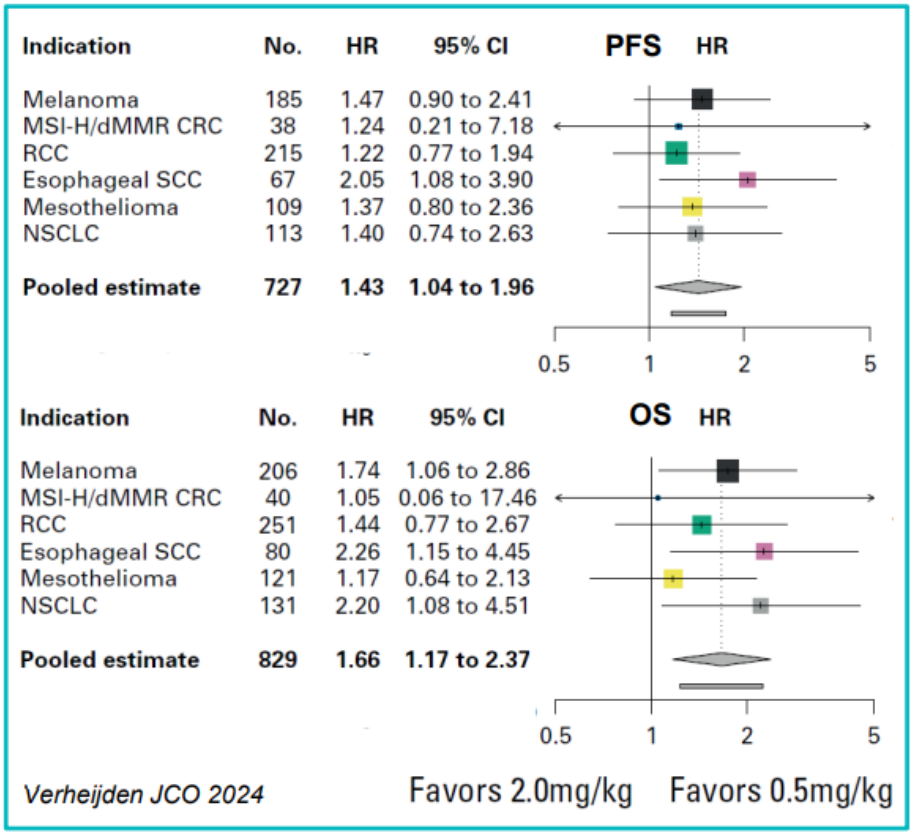
Verheijden et al., NPJ Precis Oncol. 2023

Consequences of irAE sequelae

Effect of immunosuppressants?

208/314 ipi+nivo treated patients received steroids

Would benefit of ipinivo treated patients with severe irAEs be greater if given less immunosuppression?



2- Long-term sequeale from targeted therapy (TT)

BRAF inhibitors + MEK inhibitors (vemurafenib + cobimetinib, dabrafenib + trametinib, encorafenib + binimetinib)

Charlée NARDIN, MD PhD

1, Schadendorf et al., Eur J Cancer 2024 2, Goodman et al., Eur J Cancer 2023, Picca et al., Br J Clin Pharmacol 2022 4, Gerard et al., J Neurology 2024

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  - COLUMBUS phase III trial: Arthralgia (4.5%), cardiac dysfunction (4.5%) and rash (4.5%) [1]
  - real-life : 9% with the same AEs + **fatigue** [2]

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    - **Rare (≤0,5%),** peripheral > central nervous system disorders) [3,4]
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    - ≈ 50% recovery after stopping the treatment but the others need a treatment with **possible sequelae** [4]
    - If rechallenge : avoid the same targeted therapy to prevent reccurence

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→ AEs with TT likely not chronic, low-grade and reversible with treatment discontinuation

1, Schadendorf et al., Eur J Cancer 2024 2, Goodman et al., Eur J Cancer 2022; 3, Picca et al., Br J Clin Pharmacol 2022 4, Gerard et al., J Neurology 2024

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3- Other long-term sequelae

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3- Other long-term sequelae

Local treatment

Surgery sequelae : lymphoedema (1-37%)[1,2]

Radiation therapy sequelae: Radiation-induced brain necrosis (RN) (3-22%) [3,4]

Disease

Long-term sequeale of the disease itself : rare [5]

Emotional

Long term psychological impact [6,7,8] (depression, anxiety, fatigue (35%), cognitive problems, psychiatric AEs with ICI)

Impairment of sexual life (multifactorial) affected after cancer but not evaluated after ICI

Questions?

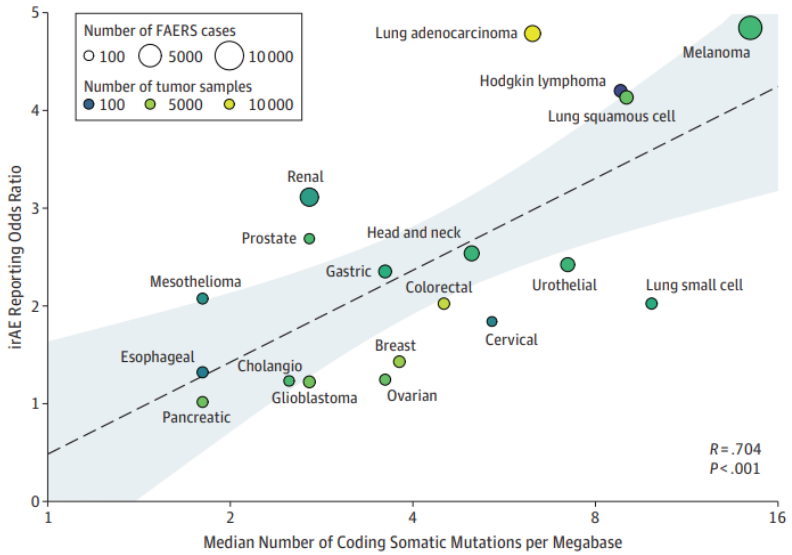
Long-term sequelae from more recent/new immune strategies? Database SERIO [9]

1, Morton et al., Ann Surg 2005; 2, Moody et al., Eur J Surg Oncol 2017; 3, Gallo et al., Clin Oncol (R Coll Radiol). 2022; 4, Thompson et al., Radiol Oncol. 2022 ; 5, Stein et al., Cancer 2008; 6, Danielsen et al., Psychooncology 2023; 7, Zhou et al., EClinicalMedicine. 2023; 8, Johnson et al., Nat Rev Clin Oncol 2022; 9, Ertl et al. Eur J Cancer 2024

Discussion : focus on irAE

Mechanisms of long-term sequelae?

