ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Workshop

Managing treatment-associated adverse events

Kyoto, floor 2

Sandrine Aspeslagh, *Jules Bordet Institute*

Moderated by
Stefan Rauh, *Centre Hospitalier Emile Mayrisch, Luxemburg*
and
Guy Jerusalem, *CHU Liège*

Mercury number IOBE18NP04371-03
Date of preparation: December 2018

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Common immune-related adverse events

Sandrine Aspeslagh

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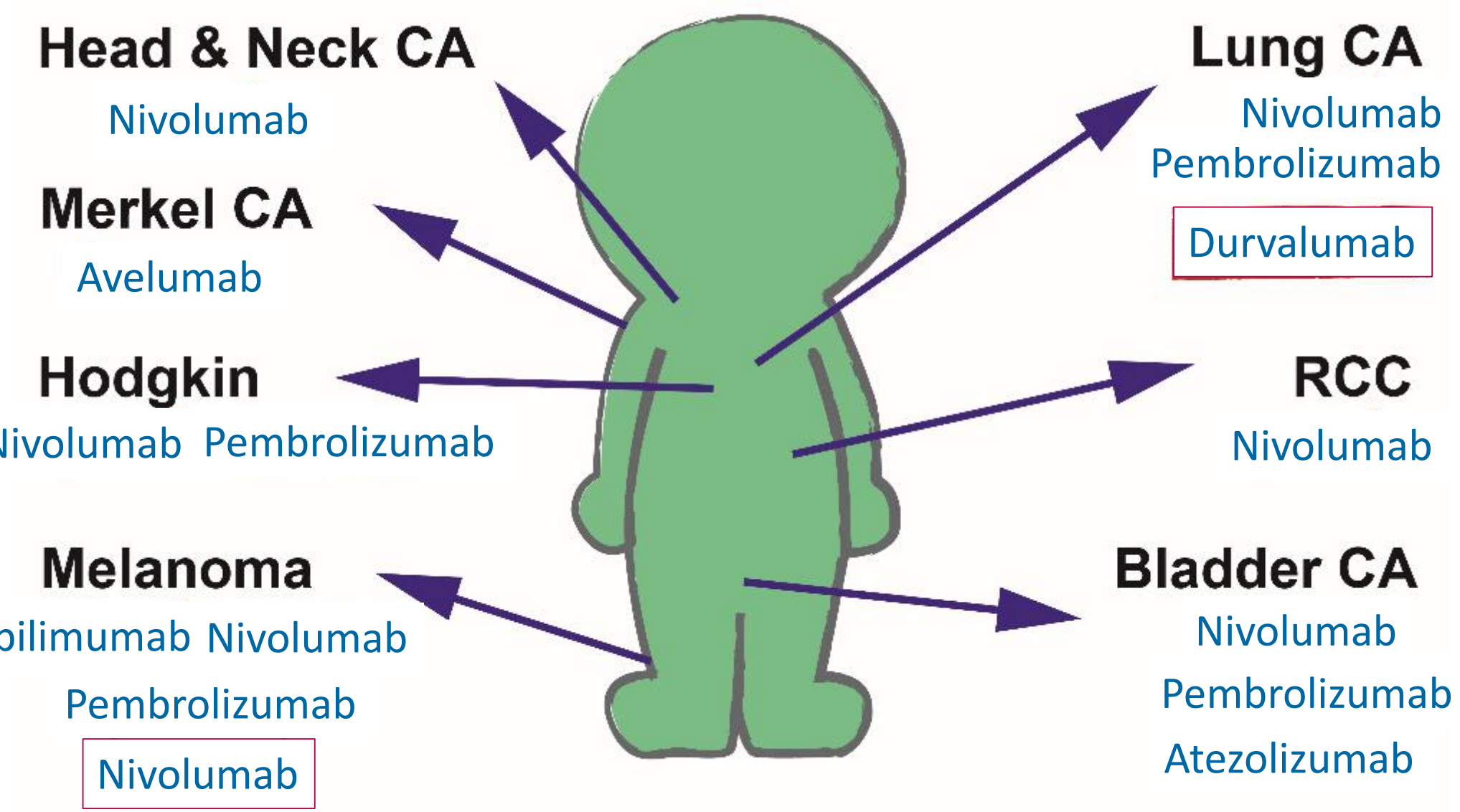
Immune checkpoint blockers

Anti-CTLA-4	Anti-PD-1	Anti-PDL1
Ipilimumab (BMS)	Nivolumab (BMS)	Atezolizumab =MPDL3280A (Roche/Genentech)
Tremelimumab (AZ)	Pembrolizumab = MK3475 (MSD)	Durvalumab=MEDI4736 (AZ/Medimmune)
	PDR001 (Novartis)	Avelumab (Pfizer)
	Cemiplimab (Sanofi)	LY3300054 (Lily)
	SHR (Chinese Ab*)	

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

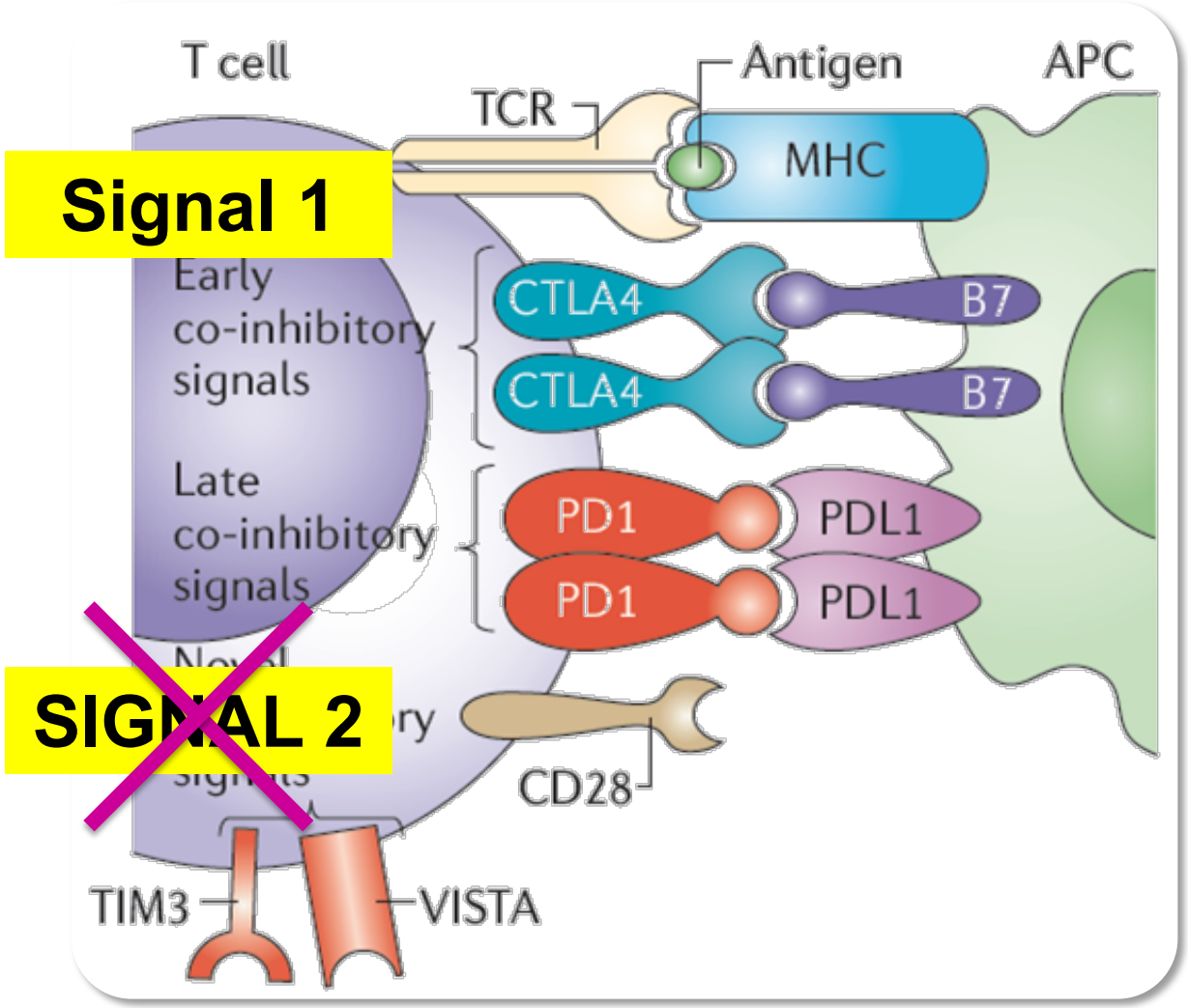
Ab, antibody; AZ, Astra-Zeneca; BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T-lymphocyte associated protein, MSD, Merck Sharp & Dohme; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.
Sandrine Aspeslagh, personal communication, 2018.



