Gestion des effets immunologiques indésirables des immune checkpoint inhibiteurs

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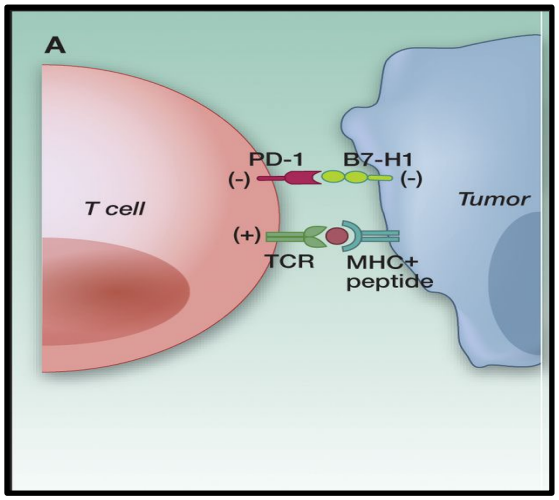
Mise au point 05/11/2021

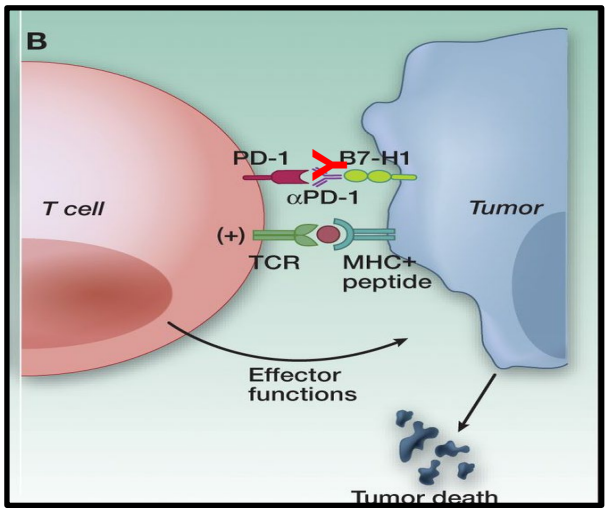
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Role des Immune check point bloqueurs = bloquer l'interaction negative T-cell <-> tumor

EXAUSTION

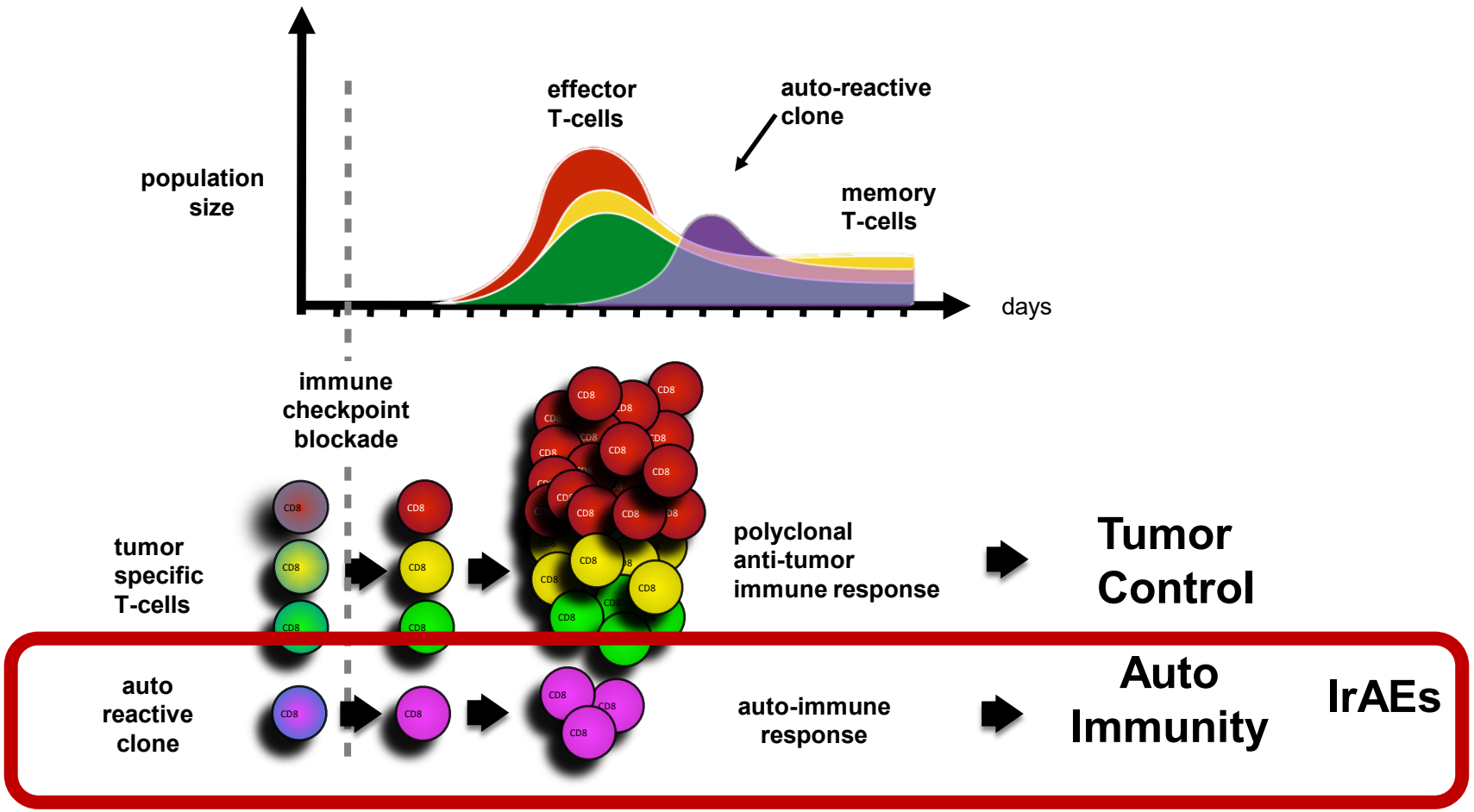
ACTIVATION





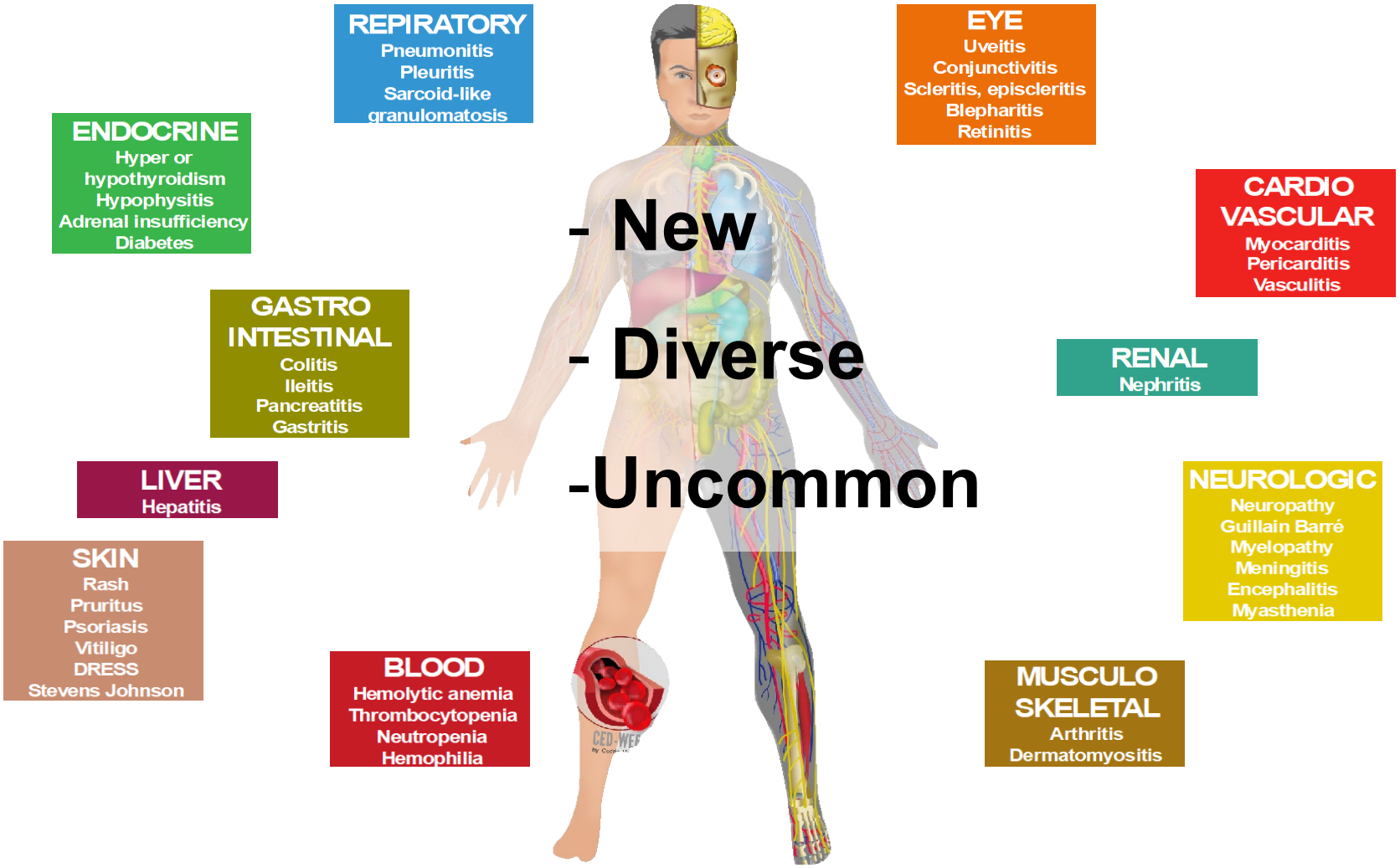
Sznol M , and Chen L Clin Cancer Res 2013;19:1021-1034