Figure. Association of Tumor Mutational Burden With Immune-Related Adverse Events During Anti–PD-1 Therapy Across Multiple Cancers



Tumor Mutational Burden (TMB) as a biomarker for expected **therapy response** [1] and **irAEs** during Anti-PD1 therapy [2]

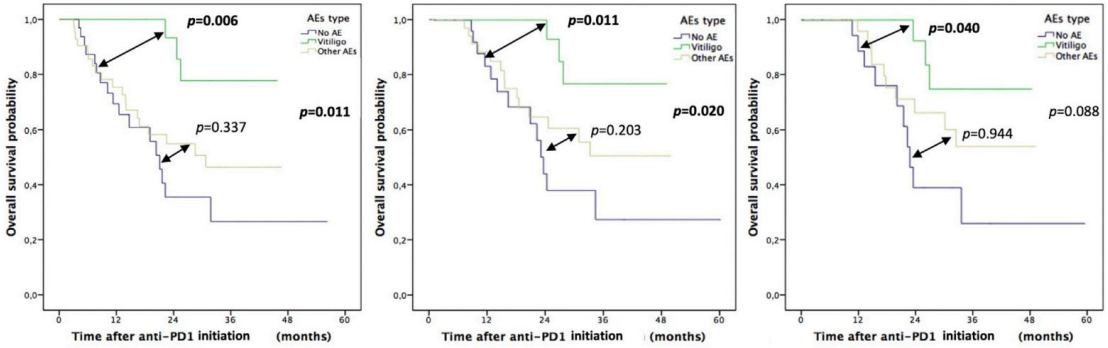
→TMB associated with anti-tumor response and irAE

1, Yarchoan et al., N Engl J Med. 2017
2, Bomze et al., JAMA Oncol 2019

Discussion

Mechanisms of long-term sequelae?

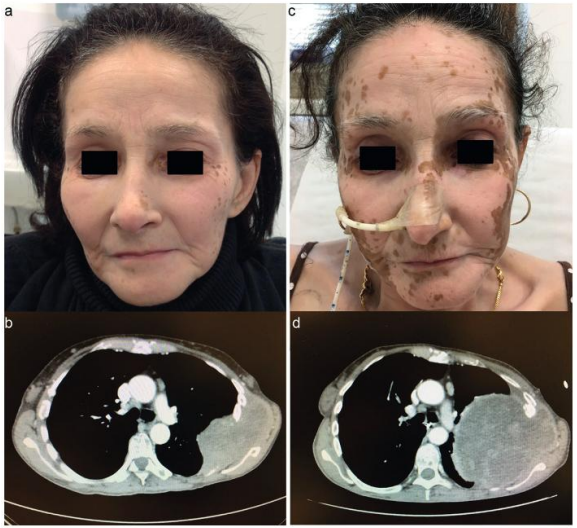
OS in melanoma patients treated with anti-PD1 agents who experienced vitiligo, other AEs



3 months 6 months 12 months

* time-dependent analysis taking into account the lead-time bias

Vitiligo re-pigmentation associated with melanoma progression during pembrolizumab treatment



Nardin et al., J Am Acad Dermatol 2021, Nardin et al., Acta Derm Venerol. 2019

Discussion

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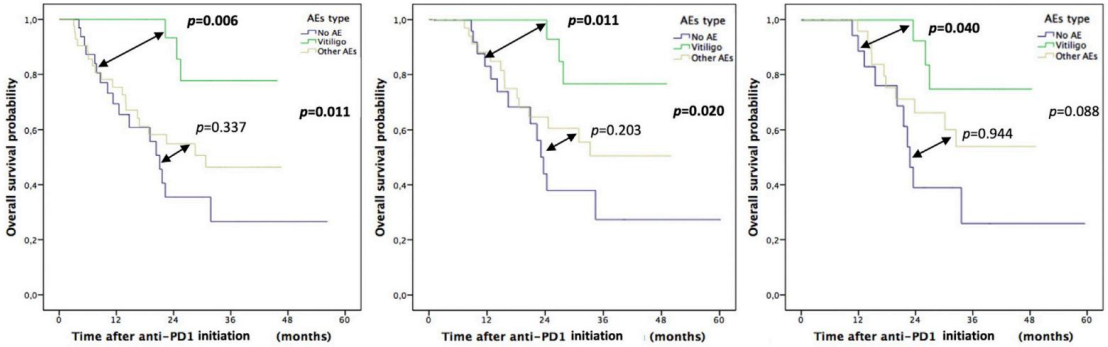