Reimbursement of immune checkpoint blockade, Belgium, November 2018

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

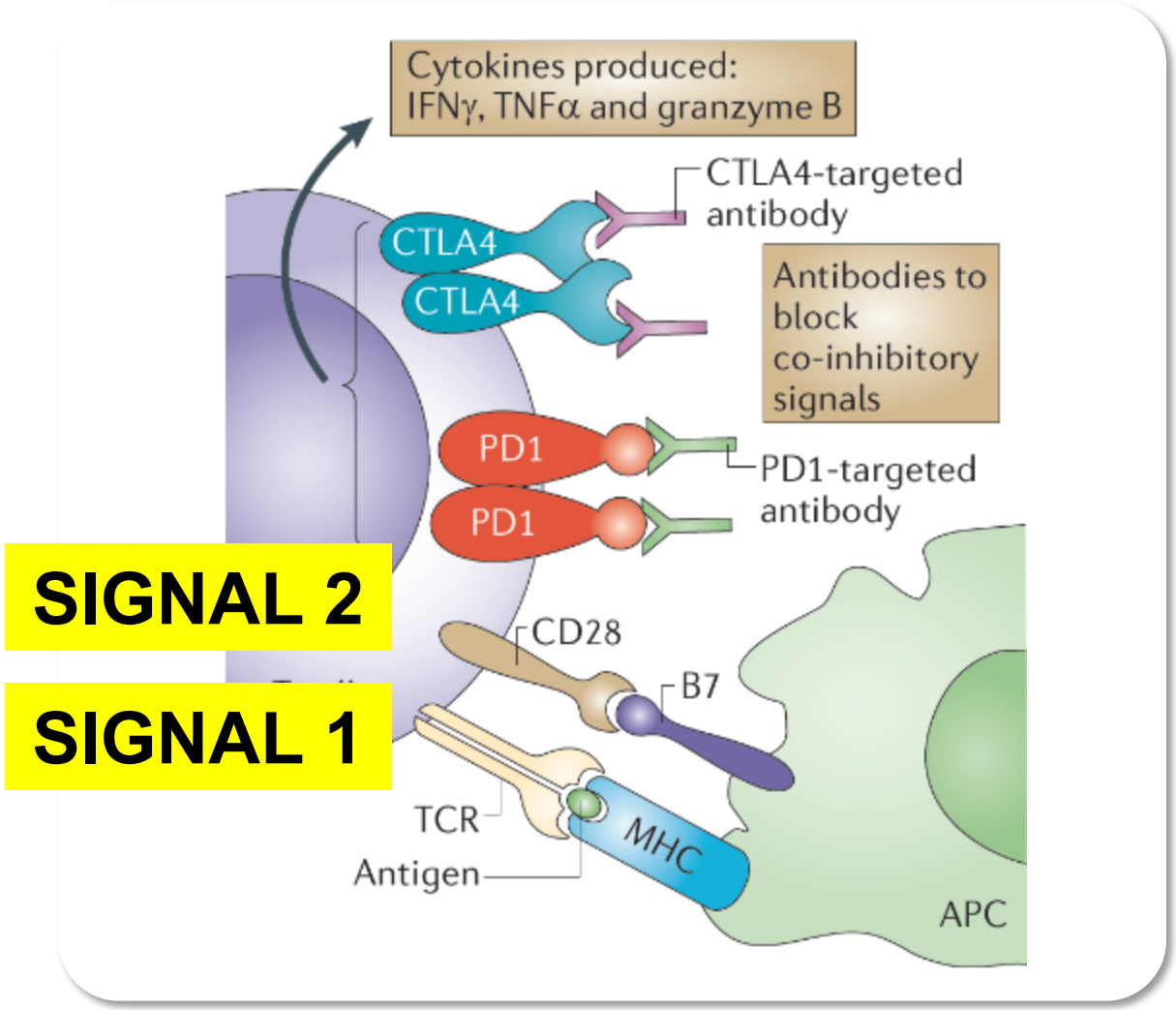
Immune checkpoints[1]



APC, antigen-presenting cell; CTLA4, cytotoxic T lymphocyte-associated protein 4; MHC, major histocompatibility complex; PD1, programmed cell death 1; PDL1, PD1 ligand 1; TCR, T cell receptor; TIM3, T cell immunoglobulin and mucin domain containing protein 3, VISTA, V-domain immunoglobulin suppressor of T cell activation

1. Sharma P et al. 2011 Nature Reviews Cancer 11, 805–812

Immune checkpoint blockade therapy[1]



TNFα, tumour necrosis factor-α, IFNγ, interferon-γ

1. Sharma P et al. Nat Rev Cancer 2011;11:805–12.

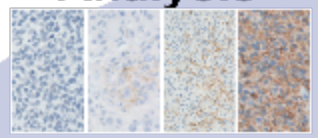
Who is in the room?

- Medical oncologist
- Radiation oncologist
- Organ specialist who prescribes ICPI
- Organ specialist who doesn’t prescribe ICPI (but is more involved in the autoimmune problems)
- Nurse
- Other

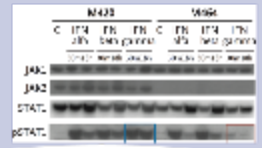
ICPI, immune checkpoint inhibitor.

NEW CHALLENGES IO approach of CA patients

Biomarker Analysis

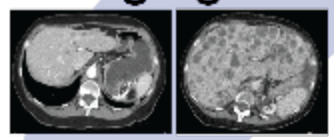


Understanding Resistance

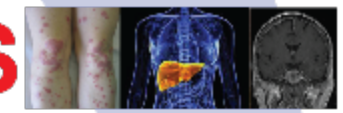


Neoadjuvant treatment

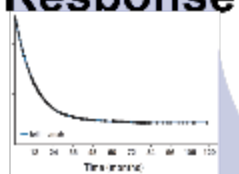
Imaging Patterns



Immunotoxicity management



Duration of Response



Clinical Trial Organisation

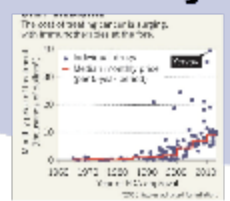
Education

ENSEIGNEMENTS IMMUNO-ONCOLOGIE

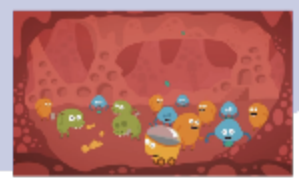
Local Therapy

Epigenetics

Financial Toxicity



Microbiome



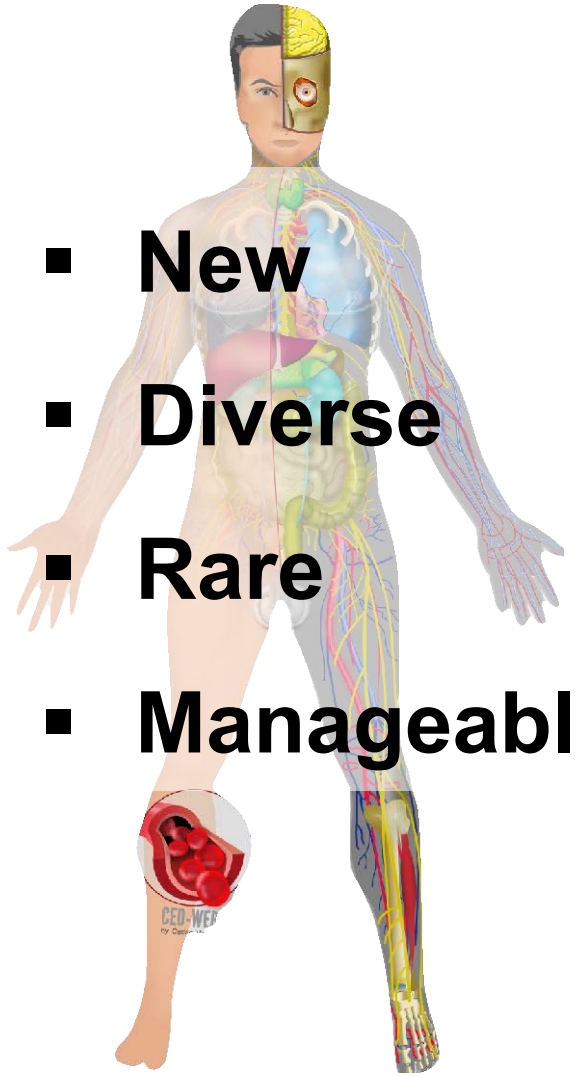
Have you been confronted with side effects of immune checkpoint blockade in your patients?

- Never
- Yes, more than one patient per month
- No, less than one patient per month

ICPI, immune checkpoint inhibitor.

Toxicity of immune checkpoint blockade agents[1]

- Uveitis; Conjonctivitis; (epi)Scleritis; Blepharitis; Rétinitis
- Hepatitis Cholangitis
- Hypo- / Hyper-thyroidy; Hypophysitis; Diabetes; Adrenal insufficiency
- Colitis; Ileitis Pancreatitis Gastritis
- Eruption; Pruritis Psoriasis; Vitiligo Stevens Johnson



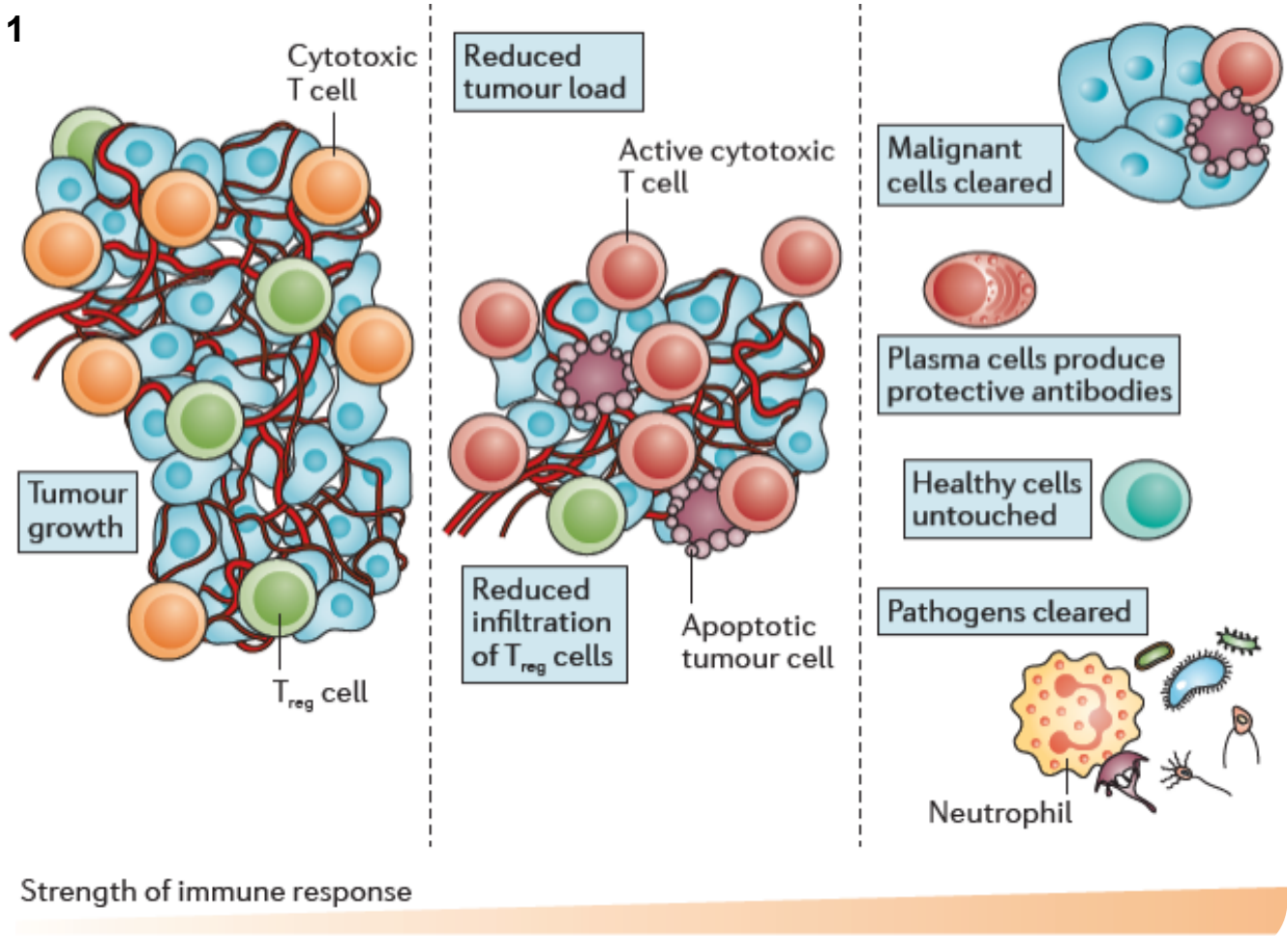
- **New**
- **Diverse**
- **Rare**
- **Manageable**