Kinetic of T-cell responses



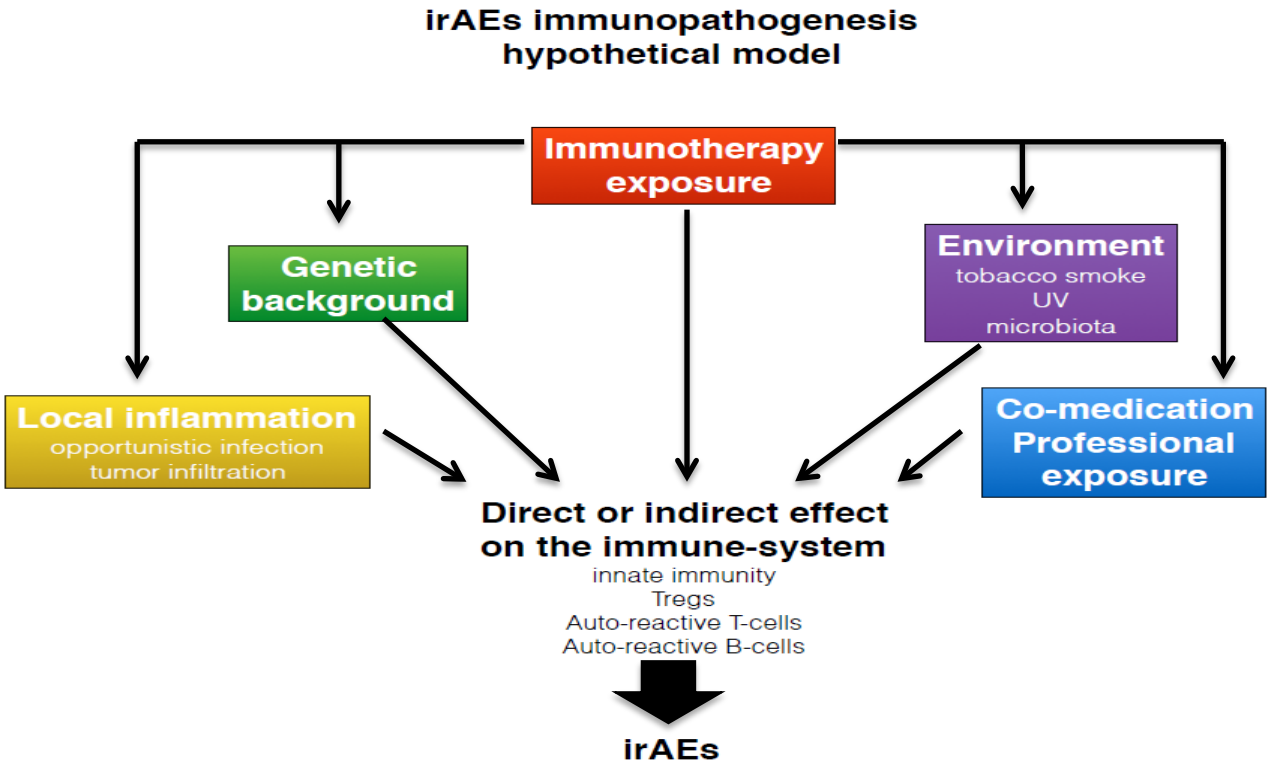
It’s not about the frequency…

It’s not about the frequency…**it’s about diversity !**

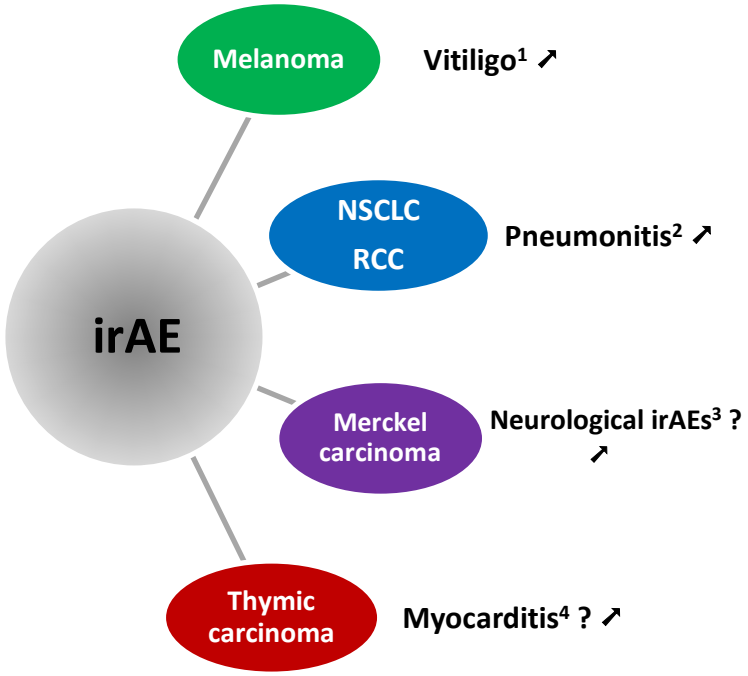


Champiat et al. (2016). Management of Immune Checkpoint Blockade Dysimmune Toxicities: a collaborative position paper. *Annals of Oncology*

Immunotherapy irAEs
Immunopathogenesis hypothetical model

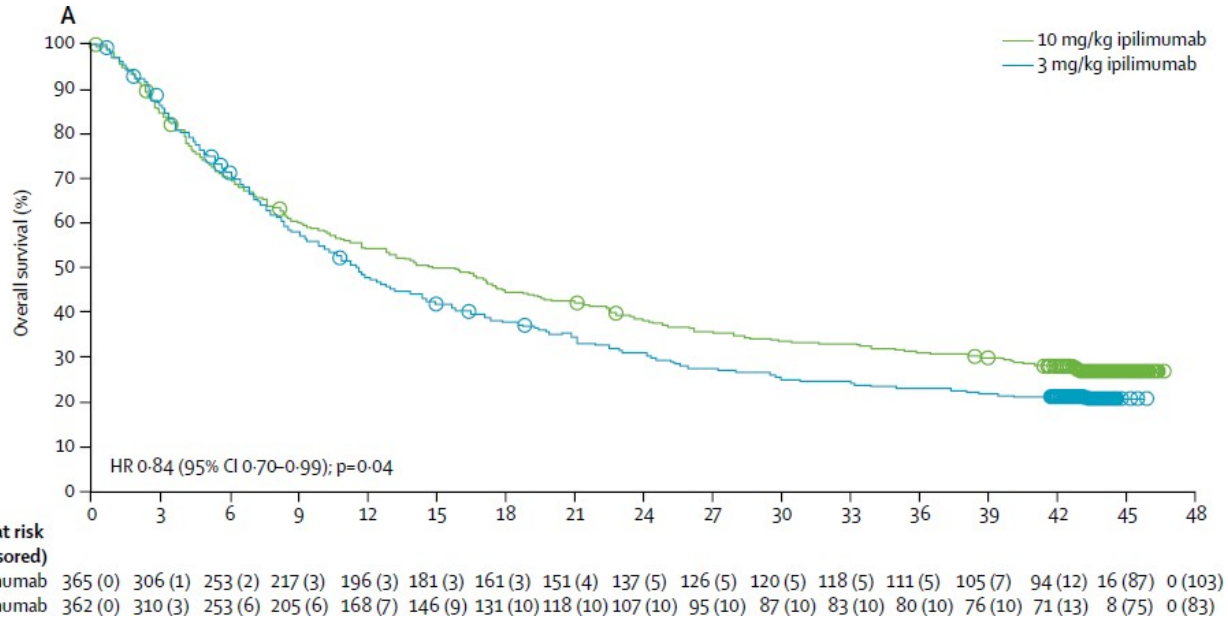


To keep in mind some iTOX specificities for each tumor type



1- M Postow, NEJM 2018; 2- Nishino, Jama Oncol, 2016; 3- S D'Angelo, JAMA oncol, 2018; 4-Giaccone G, Lancet Oncol, 2018

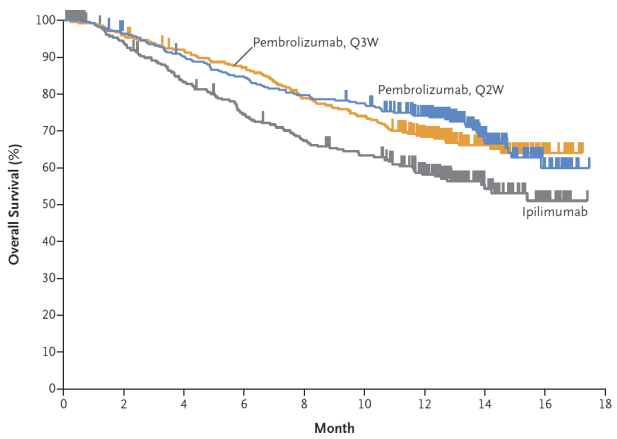
Anti-CTLA-4: Dose/Efficacy/Toxicity Correlation = yes !