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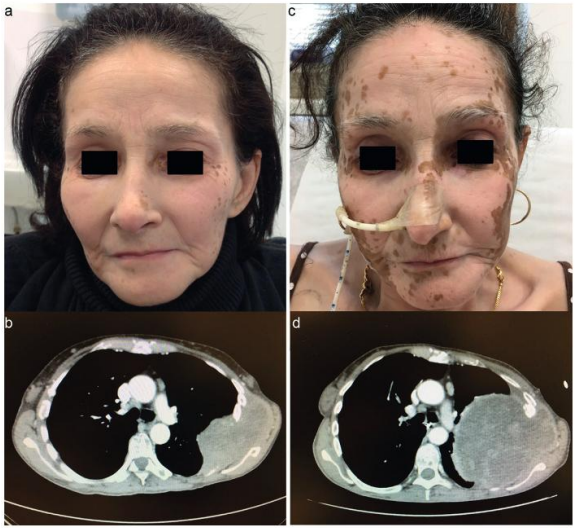
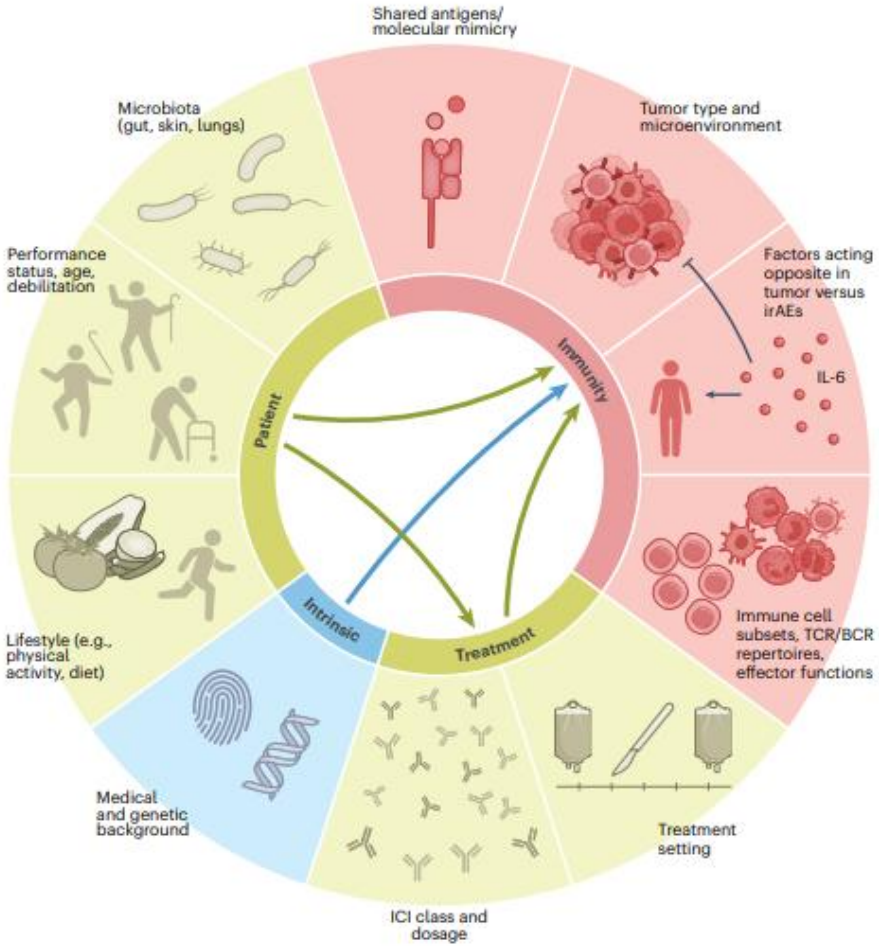


Role of shared clones of memory T cells between tumor, distant vitiligo skin lesions and blood in melanoma patients with long term response and persistant vitiligo [1]

→ shared T-cell receptor sequences and organ specific transcripts

Nardin et al., J Am Acad Dermatol 2021, Nardin et al., Acta Derm Venerol. 2019

PHYSIO VOIR PRESE ESMO



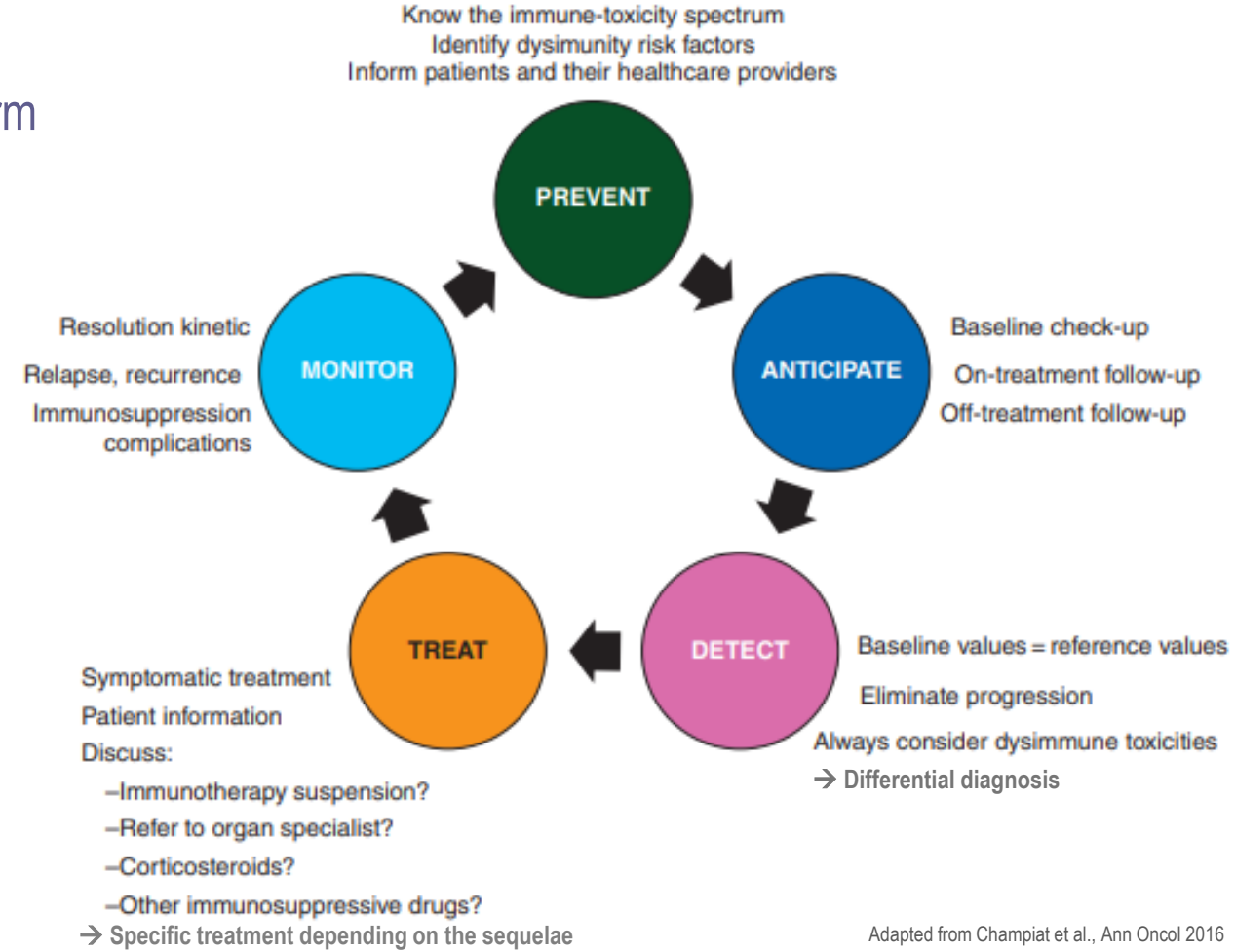
→ Many factors contributing to the emergence and burden of irAEs

→ irAEs appeared from **tumor-related** and **non-tumor related factors**

Suijkerbuijk et al., Nat Cancer 2024

Discussion

Management of the long-term sequelae?