- Neuropathy; Myelitis Meningitis; Encephalitis Myasthenia
- Pneumonitis Pleuritis Sarcoidosis
- Myocarditis Pericarditis Vascularitis
- Nephritis
- Arthritis Myositis
- Hemolytic anemia; Thrombocytopenia; Neutropenia; Hemophilia

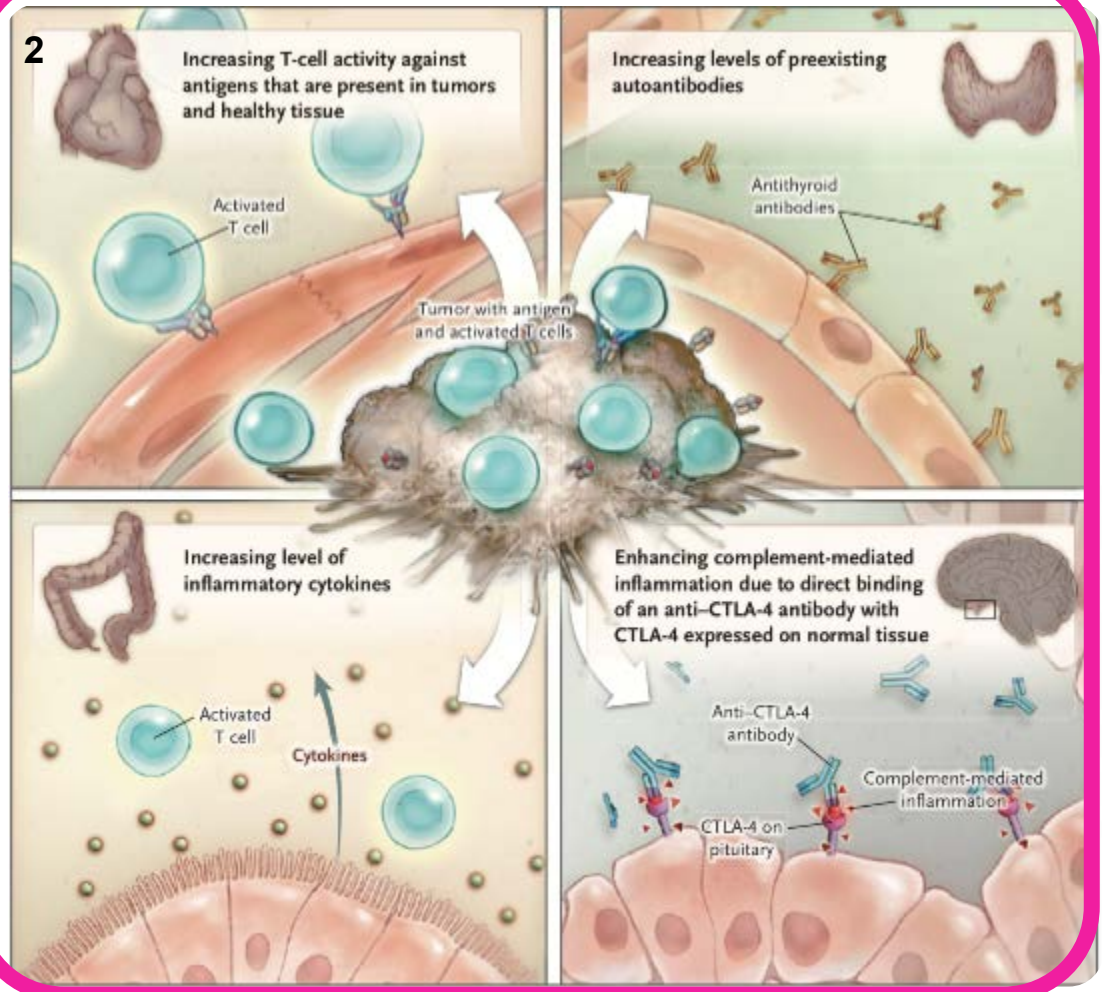
1. Adapted from Champiat et al. Ann. Oncol. 2016;27:559–74.

Immune balance[1,2]

1



2



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.

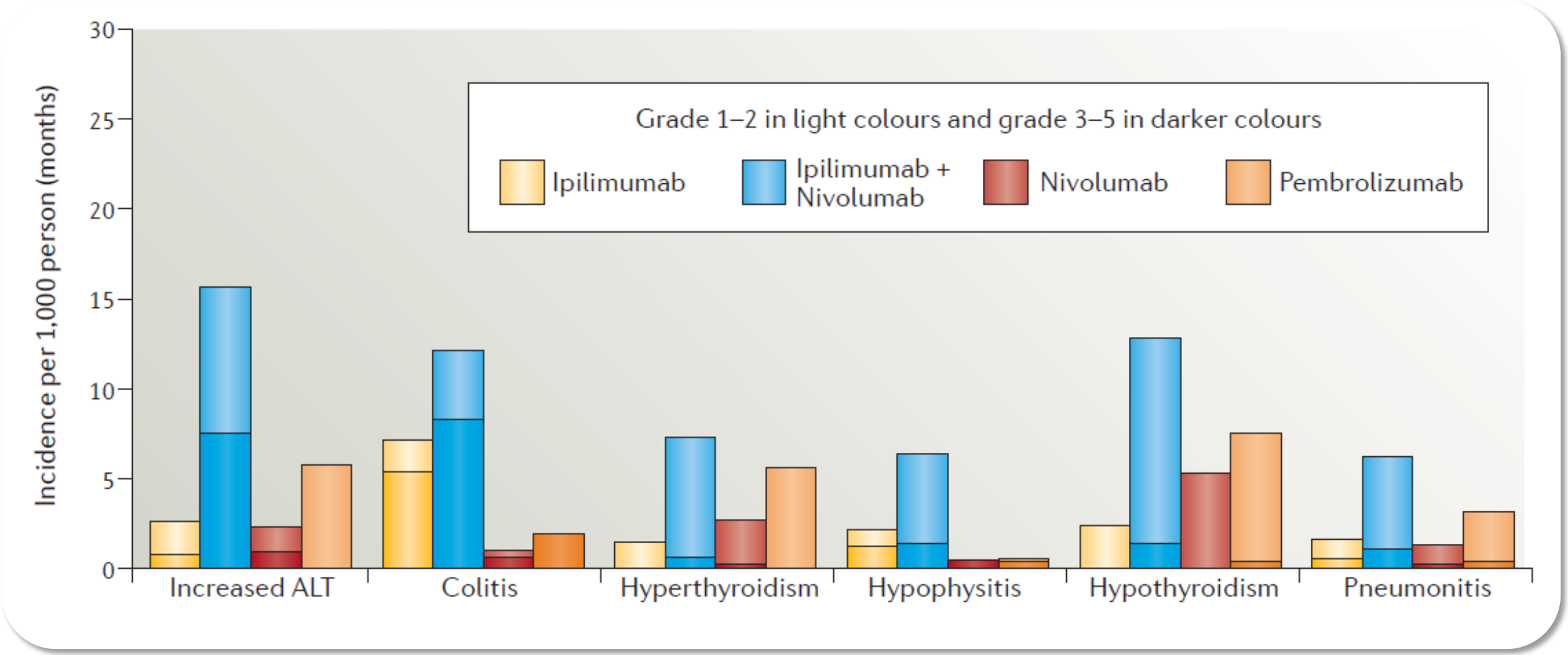
Severity[1]

Grade (CTCAE v4)	Management	Follow-up monitoring
Grade 1	• Continue immunotherapy • Treatment of symptoms	• Frequent monitoring • If worsening: treat as grade 2 or 3/4
Grade 2	• Delay immunotherapy • Treatment of symptoms	• Resume immunotherapy when symptoms improve to grade 1 • Consider glucocorticosteroids 0.5–1 mg/kg per day if symptoms persist more than 5–7 days • If worsening with steroids: treat as grade 3/4
Grade 3–4	• Discontinue immunotherapy except in patients with skin or endocrine toxicities • Initiate glucocorticosteroids 1–2 mg/kg per day • Consider hospitalization	• Continue glucocorticosteroids until grade 1 • Taper dose of steroids over at least one month • If persistent or worsening: consider alternative immunosuppressive therapy

CTCAE, Common Terminology Criteria for Adverse Events

1. Boutros C. et al. Nat Rev Clin Oncol 2016;13:473–486.

Immunotoxicity adverse events[1]