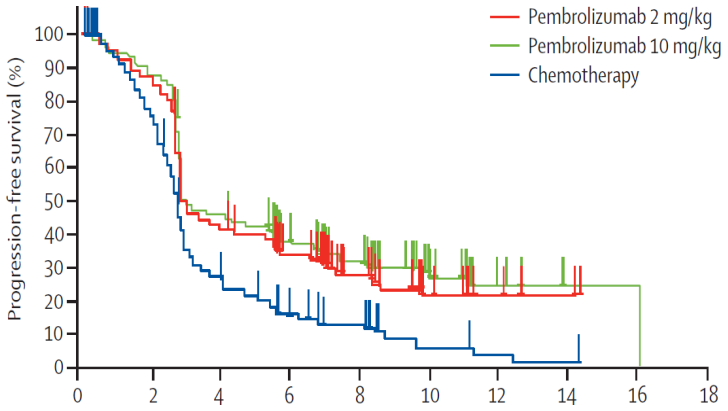


	Ipilimumab 10 mg/kg (n=364)			Ipilimumab 3 mg/kg (n=362)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	162 (45%)	99 (27%)	25 (7%)	162 (45%)	57 (16%)	9 (2%)

Ascierto et al. (2017). Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. *The Lancet Oncology*.

Anti-PD-1/PD-L1: dose/Efficacy/Toxicity Correlation = no !





Robert C, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372:2521–32.

Ribas A, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;

Adverse Event	Pembrolizumab Every 2 Wk (N = 278)		Pembrolizumab Every 3 Wk (N = 277)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)			
Related to treatment*				
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)

	Pembrolizumab 2 mg/kg (n=178)			Pembrolizumab 10 mg/kg (n=179)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Summary						
Any	101 (57%)	18 (10%)	1 (<1%)	107 (60%)	23 (13%)	2 (1%)
Serious*	3 (2%)	9 (5%)	1 (<1%)	3 (2%)	14 (8%)	2 (1%)
Led to discontinuation†	0	3 (2%)	1 (<1%)	2 (1%)	9 (5%)	1 (<1%)

Is there an ASSOCIATION BETWEEN IMMUNE-RELATED ADVERSE EVENTS AND EFFICACY ? Probably yes but TRICKY and not changing the outcome

Phase 3 Melanoma experience with Nivolumab

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

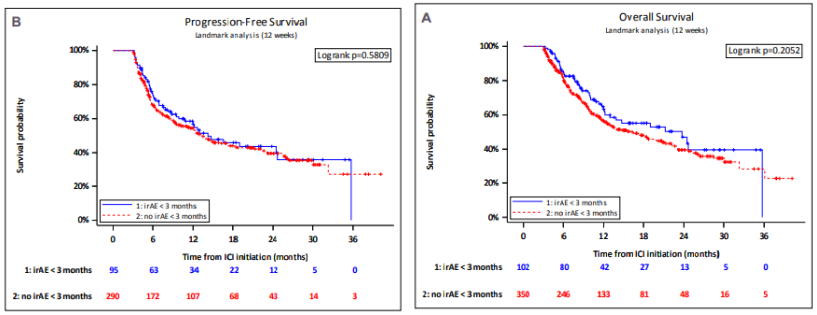
		Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
	All Patients (N = 576)	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.
†Versus no treatment-related select AEs.

irAEs are associated with higher ORR

Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma (N=576)
Weber et al. , JCO 2016

Phase 4 Gustave Roussy experience with Anti-PD1 in pharmacovigilance REISAMIC registry



Kfoury M, ESMO 2018

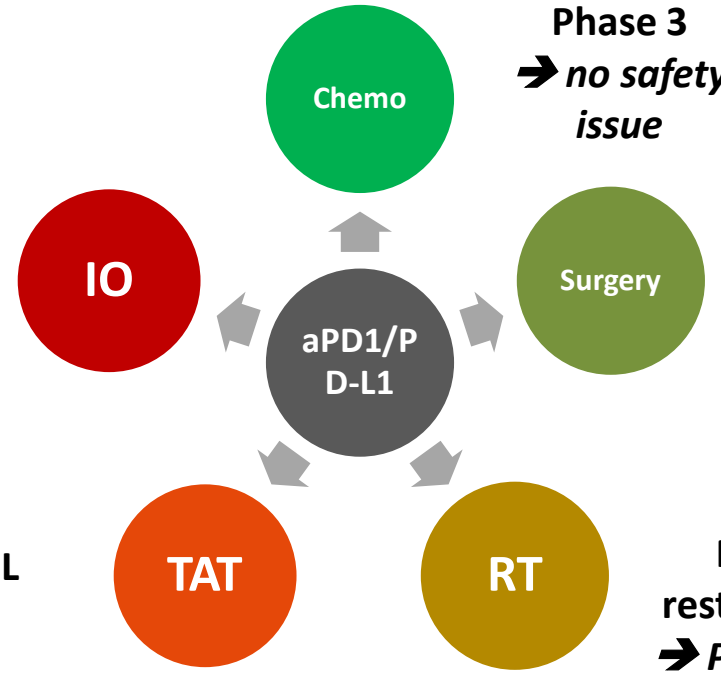
Anti PD-1 vs chemotherapy
Nivolumab vs docetaxel in NSCLC

	Nivolumab n = 287	Docetaxel n = 268
All Grade AEs, any cause	98%	99%
Treatment-related AEs	69%	88%
Grade 3-4 AEs, any cause	46%	67%
Treatment-related Grade 3-4 AEs	10%	54%
Grade 5 AEs, any cause	8%	5%
Patients withdrawing from treatment due to AEs	5%	15%

Treatment-related Grade 5 events
Nivolumab (n = 1): encephalitis (causality was changed after the database lock)
Docetaxel (n = 1): febrile neutropenia

Borghaei et al. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. *NEJM*

To situate iTOX in the context of multiple oncological treatments



Phase 3 IO-IO combo
➔ *Escalated iTOX*

Phase 3
➔ *no safety issue*

Phase 3 ongoing
➔ *no safety issue*

Phase 3 (PACIFIC) and restrospective data analysis
➔ *Possible « recall effect » ?*

Phase 3 with:
- 😣 EGFR inh in NSCLC
- 😟 BRAF inh / MEK inh in MEL
- 🙂 AG in RCC

➔ *Depending of the targeted agent*
➔ *Increase of iTOX symptoms*

Surround yourself with a team and network

1- Management of the iTOX in connection with a network of organs specialists

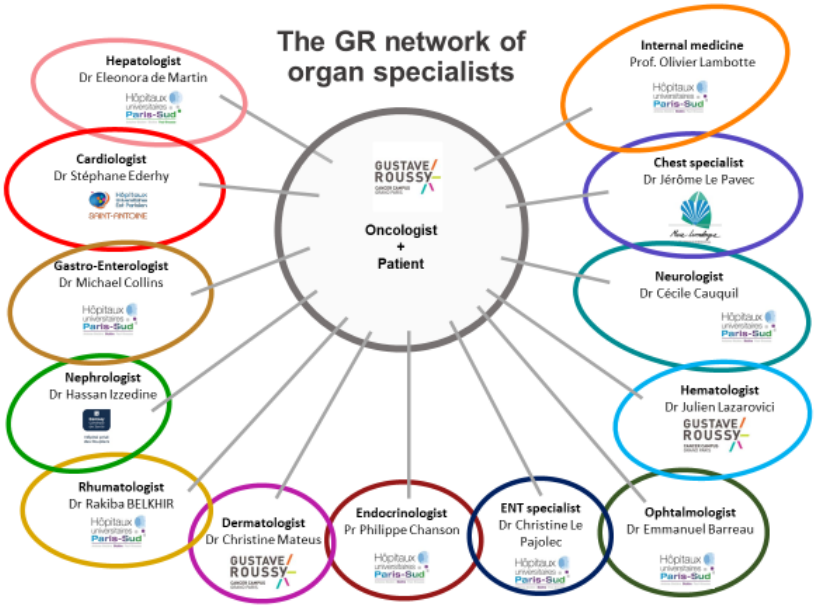
2- Discuss **a contraindication** to immunotherapy