Adapted from Champiat et al., Ann Oncol 2016

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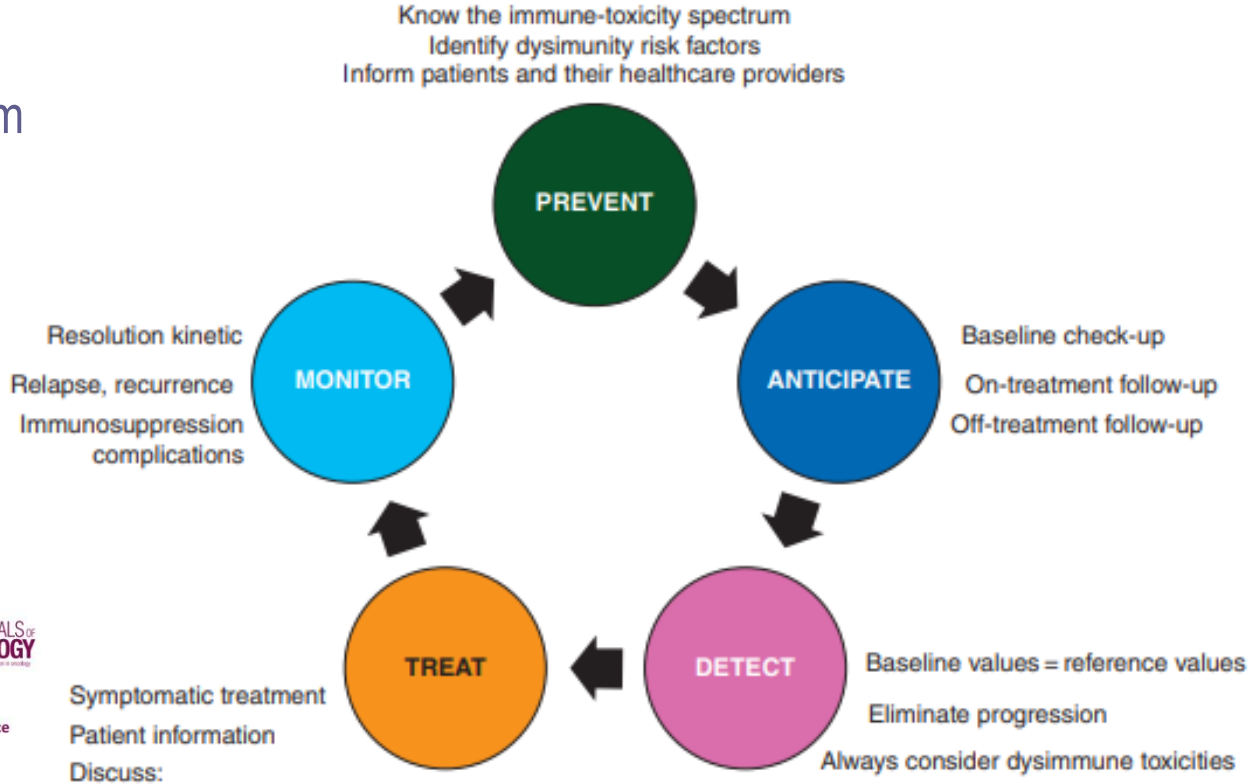

Adapted from Champiat et al., Ann Oncol 2016

ESMO

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

J. Haanen[1], M. Obeid[2,3,4†], L. Spain[5,6,7], F. Carbonnel[8,9], Y. Wang[10], C. Robert[11,12], A. R. Lyon[13,14], W. Wick[15,16], M. Kostine[17], S. Peters[9], K. Jordan[18,19] & J. Larkin[20], on behalf of the ESMO Guidelines Committee*

No specific recommandations for chronic irAE and long-term sequelae

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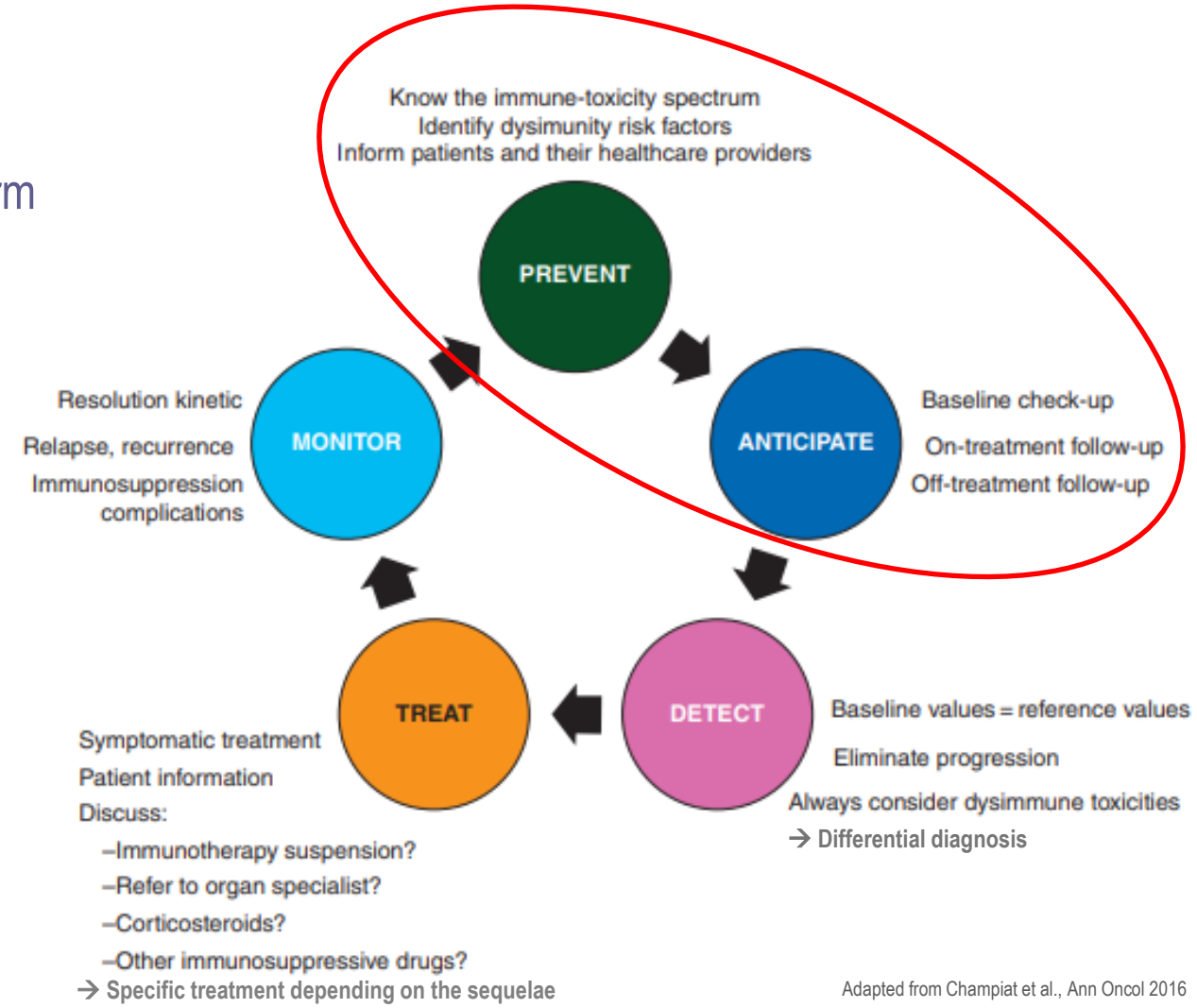
Discussion