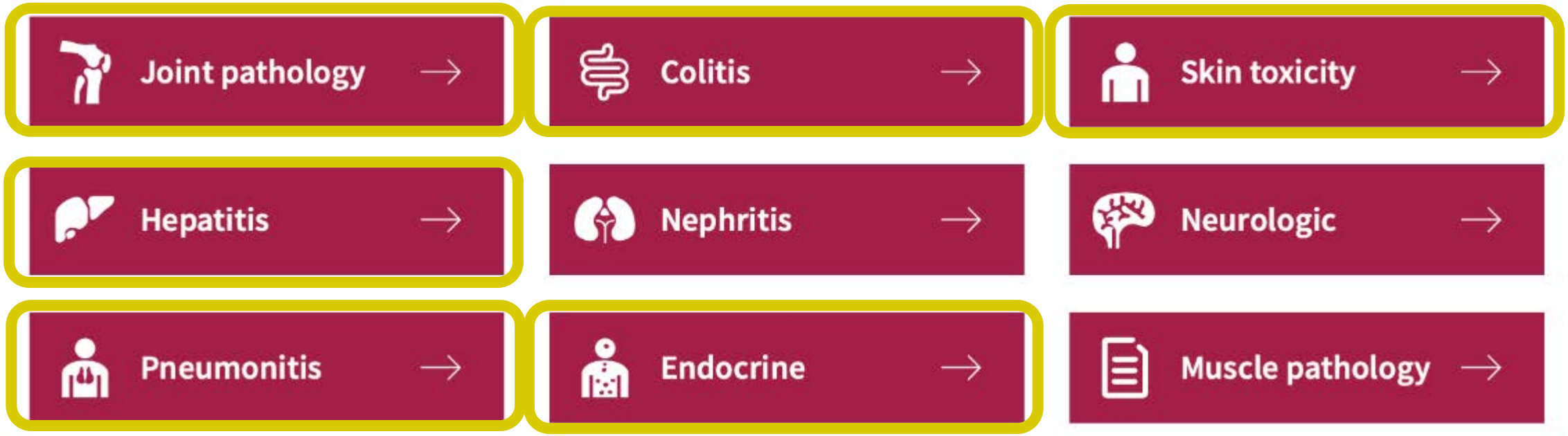


1. Boutros et al. Nat Rev Clin Oncol 2016;13:473–86.

Recommendations[1]

Immune related adverse events (irAE)

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



1. BSMO Immunomanager 2018 Joint Pathology. Available at https://www.bsmo.be/immunomanager/irae/ Accessed December 2018.

Great collaboration with KBVR/SRBR

Joint pathology [1]

Arthralgia

- No clinical swelling
- Joint pain
- Stiffness

Inflammatory arthralgia

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

Arthritis

- Signs of inflammation
- Joint swelling
- Awaking 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

1. BSMO Immunomanager 2018 Joint Pathology. Available at https://www.bsmo.be/wp-content/uploads/Joint-Pathology-IA.pdf Accessed December 2018.

Great collaboration with KBVR/SRBR

Arthralgia [1]

Symptom Grade	GRADE 1	GRADE 2
	Mild pain No signs of inflammation Pain depends on exercise	Moderate or severe pain limiting daily activities Signs of inflammatory arthralgia
Management escalation pathway	Initiate analgesia with paracetamol and/or NSAID Continue ICPi	Escalate analgesia and use NSAID (If not contraindicated) or low dose corticoids Benefit of corticoids may be reevaluated by a rheumatologist after 2 weeks Discuss withholding ICPi until resolution of pain
Assessment and Investigations	Complete rheumatological history Examination of all joints and skin Consider imaging to exclude metastases Consider ultrasound to exclude arthritis	Perform X-rays to assess inflammatory pathology, always consider other imaging to exclude possible metastasis Complete rheumatological history Examination of all joints and skin Consider ultrasound to exclude arthritis Autoimmune panel: • ACPA; RF; ANA

ACPA, anti-citrullinated antibody; ANCA, anti-neutrophil cytoplasmic antibody; ANF, anti-nuclear factor; ICPi, immune checkpoint inhibitor; NSAID, non-steroid anti-inflammatory drugs; RF, rheumafactor. 1. BSMO Immunomanager 2018 Arthralgia https://www.bsmo.be/wp-content/uploads/Arthralgia-3.pdf Accessed December 2018.

Adverse events[1]

Adjuvant ICB treatment for melanoma patients

Event	Nivolumab (N = 452)		Ipilimumab (N = 453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Treatment-related adverse event†	385 (85.2)	65 (14.4)	434 (95.8)	208 (45.9)
Fatigue	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
Diarrhoea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	**57 (12.6)**	**1 (0.2)**	**49 (10.8)**	**2 (0.4)**
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

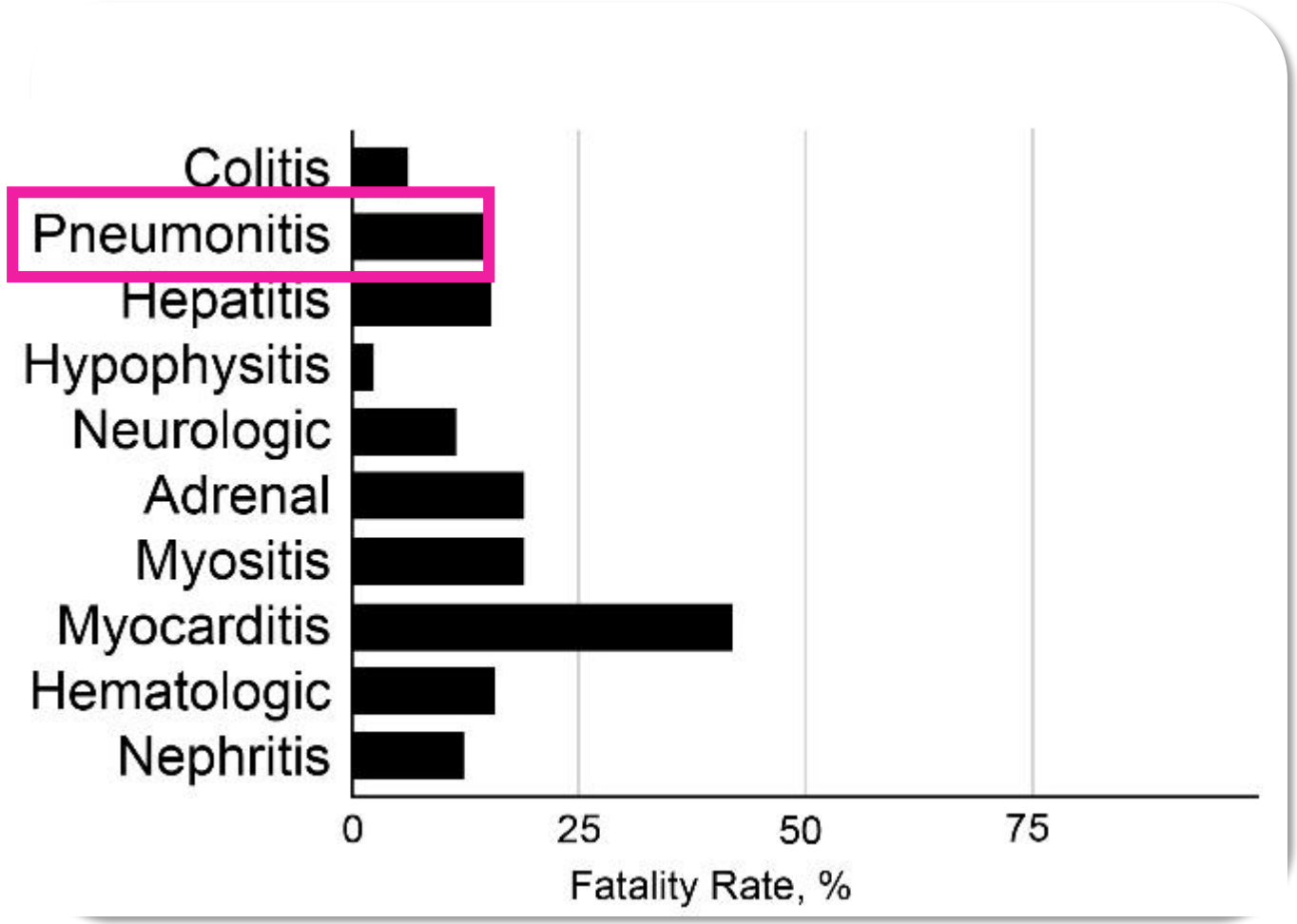
1. Weber et al. N Engl J of Med 2017;377:1824–35.

Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis[1]

report them accurately. Investogators may be less aware of other potentially relevant adverse events such as musculoskeletal problems and may therefore inaccurately diagnose and record them. Emerging case reports and case series have described rheumatologic and musculoskeletal syndromes related to systemic inflammation that have been seen in clinical practice but not described in primary publications of trial results.[9 10 40] Similar attention has been turned to less frequent, but important adverse events impacting the neurologic, cardiac, and ocular systems.[41-44] As these receive more attention, problems such as arthritis, arthralgia, and myalgia may become more accurately reported in future studies.

1. Baxi et al. 2018 BMJ;360:k793.

Fatal toxic effects associated with immune checkpoint inhibitors a systematic review and meta-analysis[1]



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

Pneumonitis[1]

Symptom Grade	GRADE 1	GRADE 2	GRADE 3
	Radiographic changes only Ground glass charge, non-specific interstitial pneumonia	Mild /moderate new symptoms Dyspnoea, cough, chest pain	Severe new symptoms New or worsening hypoxia Life threatening Difficulty in breathing, ARDS
Management escalation pathway	Consider delay of treatment Monitor symptoms every 2-3 weeks When worsening treat as grade 2 or 3-4	**Withhold ICPI** Start Ab if suspicion of infection (fever, CRP, neutrophil counts) If no evidence of infection or no improvement with Ab after 48h add in prednisolone 1 mg/kg/day orally High resolution CT +/bronchoscopy and BAL Consider Pneumocystis prophylaxis	**Discontinue ICPI** Admit patient, baseline tests as above (methyl) prednisolone i.v. 2 mg/kg/day High resolution CT ad respiratory review +/- bronchoscopy and BAL pending appearances Cover with empiric AB

ICPI, immune checkpoint inhibitor

1. BSMO Immunomanager 2018 Pneumonitis. Available at https://www.bsmo.be/wp-content/uploads/Pneumonitis-IA.pdf. Accessed December 2018.

Non specific interstitial pneumonitis

COP-like

Hypersensitivity

AIP/ARDS

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ULB iris

Adapted from Castanon. Clin Cancer Res 2016;22:5956–58.