3- Discuss **a rechallenge** to immunotherapy

4- Continuing Medical Education
And improvement of guidelines

5- Pharmacovigilance
ITOX News - REISAMIC Report

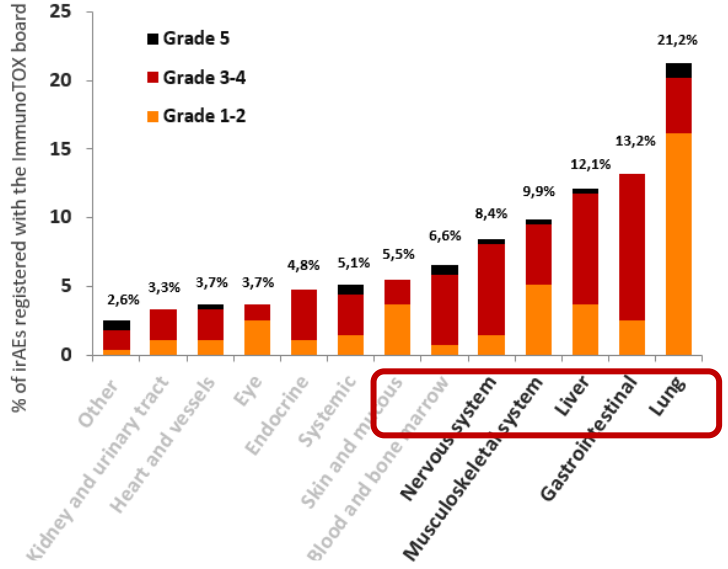
iTOX comittee



Michot JM and Al, The 2019 ImmunoTOX Assessment Board report, EJC 2020

Estimate the medical need by the organs involved in ITOX

Distribution of irAE organ categories by the immunoTOX assessment board



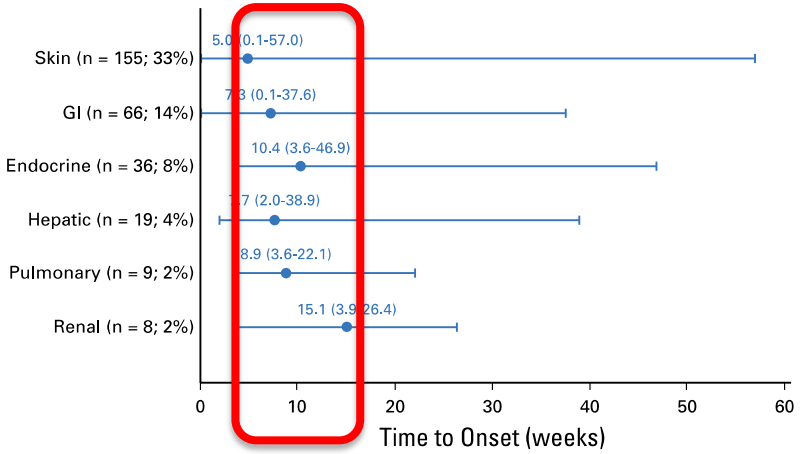
4 organs = 65% of iTOX advices

- **Lung**
- **Digestive tract**
- **Liver**
- **Neuromuscular system**

Michot JM and Al, The 2019 ImmunoTOX Assessment Board report, *EJC 2020*

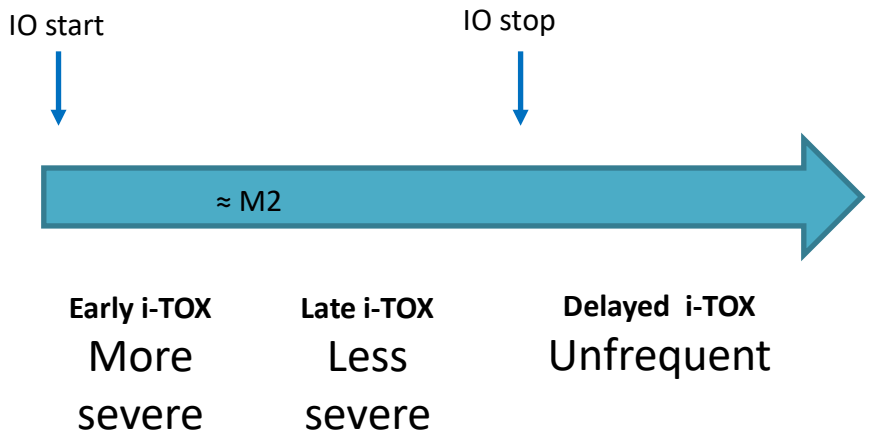
Diagnose an inTOX at the right time

Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma (N=576)[1]



10 weeks is the « warning zone »

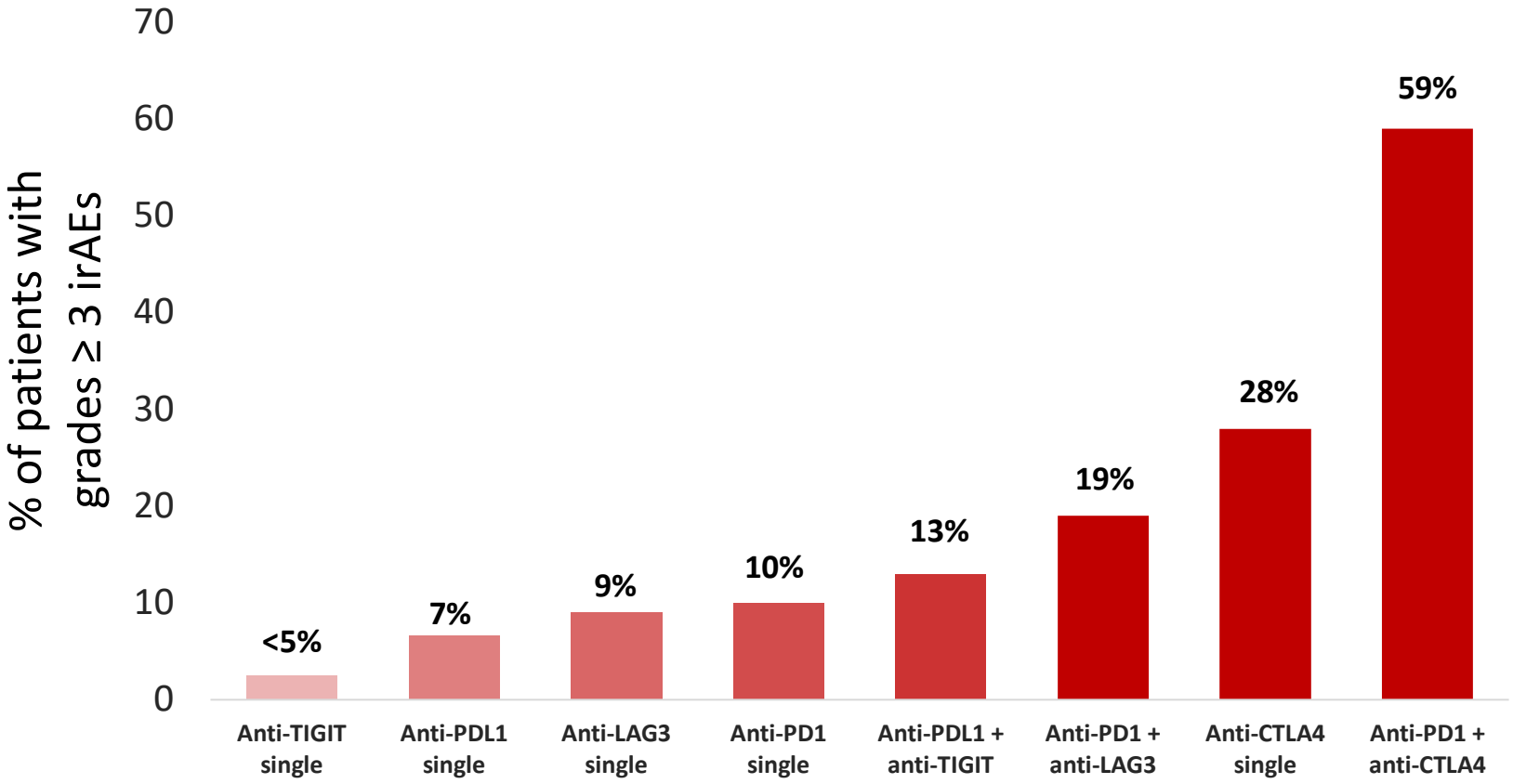
Different iTOX depending on the exposure time[2]