Management of the long-term sequelae?

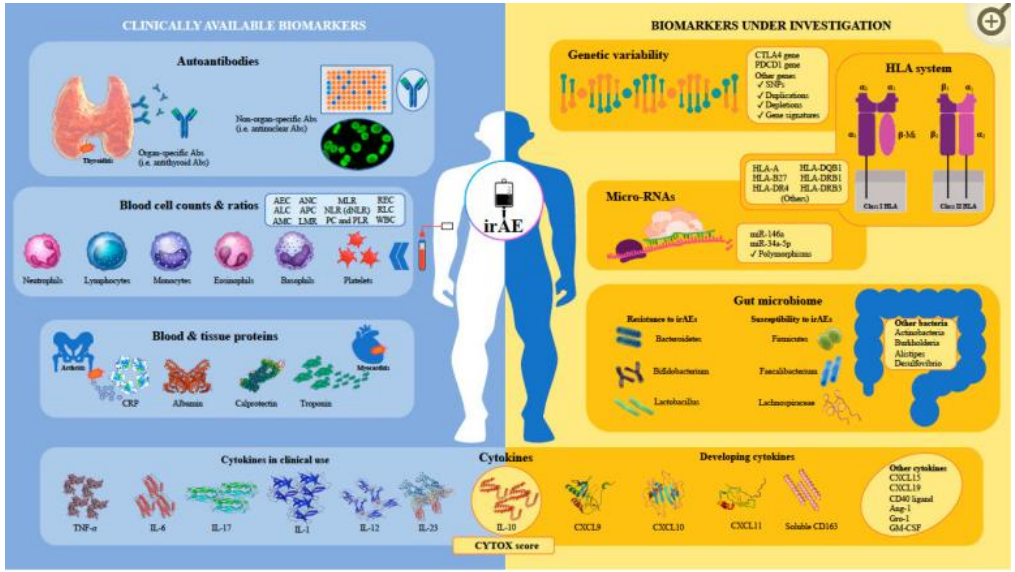


Adapted from Champiat et al., Ann Oncol 2016

Discussion

Prediction of long-term sequelae? [1]

Biomarkers of irAE:



→ However, biomarkers mostly designed to predict early irAEs, often depend on tumor response, vary according to the type of irAE, cancer, and ICI

→ Prospective studies are needed to validate biomarkers of irAEs and chronic irAEs

→ Artificial intelligence could be instrumental in developing risk scores using omics data.

1, Les et al., Cancers 2023
2, Hailemichael et al., 2022
3, Dubin et al., Nat Commun 2016

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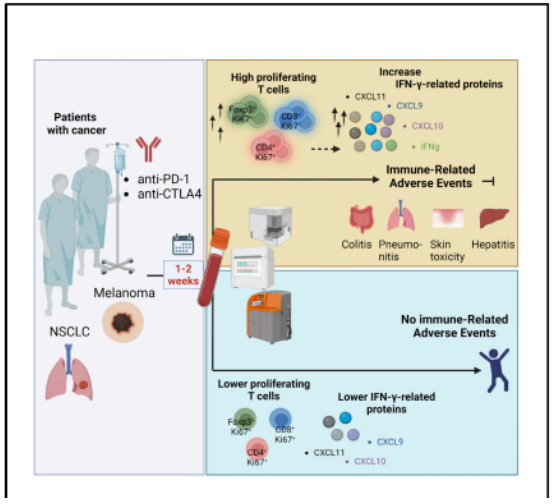
Clinical and Translational Article

Immune signatures predict development of autoimmune toxicity in patients with cancer treated with immune checkpoint inhibitors



Nicolas Gonzalo Nuñez, Fiamma Berner, Ekaterina Friebel, ..., Martin Früh, Burkhard Becher, Lukas Flatz

becher@immunology.uzh.ch (B.B.)
lukas.flatz@med.uni-tuebingen.de (L.F.)

Highlights

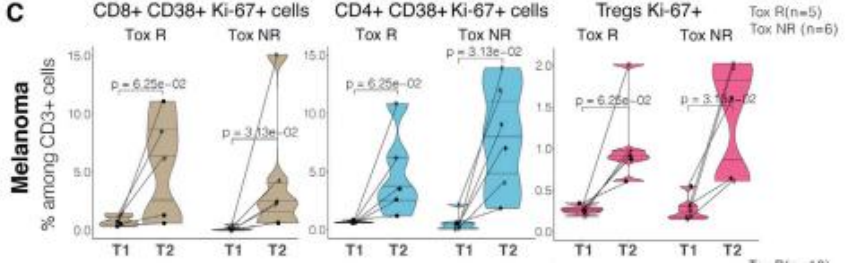
Systemic immune signatures shortly after the start of ICI therapy are linked to irAEs