What would you do?
Patient under immunotherapy has 2 isolated lung lesions

- Pursue immunotherapy and perform biopsy
- Stop immunotherapy and perform biopsy
- Pursue immunotherapy without biopsy
- Stop immunotherapy without biopsy

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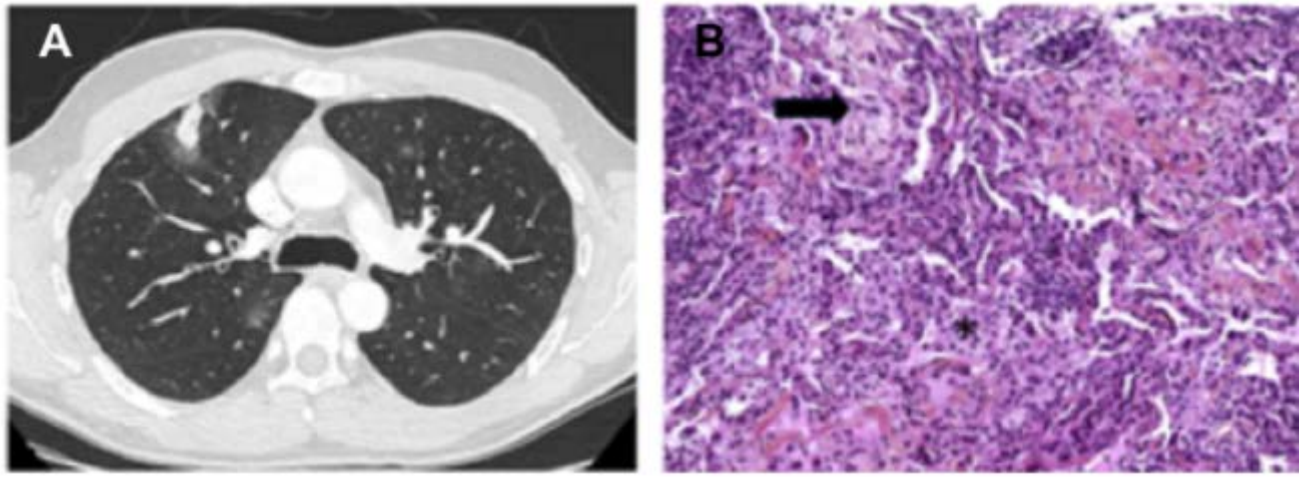
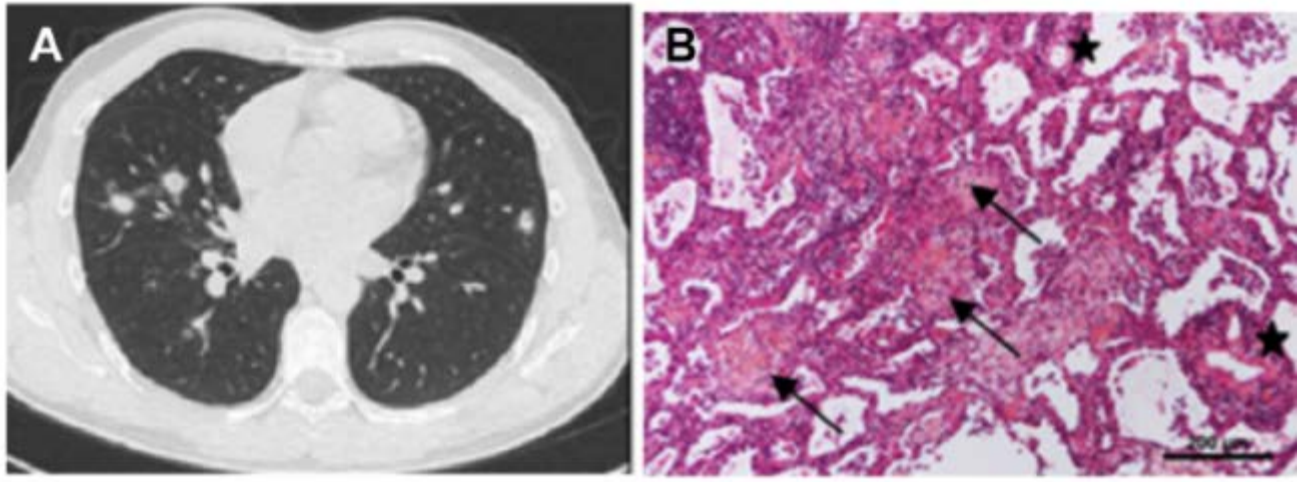
ICPI, immune checkpoint inhibitor.
Image from Pradère et al. Eur J Cancer 2018;93:144–6.

This is not disease progression!!!



BOOP



Pneumonitis

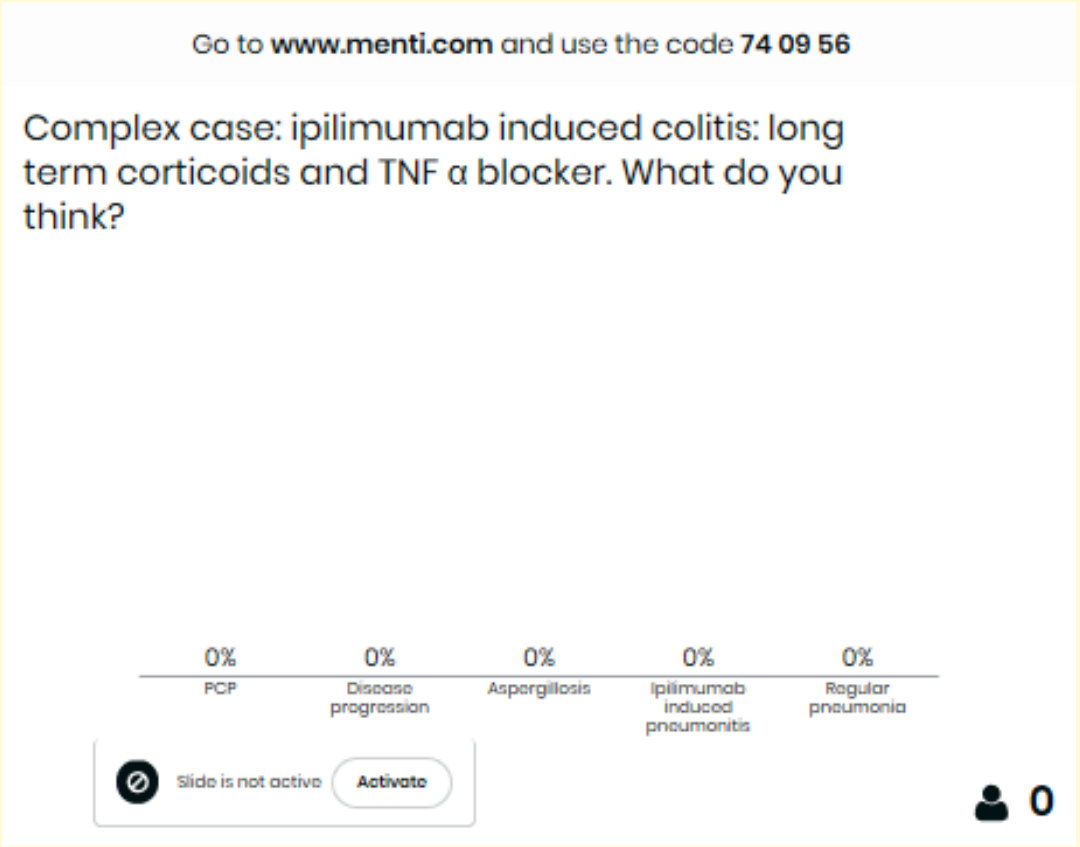
Pradère et al. Eur J Cancer 2018;93:144–6.

Complex case: ipilimumab induced colitis: corticoids and TNFα blocker. What do you think?

- Ipilimumab induced pneumonitis
- Aspergillosis
- PCP
- Disease progression
- Regular pneumonia

PCP, pneumocystis jirovecci pneumonia

Complex case: ipilimumab induced colitis: corticoids and TNFα blocker. What do you think?



PCP, pneumocystis jirovecci pneumonia

Complex case

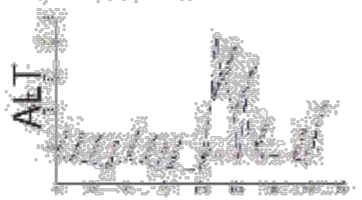
Melanoma thumb R
Breslow 1.8 mm
Clark IV
amputation +
Inn resection: neg

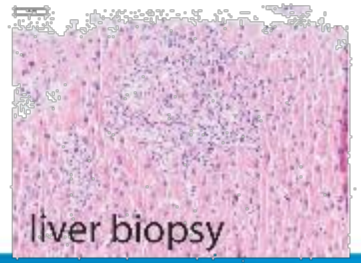
oct 2016

April 2018
start Nivolumab
start gamma knife

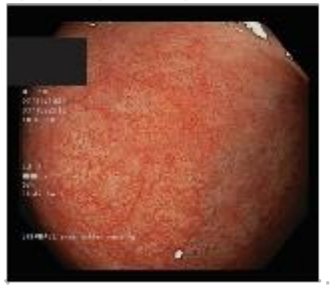
July 2018
stop Nivolumab
start Ipilimumab

Aug 2018
stop Ipilimumab (2),
start steroids





Sept 2018
steroid taper
nausea & diarrhea G3
steroids increased
and TNFblocker



colon biopsy: colitis

Oct 2018
steroid taper (16mg)
cough and dyspnea
2weeks high dose bactrim

Nov 2018

Can we rechallenge patients with immune checkpoints after an irAE?

1. Never
2. Depends of type and severity of toxicity
3. Ipilimumab induced colitis: no problem

irAE, immune-related adverse event

Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients

Myriam Delaunay[1], Jacques Cadranel[2], Amélie Lusque[3], Nicolas Meyer[4], Valérie Gounaut[5], Denis Moro-Sibilot[6], Jean-Marie Michot[7], Judith Raimbourg[8], Nicolas Girard[9], Florian Guisier[10], David Planchard[11], Anne-Cécile Metivier[12], Pascale Tomasini[13], Eric Dansin[14], Maurice Pérol[15], Marion Campana[16], Oliver Gautschi[17], Martin Früh[18], Jean-David Fumet[19], Clarisse Audigier-Valette[20], Sébastien Couraud[21], Stéphane Dalle[22], Marie-Thérèse Leccia[23], Marion Jaffro[24], Samia Collot[24], Grégoire Prévot[1], Julie Milia[1] and Julien Mazieres[1]

Evolution and recurrence of gastrointestinal immune-related adverse events induced by immune checkpoint inhibitors

Alice de Malet [a], Guillemette Antoni [b], Michael Collins [a,c], Emilie Soularue [a,c], Lysiane Marthey [a], Thibaut Vaysse [a], Clelia Coutzac [d], Nathalie Chaput [d,e], Christine Mateus [f], Caroline Robert [f], Franck Carbonnel [a,c,*]

Pneumonitis: restarted in 10 pts: 7 had no toxicity

Colitis: restarted in 26 pts: 71% (anti-CTLA4) and 95% (anti-PD1) had no recurrence of toxicity

1. Delaunay et al. Eur Respir J 2017;50:

Questions about immune-related adverse events[1]

Can we rechallenge after iRAE?