1- Weber et al., JCO 2016

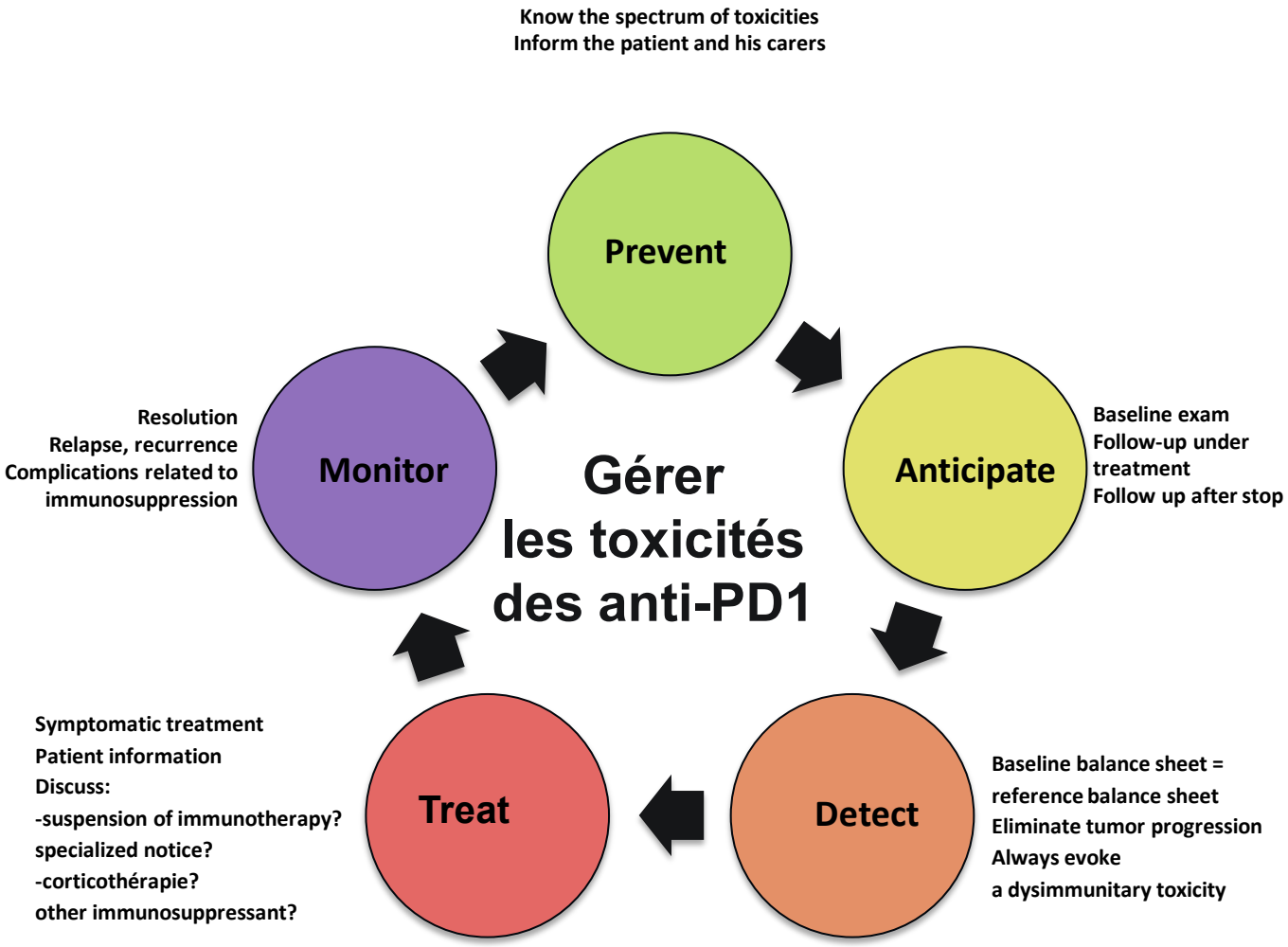
2- Michot JM and al., work in progress

Incidence des immunotoxicités selon les principaux régimes d'immune checkpoint blockers



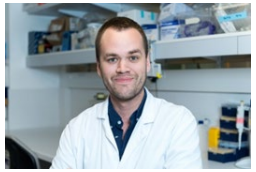
Bendell J, AACR 2020, abstract CT302	Herbst R, NEJM 2020	Lipson E, SITC 2016, abstract P232	Weber J, JCO, 2016	Rodriguez-Abreu D, ASCO 2020, abstract 9503	Lipson E, ASCO 2021, abstract 9503	Hodi F, Lancet oncol 2018	Hodi F, Lancet oncol 2018

Safe usage of IO : 5 rules



Champiat et al. (2015). Management of Immune Checkpoint Blockade Dysimmune Toxicities: a collaborative position paper. *Annals of Oncology*

To start and monitor immunotherapy in a patient with comorbidities ?



The immunological "heat" of comorbidities

"Cold" comorbidities

- ✓ Cardiovascular
- ✓ Renal failure
- ✓ Pulmonary emphysema
- ✓ Post-therapeutic neuropathies…

"Hot" comorbidities

- ✓ Immune-allergic diseases
- ✓ Auto-inflammatory disease
- ✓ Organ transplant
- ✓ Autoimmune diseases
- ✓ Paraneoplastic syndromes

Anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease[1]

Higher risk of irAE	No impact in OS

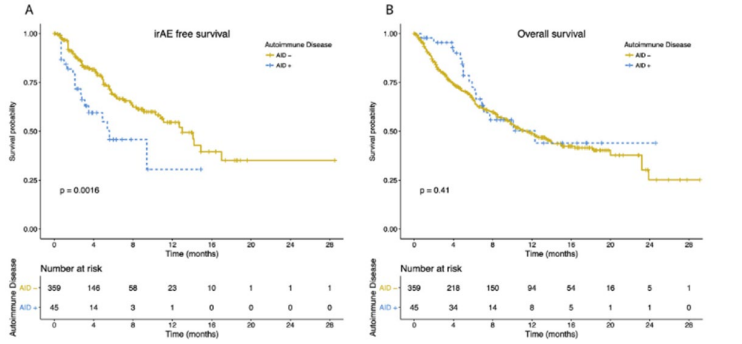


Fig. 2. **Outcomes in REISAMIC patients: irAE-free survival and OS.** A. Kaplan–Meier plots for irAE-free survival, which was shorter in AID patients (median: 5.4 months) than in AID-free patients (median: 13 months; $p = 2.1 \times 10^{-4}$ in a log-rank test). B. Kaplan–Meier plots for OS: the difference between AID and AID-free patients was not significant ($p = 0.38$ in a log-rank test).

1- Danlos FX, Europ. Journal of Canc., 2018

how to start and monitor immunotherapy in a patient with comorbidities ?

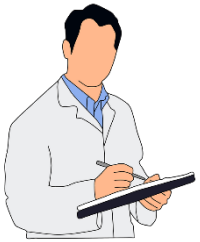
Double CHECK

Before to start IO

- OK controlled and stable underlying autoimmune condition (inactive)?
- OK organ specialist to start IO?
- OK treatment plan in case of flare-up ?
- OK patient information and care-givers?

Double MONITOR

During IO therapy



Oncologist

+

Organ specialist

➔ **Consider a case-by-case approach for autoimmune comorbidities, and regard preferably as a use precaution and not systematically contra-indication**

resume an IO after a previous iTOX if the patient can benefit.

Key Points

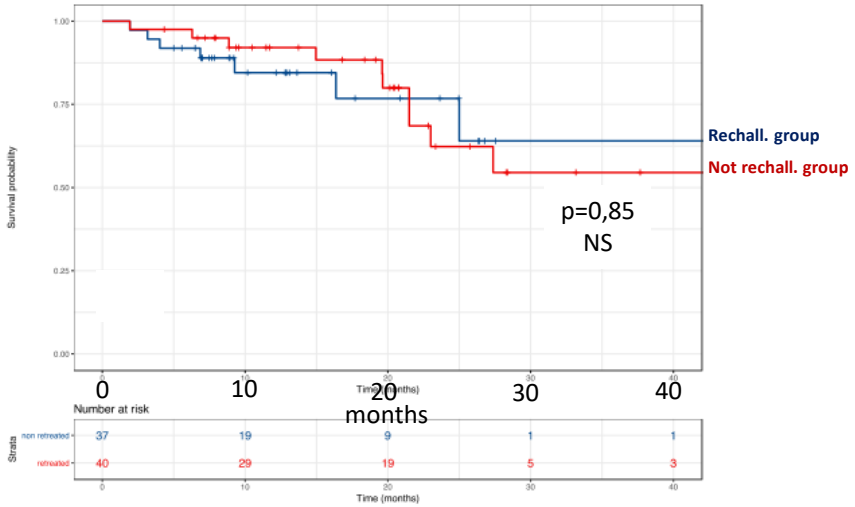
Question After a grade 2 or higher immune-related adverse event, is an anti–PD-1 or anti–PD-L1 inhibitor rechallenge safe?

Findings In this cohort study of 93 French adults who experienced a grade 2 or higher immune-related adverse event and had an anti–PD-1 or anti–PD-L1 rechallenge, 55% experienced a second adverse event. Earlier initial toxic effect was associated with more frequent recurrence, and the second event was not as severe as the first.

Meaning The risk-reward ratio for anti–PD-1 or anti–PD-L1 rechallenge appears to be acceptable, although these patients require close monitoring; rechallenge conditions warrant further investigation in a prospective clinical trial.

Overall survival of patients who were rechallenged *versus* non-rechallenged[1].

(following iTOX G2 in 46% of cases or G3-4 in 54% of cases. Patients with tumor progression at time to selection were not included in the analysis).



1- Simmonagio A, JAMA Oncol, 2019

Know to resume an IO after a previous iTOX if the patient can benefit.

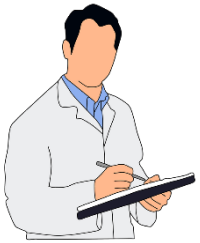
Double CHECK

Before to rechallenge IO

- **OK with not exist other consistent treatment option?**
- **OK on a pretreatment time not long enough (< 12 months)*?**
- **OK on an incomplete anti-tumor response?**
- **OK with recurrence of iTOX - if happened - would be manageable not exposing the patient to inconsiderate risk**
- **OK patient information and care-givers?**

Double MONITOR

During IO rechallenge



Oncologist

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Organ specialist

➔ **Consider a case-by-case approach for rechallenge over a grade ≥3, and regard preferably as a use precaution and not systematically contra-indication**

*12 months was choosen as an example and will have to be adapted for each histological type