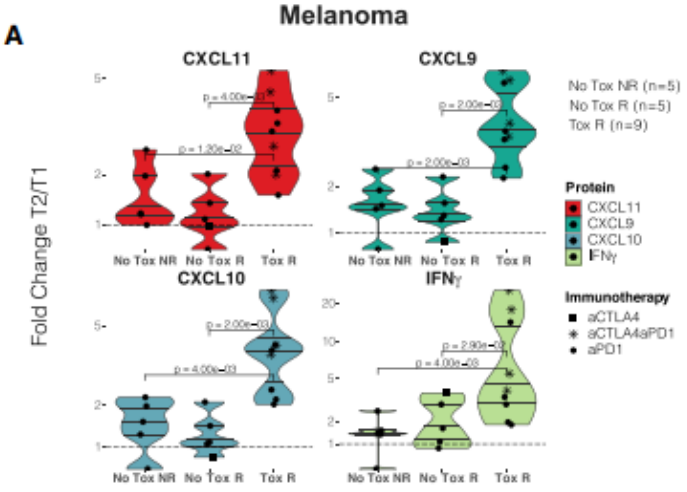
ICI-treated patients with cancer with irAEs show an expansion of Ki-67$^+$ T cell subsets

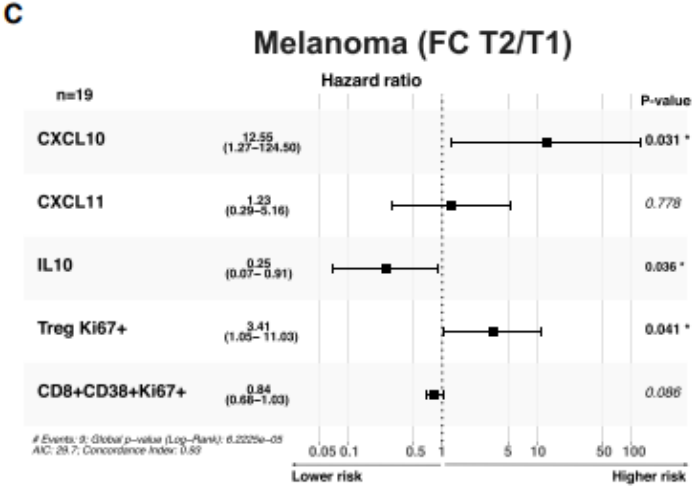
IFN-γ and IFN-γ-related proteins CXCL9/10/11 are increased in ICI-treated patients with irAEs

Early blood ICI immune signatures may provide a predictive biomarker profile for irAEs

Validation cohort







ontent of

-use.

Discussion

Prevention of long-term sequelae?

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1, Weber et al., JCO 2024; 2, Caroll et al., Lancet 2022; 3, Hanna et al., JCO 2024; 4, Keilholz., Ann Oncol 2020

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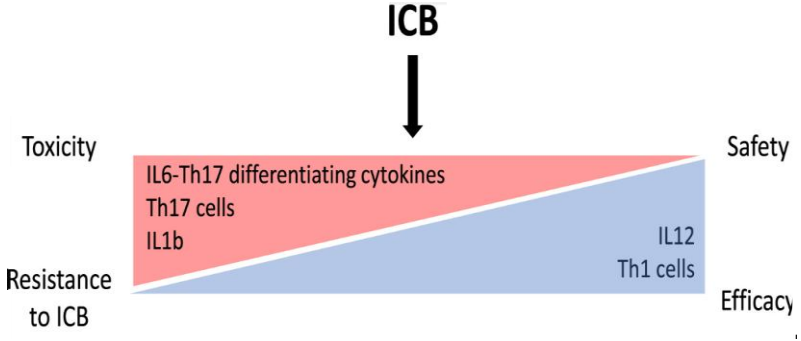

Delyon et al. Cancer Cell 2022

IL-6 inhibitors → to decrease severe irAE:

- Phase II in solid tumors (including melanoma) :

  Tocilizumab + Ipi 1mg/kg + Nivo 3mg/kg in advanced melanoma : ORR 70%, AE G3/4 25%

  What impact on long-term AEs?

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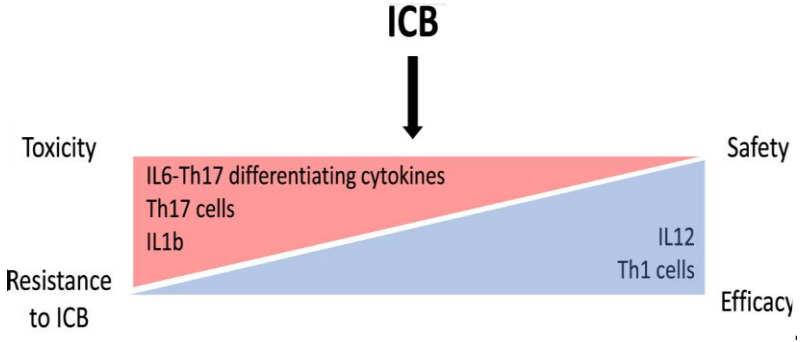

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- Maintenance of immunosuppression with ICI
- Pulse of steroids + mTOR inhibitors with ICI to treat advanced cutaneous squamous cell carcinoma

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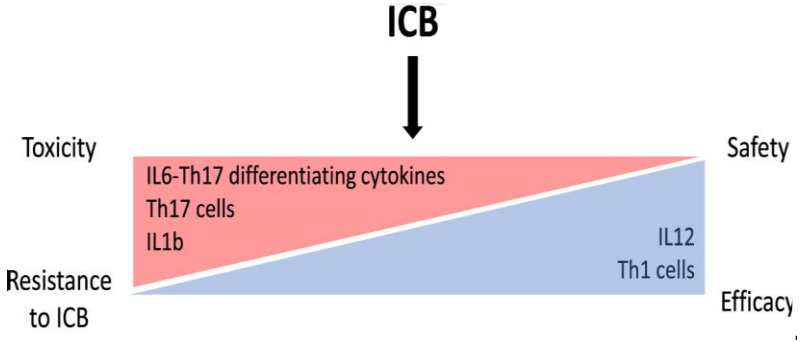

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No need to prolonge ICI treatment when it is safe to stop ICI → to avoid AE?