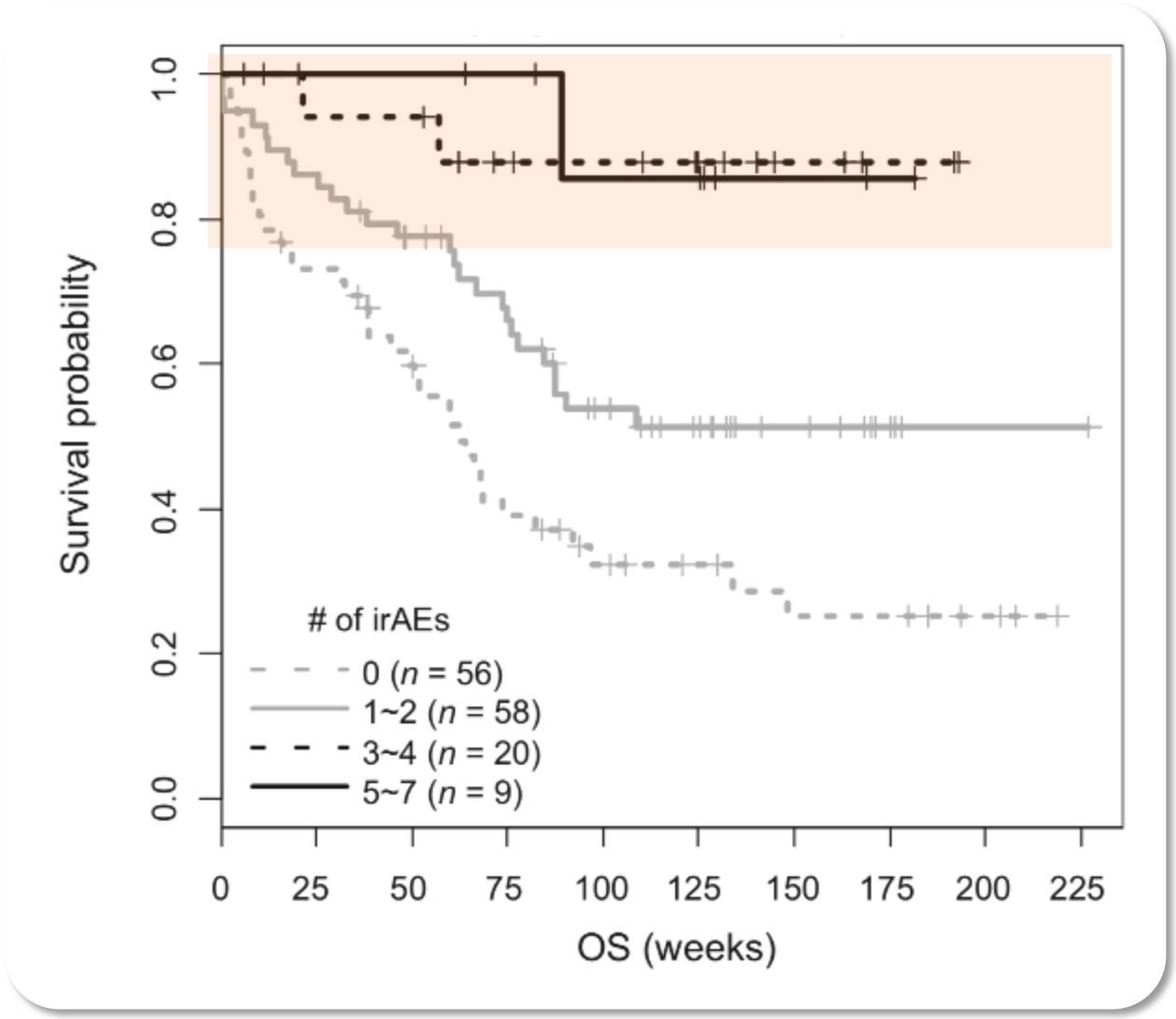
- Depends on type and severity
- Depends on the tumor response (CR vs SD?)
- Multidisciplinary discussion
- Clear communication with the patient

1. Postow et al. NEJM 2018;378;158–68.

Do patients experiencing toxicity have a better prognosis?

- Yes
- No
- Sometimes

Good news



Freeman-Keller et al. Clin Cancer Res 2016;22:886–94.

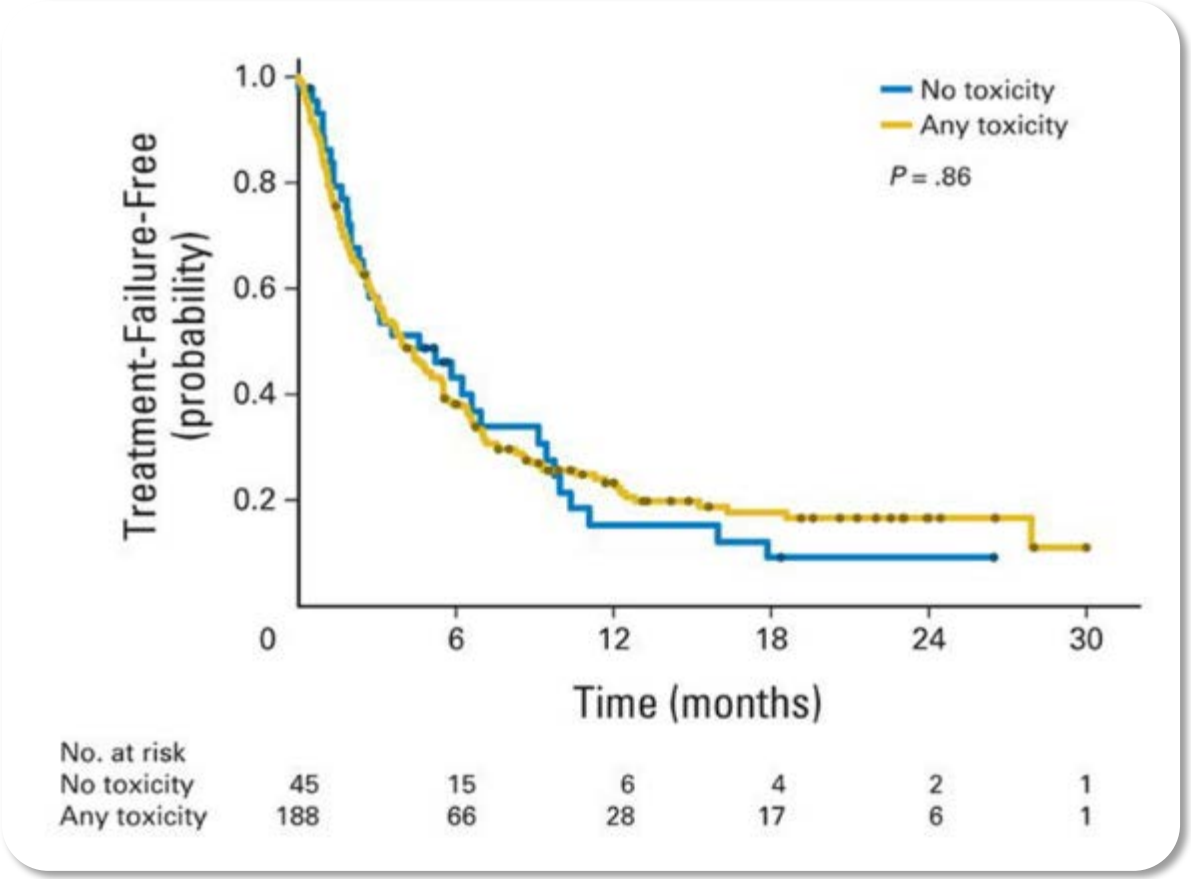
Does corticoid treatment affect long term outcomes?

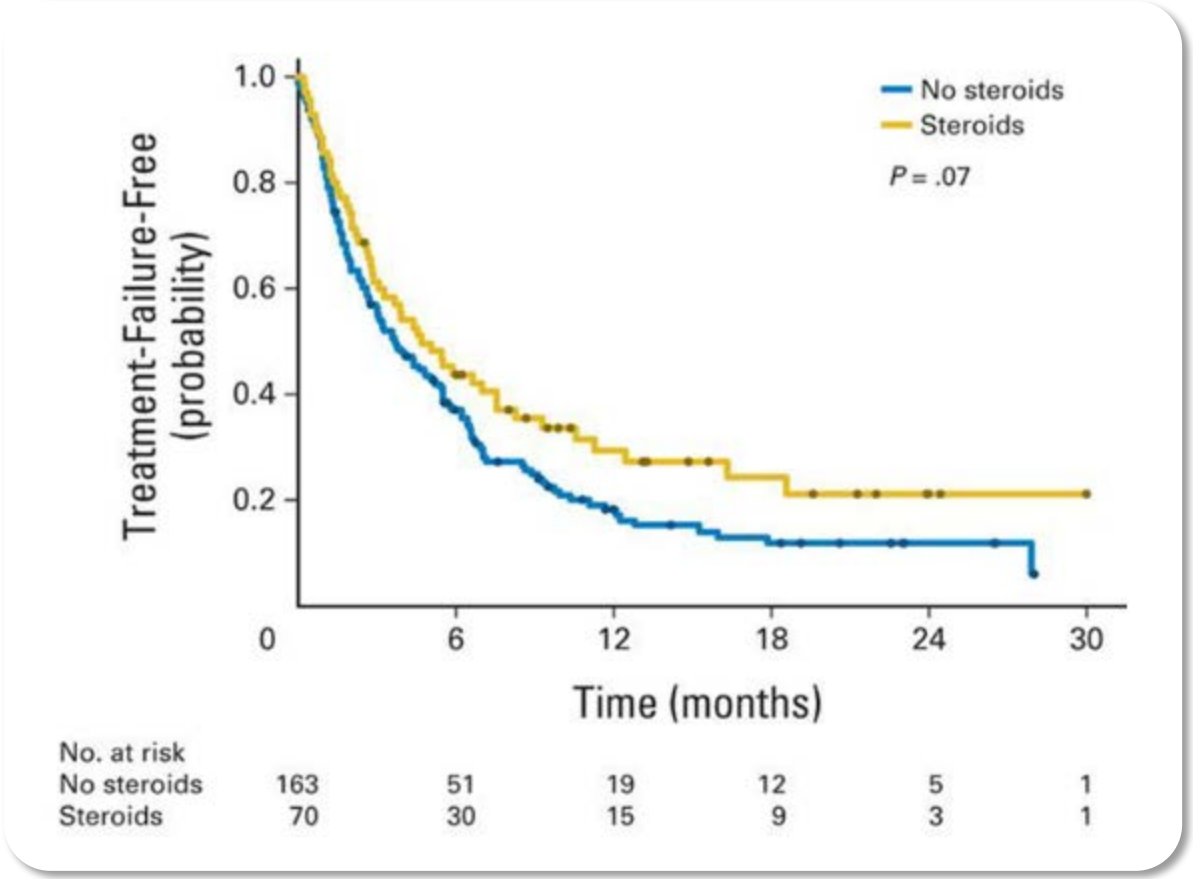
- Probably not
- Probably
- Definitely

ICPI, immune checkpoint inhibitor.