For more informations
REFER to GUIDELINES

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

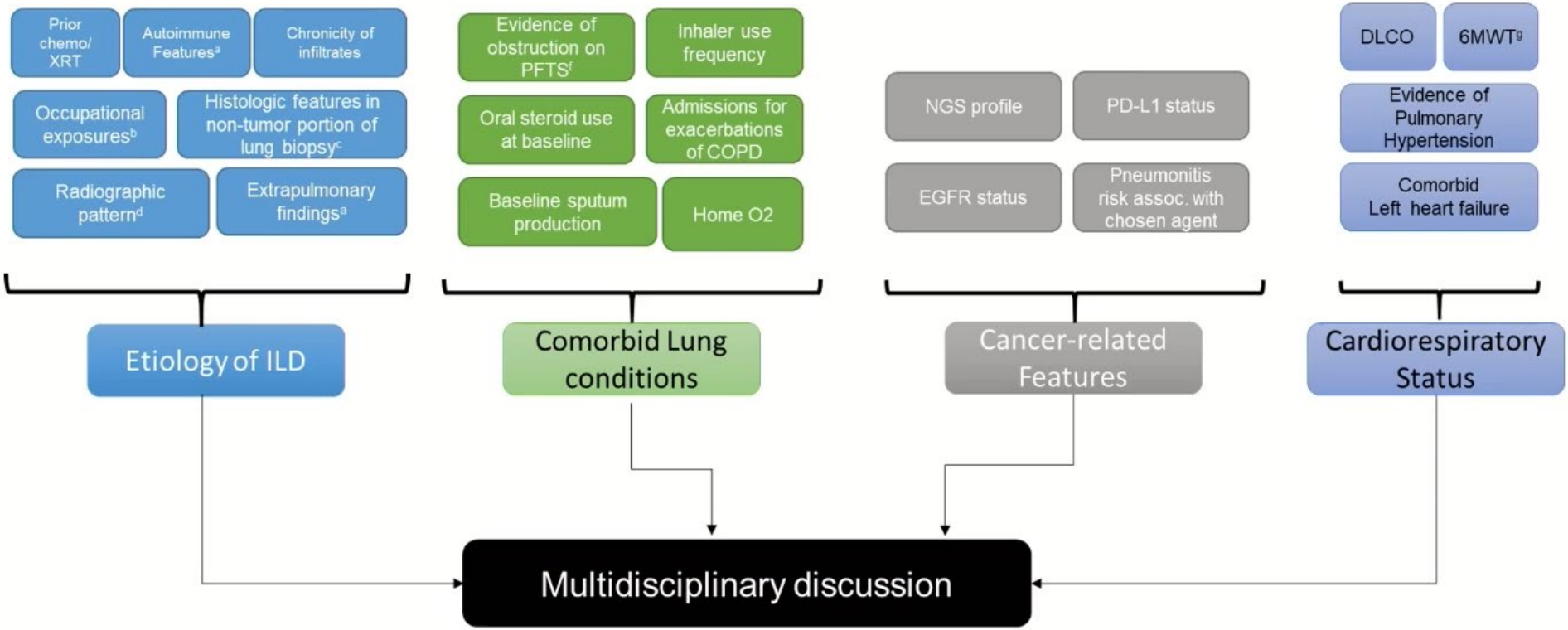
ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

Lung

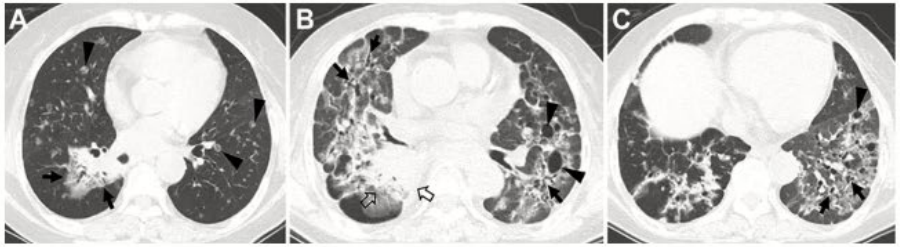
Pneumonitis
A Diagnosis of Exclusion



Naidoo, Suresh, *Oncologist 2020*.

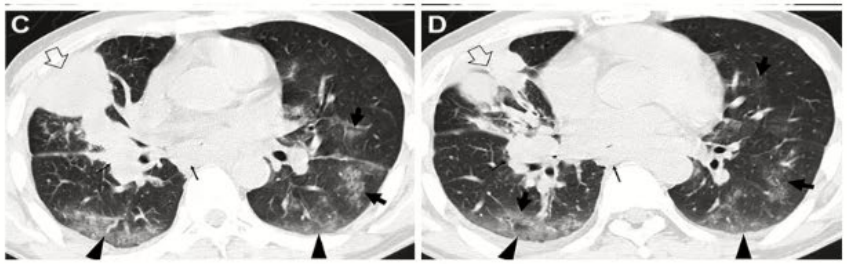
Pneumonitis
Fleishner Radiographic Criteria

NSIP Type



- Patchy areas of GGO
- Reticular opacities/architectural distortion, traction bronchiectasis
- +/- areas of consolidation;
- Bilateral, symmetric; lower-lung involvement

Organising Pneumonia Type

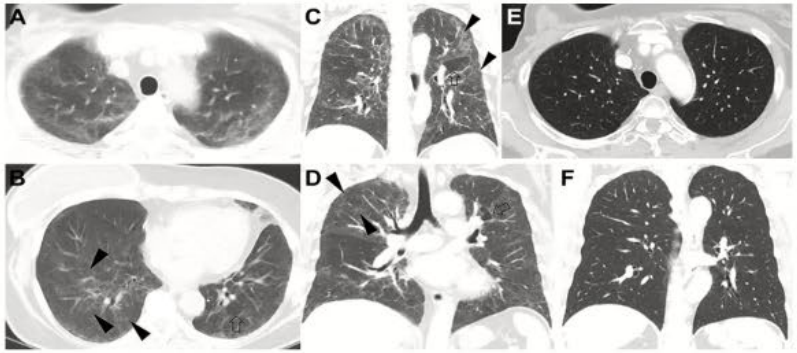


- Multifocal patchy alveolar opacities
- Peribronchovascular +/- peripheral
- Reversed halo sign

Johkoh et al, Chest 2021

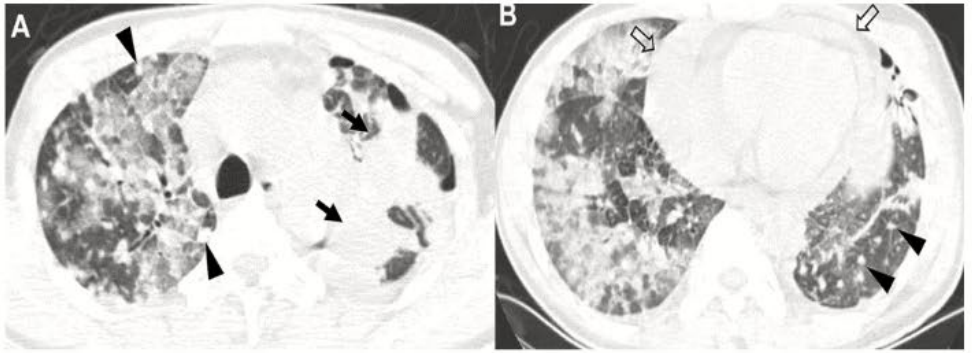
Pneumonitis
Fleishner Radiographic Criteria

Hypersensitivity Pneumonia



- Small centrilobular nodules
- Bilateral GGO
- Areas of decreased attenuation/ vascularity

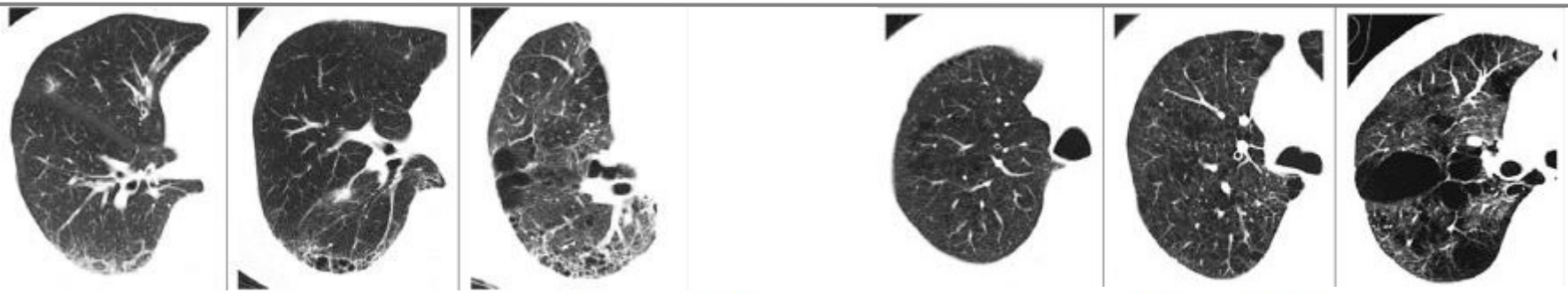
Diffuse Alveolar Damage



- Extensive bilateral GGOs
- airspace consolidation in exudative phase;
- traction bronchiectasis
- decreased lung volumes
- organizing and fibrotic phases

Johkoh et al, Chest 2021

Maladie pulmonaire pré-existante



		Univariate Model			Multivariate Model		
		OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
Age, years	≥65 vs. < 65	2.15	(0.71–8.01)	0.18			
Sex	Females vs. Males	0.27	(0.042–1.03)	0.057	0.58	(0.079–2.98)	0.53
Smoking status	Smoker vs. Never smoker	2.63	(0.69–17.35)	0.17			
Performance status	≥2 vs. 0 or 1	0.38	(0.020–2.11)	0.31			
Histology	Sq vs. Non-Sq	2.00	(0.63–5.81)	0.23			
Fibrosis score (0–5)	≥1 vs. 0	8.77	(2.99–29.69)	< **0.0001**	9.53	(2.47–44.79)	**0.0008**
Emphysema score (0–4)	≥1 vs. 0	2.89	(1.05–8.45)	**0.040**	0.68	(0.16–2.73)	0.58
Treatment line	First vs. ≥ Second	1.29	(0.34–4.09)	0.68			
LDH (IU/l)	≥240 vs. < 240	0.45	(0.12–1.34)	0.16			
CRP (mg/dl)	≥1 vs. < 1	0.67	(0.23–1.85)	0.44			