- > 6 months if complete response in advanced melanoma or > 2 years if partial response or stability

1, Weber et al., JCO 2024; 2, Caroll et al., Lancet 2022; 3, Hanna et al., JCO 2024; 4, Keilholz., Ann Oncol 2020

Discussion

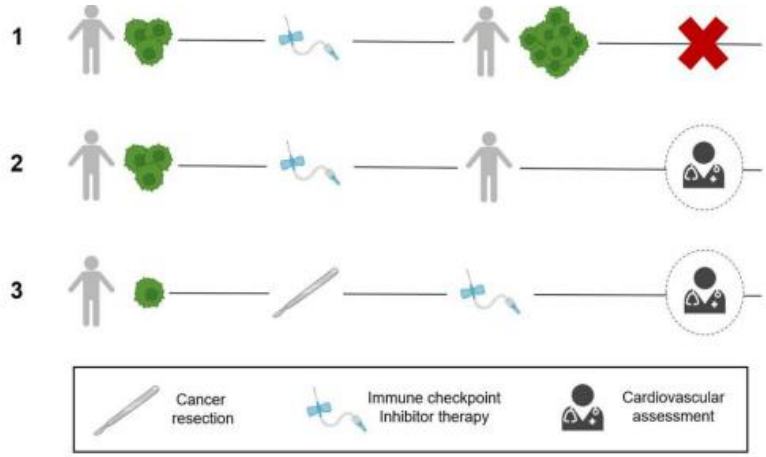
Prevention of long-term sequelae?

- **Cardiovascular risk:**

European Society of Cardiology Cardio-Oncology Guidelines :

➢ **screening at baseline and during treatment**
(CVRF assessment, ECG, transthoracic echocardiography, Troponin, BNP)

Tan et al. proposed a **follow-up if durable response or curative treatment**



1, Lyon et al. Eur Heart J. 2022 2, Tan et al. Eur J Preventive Cardiology 2024 3, Kim JCO Oncol Practice 2022

Discussion

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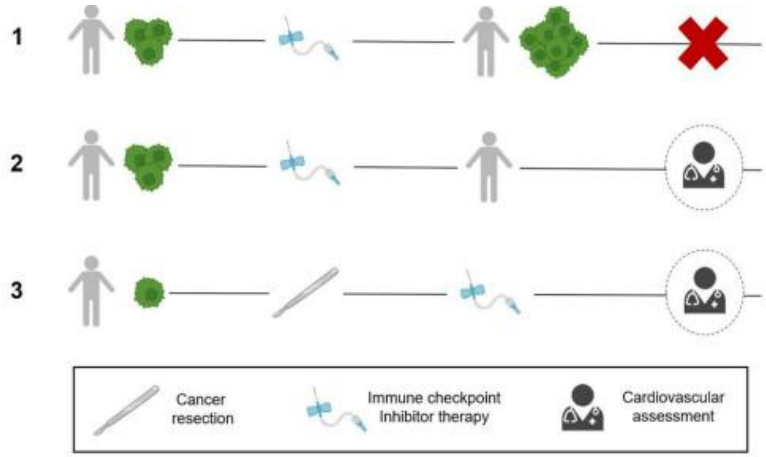

- **Fertility risk:**

➢ Recommendation: **fertility-preservation** strategies offered, +/- avoid pregnancy during and 3-12 months after ICI [3]

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1, Lyon et al. Eur Heart J. 2022 2, Tan et al. Eur J Preventive Cardiology 2024 3, Kim JCO Oncol Practice 2022

Discussion

Management of long-term treatment sequelae?

Supportive care :

- Positive impact in melanoma patients [1]
- Interventions :
  - **adapted physical activity** [2,3]
  - **psychological support** (« *Psychological support and resilience* », Marie van der Lee)
  - **cognitive support** (« *Neuro-cognitive remediation in case of permanent neurological deficits* », Anne Rogiers)
  - multidisciplinary approch

1, Thompson et al., Cancer Med. 2023
2, Charles et al., J Telemed Telecare 2023
3, Boileau et al., Melanoma Res 2023

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Conclusion

Management of long-term treatment sequelae in melanoma patients?

- Paradigm changes for the management of melanoma patient since the long-term efficacy of treatment particulary with immune checkpoint inhibitors
- Adequate follow-up to diagnose these diverse long-term treament sequelae (physical with irAE, psychological, social)

WE STILL NEED

→ Studies to describe these long-term sequelae and understand their physiopathology

→ Draw recommandations for their managment and to prevent them

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Acknowledgements

- Prof. François AUBIN
- Physicians from the Dermatology, Oncology and Pharmacy Departments, interns, nurses and secretaries of Minjoz Hospital, Besançon
- Groupe de Cancérologie Cutanée, France (GCC)
- Société Française de Dermatologie (SFD)
- INSERM UMR RIGHT, Besançon
- Association A Fleur de Peau

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esmo@esmo.org

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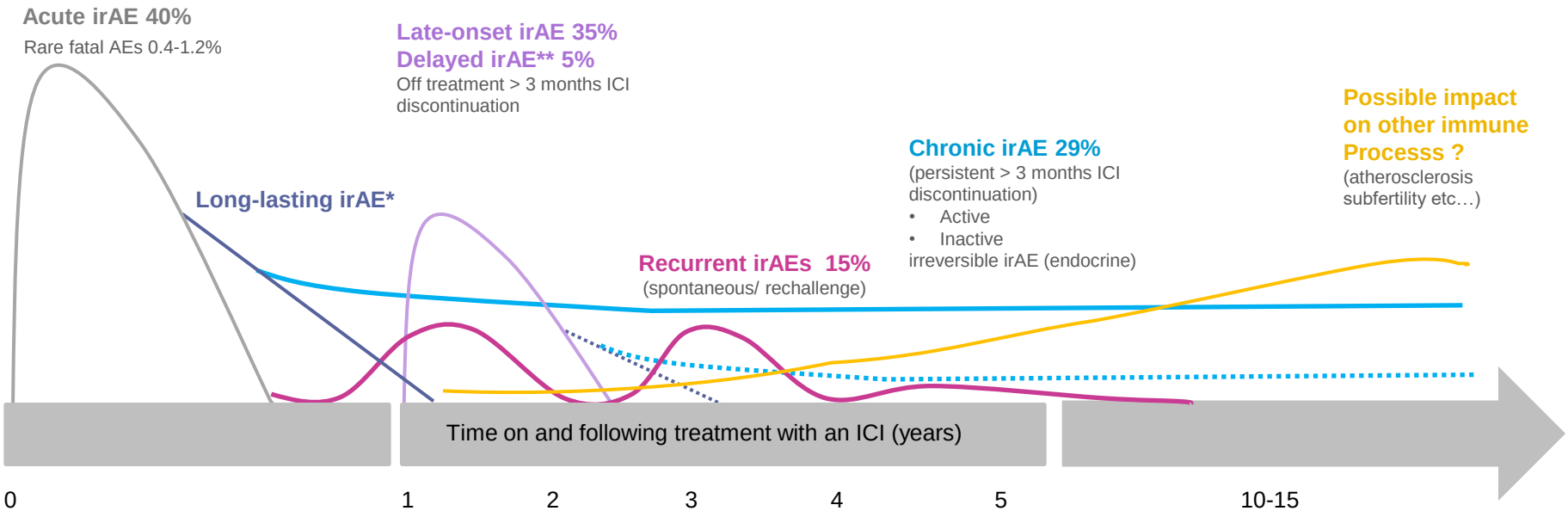
Time course of immune-related adverse events