Quid effect corticoids?

Single center retrospective study[1]





1. Horvat et al. J Clin Oncol 2015;33:3193–8.

Is quality of life affected by irAEs?

1. Yes
2. No
3. Some symptoms like pruritis affect quality of life
4. It remains to be investigated

irAE, immune-related adverse event

Melanoma metastatic setting

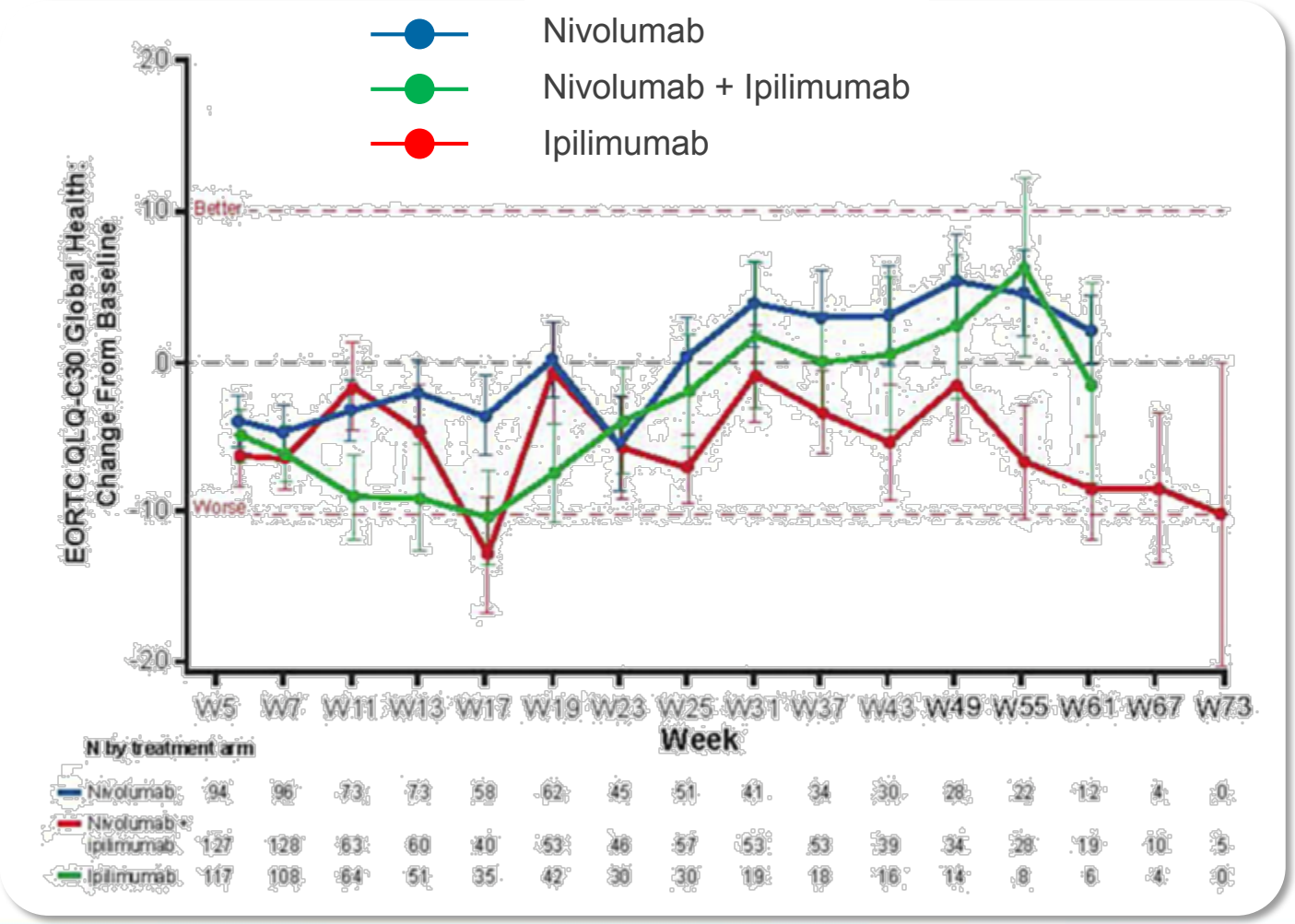
- **Keynote-002:** pembrolizumab vs CT (ipilimumab R): QLQ-C30: HRQoL better maintained for pembrolizumab vs CT (-2.6 vs -9.1 p=0.01)[1]
- **Keynote-006:** pembrolizumab vs ipilimumab (1st or 2nd line): QLQ-C30, EQ-5D-3L: HRQoL acc to both scales better maintained for pembrolizumab Q2W vs ipilimumab (-2.5 vs -10.0 p<0.001)[2]
- **Checkmate 067:** nivolumab + ipilimumab vs nivolumab vs ipilimumab 1st line: QLQ-C30, EQ-5D-3L: no difference between 3 groups and Grade 3/4 AE: no clinical meaningful differences in HRQoL[3]
- **Checkmate 066:** nivolumab vs dacarbazine 1st line QLQ-C30, EQ-5D-3L HRQoL for nivolumab maintained, after week 13: high attrition rate for CT[4]

EQ-5D, European Quality of Life-5 Dimensions; HRQoL, health-related quality of life; QLQ-C, Quality-of-Life Questionnaire-Core

1. Schadendorf et al. Eur J Cancer 2016;67:46–54. 2. Petrella et al. Eur J Cancer 2017;86:115–24. 3. Schadendorf et al. Eur J Cancer 2017;82:80–91. 4. Long et al. Ann Oncol 2106;

Checkmate 067: nivolumab + ipilimumab vs nivolumab vs Ipilimumab 1st line[1]

Sub analysis of patients with grade 3/4 toxicities



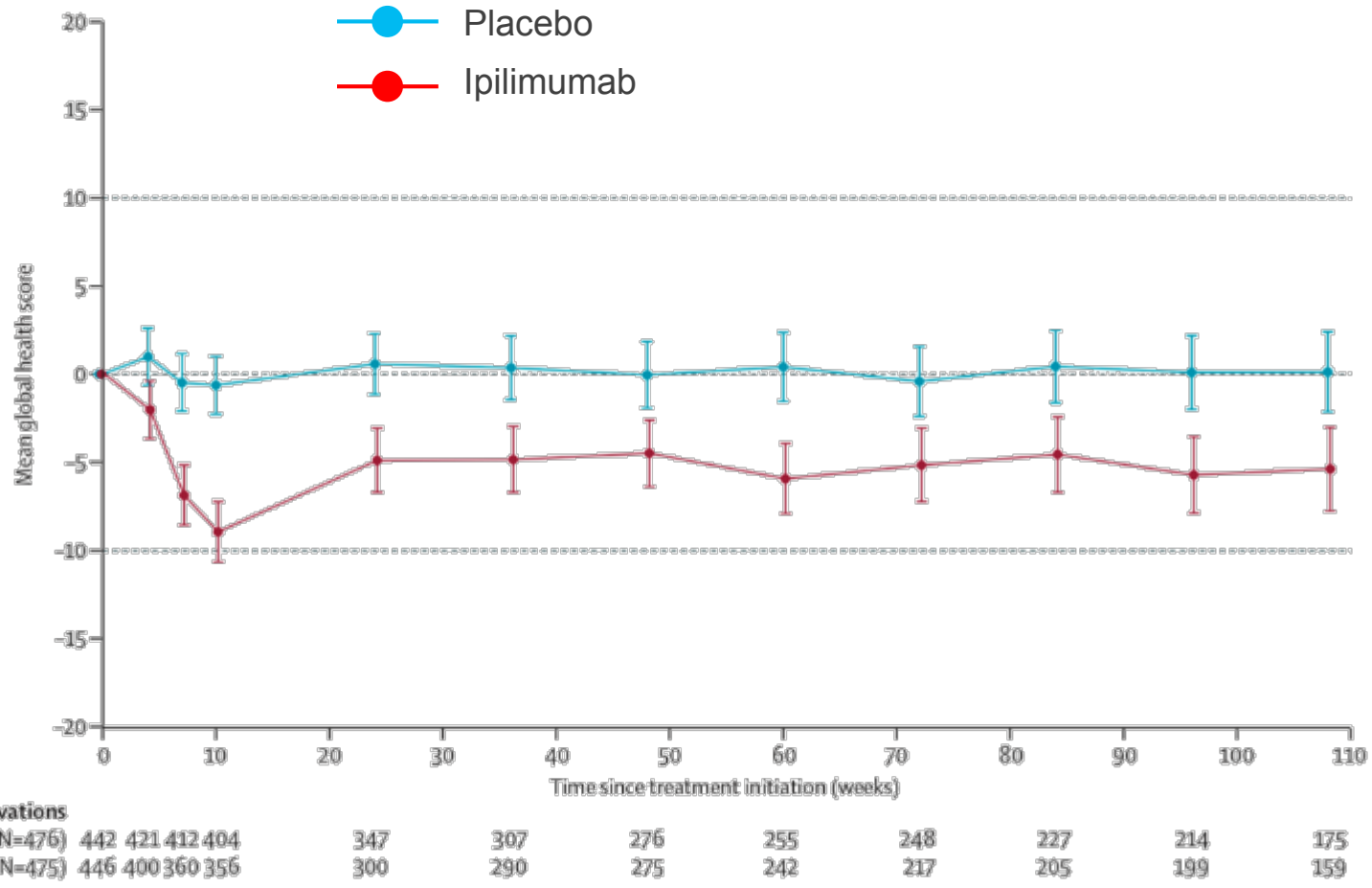
QLQ-C30

1. Schadendorf et al. Eur J Cancer 2017;82:80–91.

Melanoma adjuvant setting: ipilimumab vs placebo[1]

After 4 cycles of ipilimumab: no significant differences in HRQoL?