Yamaguchi T, Lung cancer, 2018

Diagnostic différentiel : place du LBA

	Pseudoprogression	Progression	Infection	Immune-related pneumonitis
Clinique	Asymptomatique	Symptomatique	Symptomatique	Symptomatique
Radiologie	Majoration de la tumeur initiale	Majoration de la tumeur initiale et apparition de nouvelle(s) lesion(s)	Syndrome interstitiel, syndrome alvéolaire, condensation	Syndrome interstitiel, pneumonie organisée, fibrose, condensation sarcoidosique
LBA	Lymphocytes, macrophages	Lymphocytes, macrophages, cellules malignes	Neutrophiles, pathogènes	Lymphocytes
Evolution sous corticoides	Diminution ou stabilité	Progression sous stabilité	Majoration	Diminution

Sympo ITOX 2018, IGR, Dr P Tomasini

Traitement pneumonitis

Grade of pneumonitis	Symptoms	Management
Grade 1	None	Delay treatment
	Radiographic changes only	Repeat imaging every 3 weeks
Grade 2	Mild to moderate	Delay treatment
	Dyspnea and cough	Consider admission to hospital
		Methylprednisolone IV 0.5–1.0 mg/kg/day
		Taper steroids over 1 month
		Repeat imaging in days to weeks
Grade 3–4	Severe	Delay treatment, consider permanent cessation
	Hypoxia	Admit to hospital or ICU
	Life-threatening respiratory	Methylprednisolone IV 2–4 mg/kg/day
	compromise	Consider additional immunosuppression at 48 hours
		Taper steroids over 6 weeks
		Repeat imaging in days to weeks

Chuzi S, Cancer Management and Research, 2017

Gastro-intestinal

Gastro-intestinal irAE

	Anti-CTLA-4	Anti-PD-1
Incidence of diarrhoea/colitis	30.2%/5.7%	12.1%/0.7%
Incidence of grade 3–4 diarrhoea/ colitis	7.4% / 4.1%	1%/0.4%
Immunopathological features	Predominance of colonic mucosal CD4+ T cells and high TNF-α secretion	Predominance of colonic mucosal CD8+ T cells
Time to onset after first infusion	1 month	2–4 months
Time to resolution of GI irAE	0.5–1.6 months	1.1–4.2 months
Response rate to corticosteroids	80%	80%

Soularue E, Gastroenterology, 2018

Entérocolite: présentation clinique

- Diarrhée et douleurs abdominales
- Rectorragies et fièvre
- Colites aiguës sévères parfois compliquées de déshydratation, megacôlon toxique, perforation (1% à 6.6% des patients) et décès, particulièrement en cas de retard diagnostic.

Entérocolite: présentation clinique

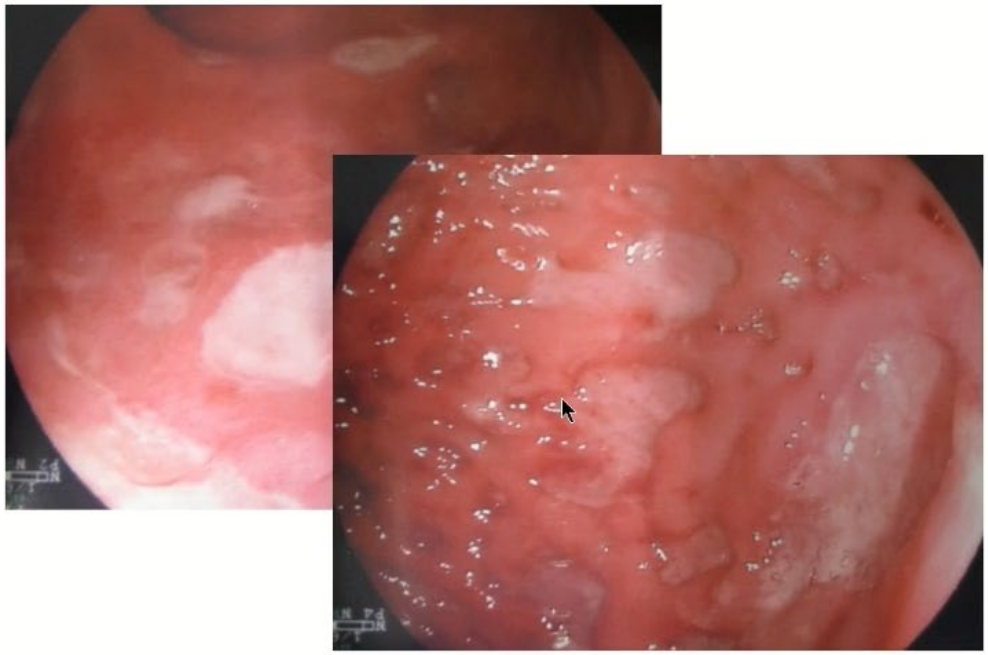
- Diarrhée et douleurs abdominales

Principaux diagnostics différentiels : infections, diverticulites, metastases intestinales (particularly from NSCLC and melanoma).

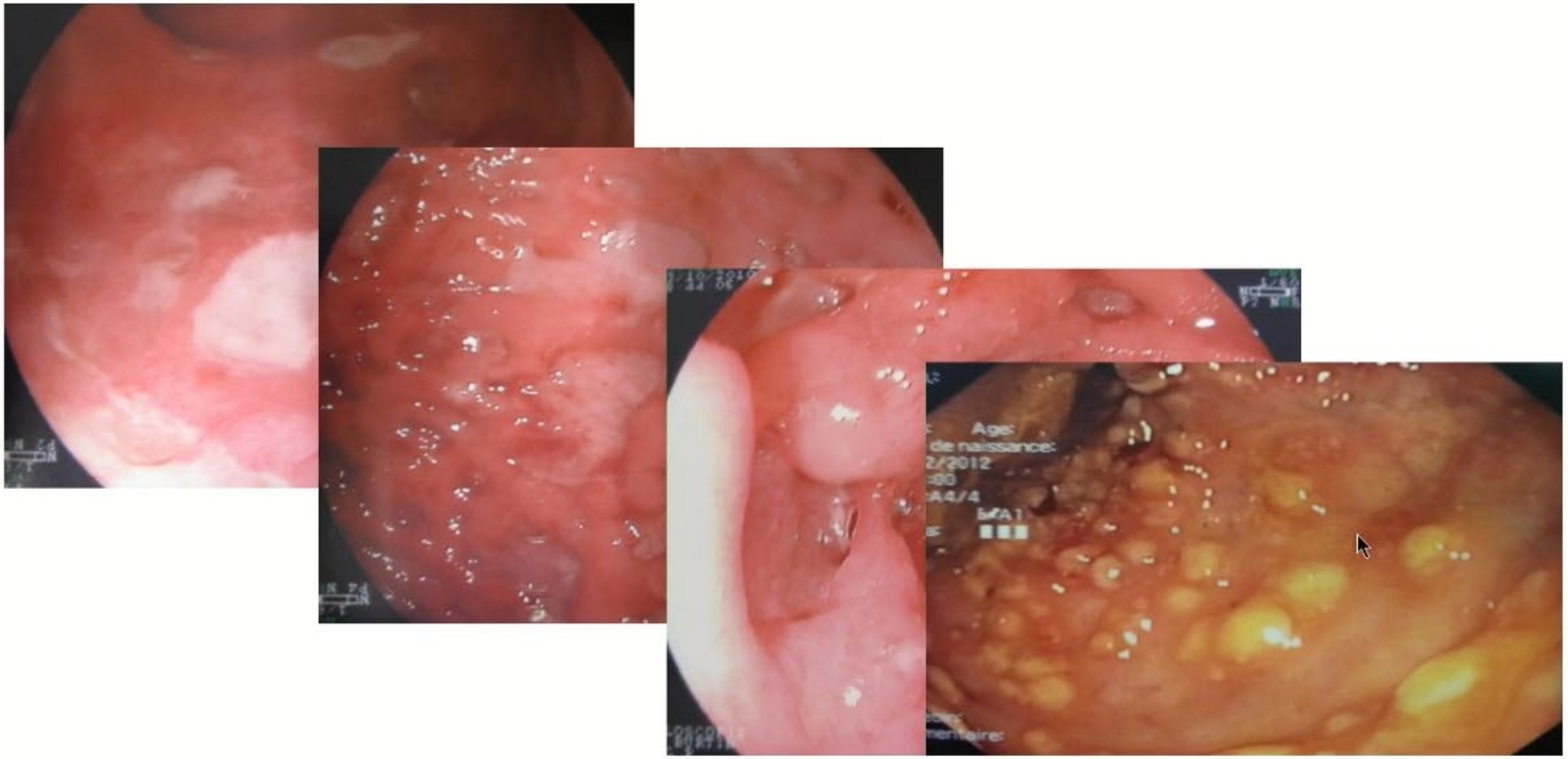
perforation (1% à 6.6% des patients) et au décès, particulièrement en cas de retard diagnostic.