* Long-lasting irAEs were frequently reported as irAE lasting more than 6 months

** Late-onset/delayed irAEs were frequently reported as irAE occuring after 1-2 years of ICI treatment during or after treatment discontinuation but was more recently defined as occuring > 3 months ICI discontinuation

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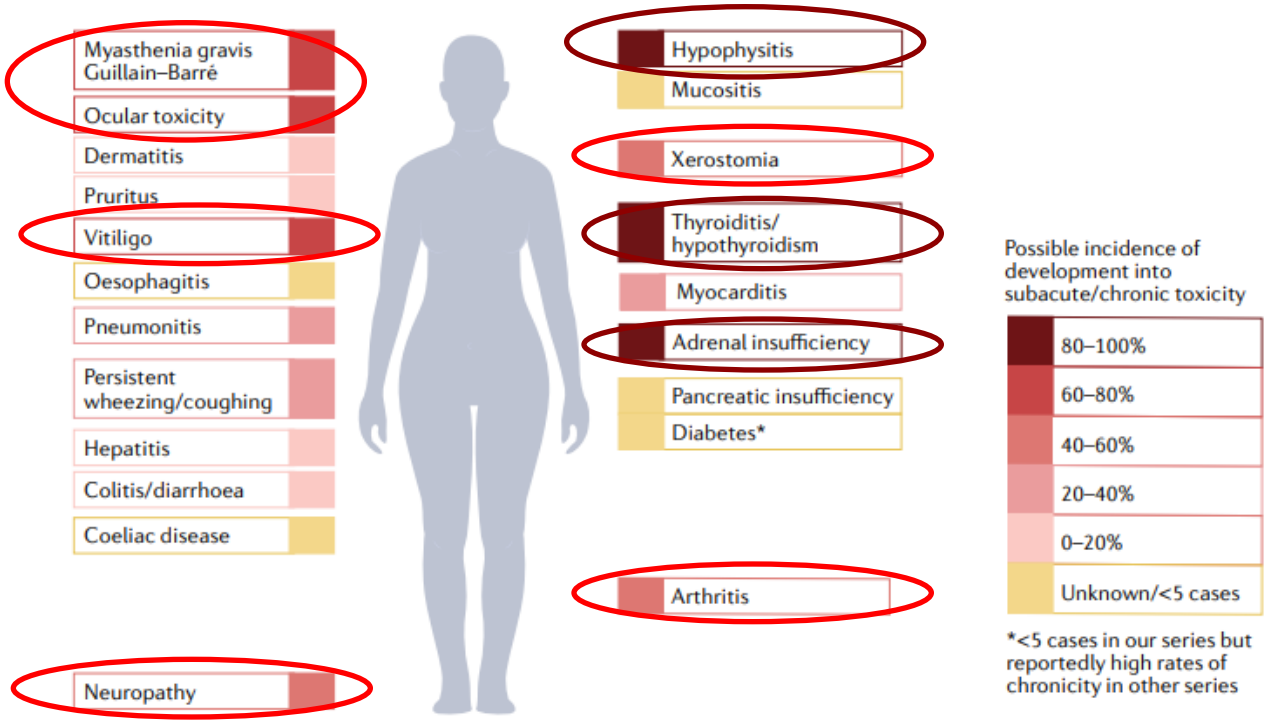
Chronic irAEs

irAE **persistent > 3 months ICI discontinuation** (time to clearance of ICI)



Johnson et al., Nat Rev Clin Oncol 2022

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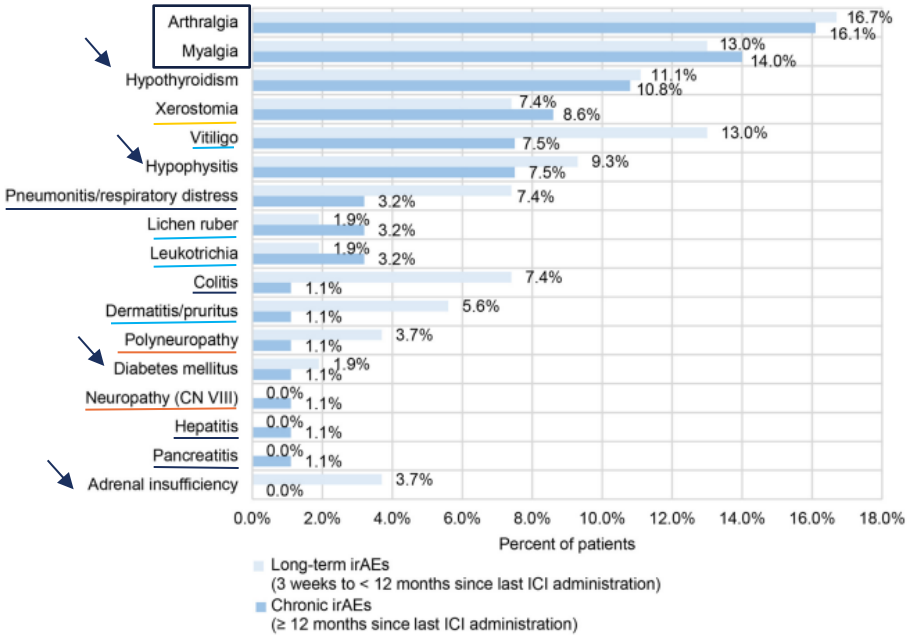

The multicentre, cross-sectional study included 200 patients with cancer (96% of melanoma patients) ≥ 3months after ICI cessation (ICI-patients)

Persistent irAEs

- 51% ≥ 3 months after treatment discontinuation
- 35% >12 months after treatment discontinuation

→ Chronic irAE are frequent
→ Mostly non visceral organ

Schulz et al., Eur J Cancer 2022