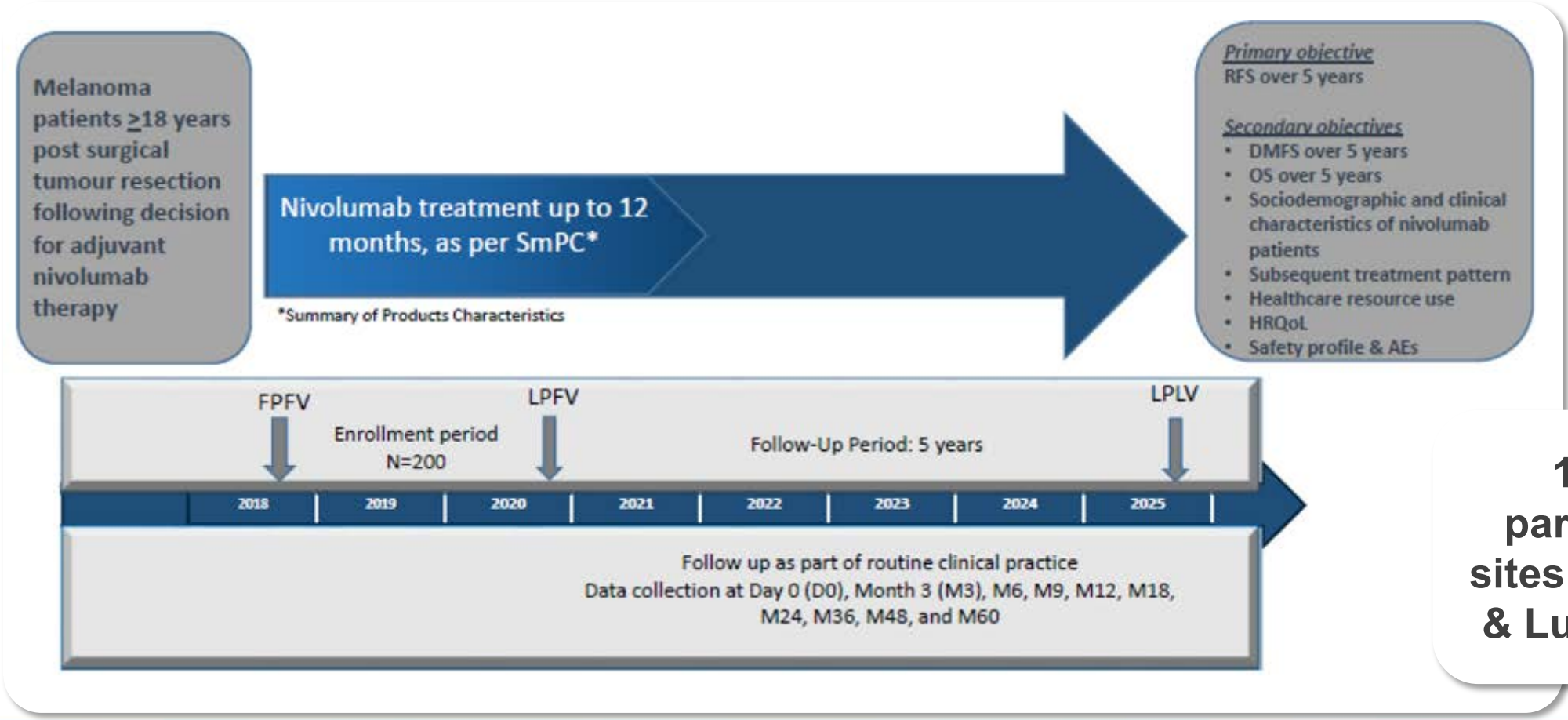
QLQ-C30



1. Coens et al Lancet Oncol 2017;18:393-403.

CA209-8RX: Adjuvant nivolumab real-world evidence study

A Belgian national, prospective, therapeutic non-interventional clinical trial in patients receiving adjuvant nivolumab for resected melanoma

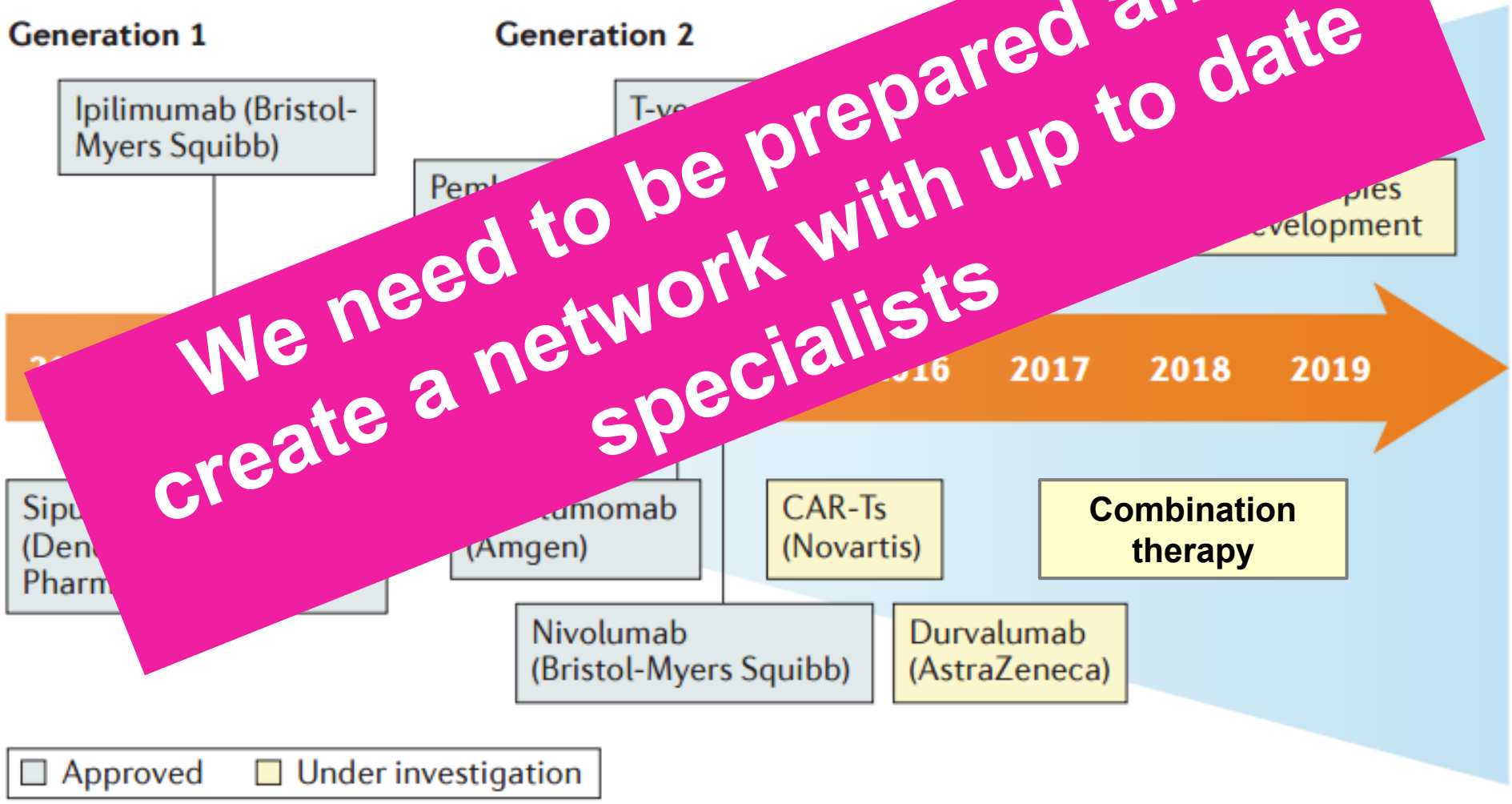


PRO:
QLQ-C30
FACT-M

12 to 15 participating sites in Belgium & Luxembourg

FACT-M, Functional Assessment of Cancer Therapy - Melanoma

Future of immunotherapy



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

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

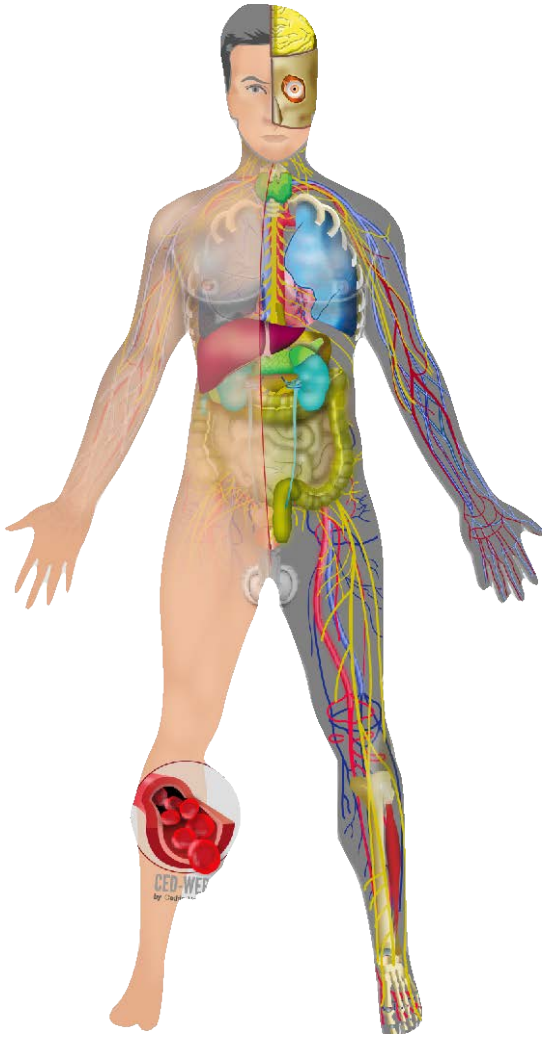
Future perspectives: how to handle irAEs

Immunotoxicity board

Great collaboration with KBVR/SRBR and BNS

BSMO Immunotaskforce

Translational Research



A register would be great ☺

Clinical Care Path for dysimmunity patients

ENSEIGNEMENTS IMMUNO-ONCOLOGIE

Prospective analysis of autoimmune serology

Image: Champiat et al. Ann Oncol 2016;27:559–74.

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