Endoscopie des colites à l'ipilimumab

- 79% de colites ulcérées



Endoscopie des colites à l'ipilimumab



Incidence and Types of Immune Checkpoint Inhibitor-Related Fatalities From Systematic Review and Meta-analysis

Variable	Anti-CTLA-4 (n = 5368)	Anti-PD-1 (n = 9136)	Anti-PD-L1 (n = 3164)	Anti-PD-1/PD-L1 Plus CTLA-4 (n = 1549)
Deaths, No. (%)	58 (1.08)	33 (0.36)	12 (0.38)	19 (1.23)
Type of fatal toxic effect				
Colitis	23 (40)	2 (6)	0	2 (11)
Pneumonitis	3 (5)	14 (42)	5 (42)	4 (21)
Hepatitis	5 (9)	0	1 (8)	2 (11)
Cardiac	9 (16)	4 (12)	3 (25)	4 (21)
Neurologic	1 (2)	1 (3)	0	3 (16)
Nephritis	1 (2)	0	0	1 (5)
Hematologic	2 (4)	2 (6)	0	2 (11)
Infectious	8 (14)	5 (15)	2 (18)	3 (16)
Hemorrhagic/thrombotic	2 (4)	1 (3)	0	1 (5)
Electrolyte imbalance	1 (2)	2 (6)	0	0
Multiorgan failure	3 (5)	0	0	0
Other	1 (2)	2 (6)	1 (8)	0

Wang et al. JAMA Oncology 2018

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Wang et al. JAMA Oncology 2018

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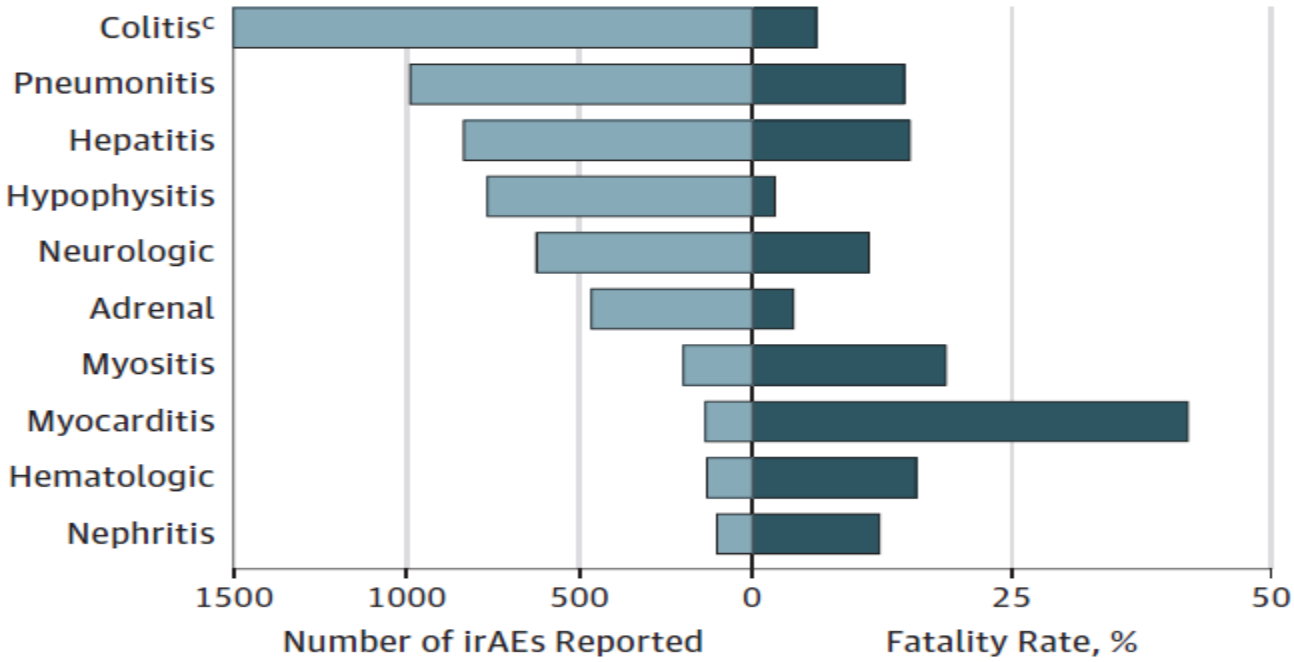
Wang et al. JAMA Oncology 2018

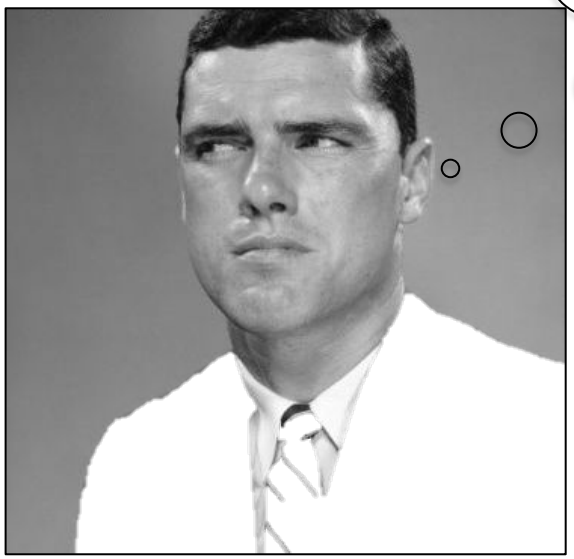
Number of cases and fatality rate for each class of toxic effect



Wang et al. JAMA Oncology 2018

In case of immunity-related toxicity

Have the corticosteroid reflex !



We think about it too late
...We stop them too soon

☑ **Differential diagnostics?**

Infectious+++

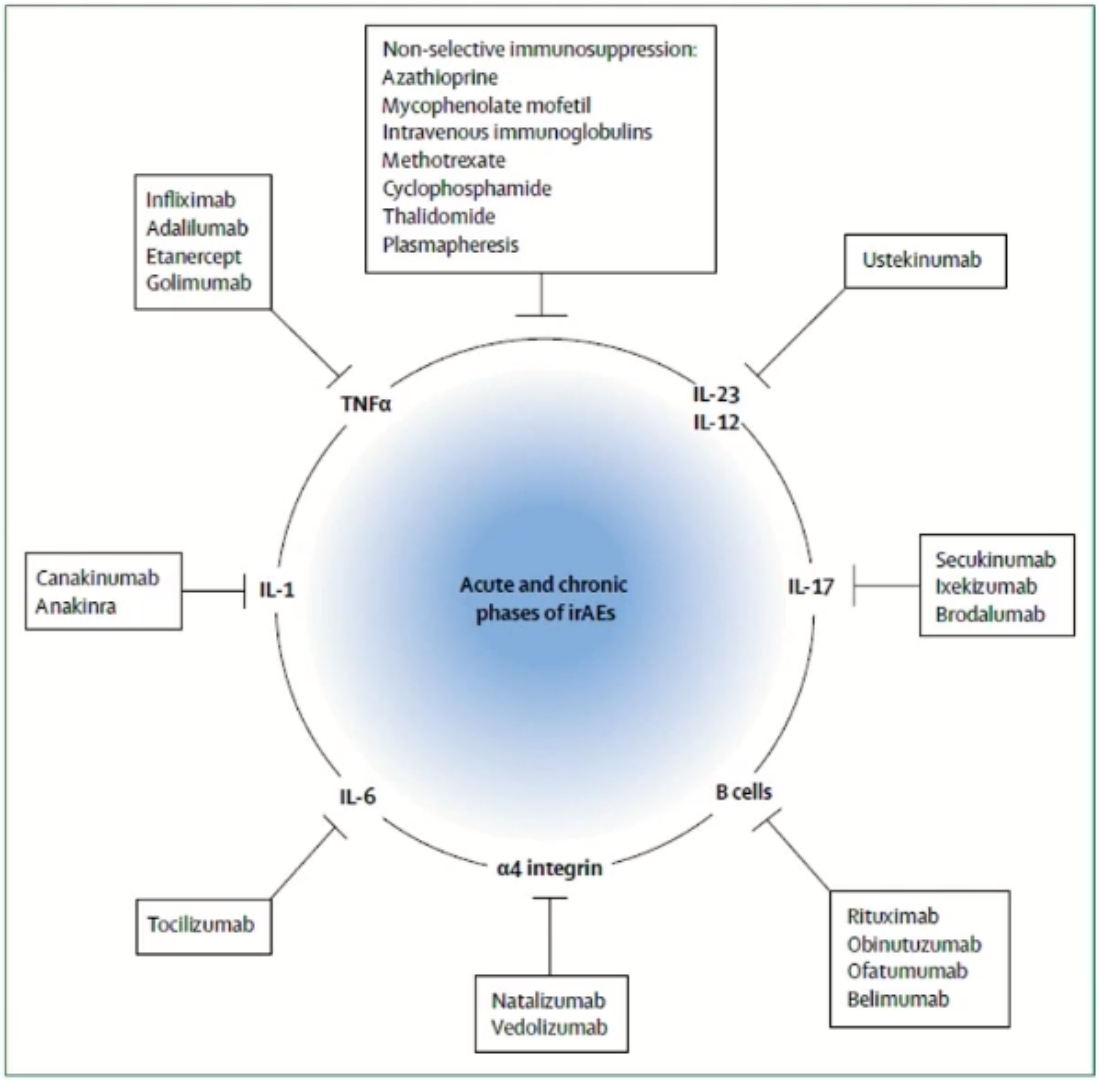
☑ **Severity ?**

If severe, do not delay steroid therapy

☑ **Specialized referral ?**

Complex pathology, other immunosuppressive therapy

Options de 2ème ligne



Haanen 2017; Majem 2018; Brahmer 2018; Martins 2020

Take to your house MESSAGES

1. Les toxicités immunologiques sont fréquentes avec les immune checkpoint inhibiteurs mais surtout très variés.

2. Le délai médian de diagnostic est à 10 semaines.

3. Elles sont pour la plupart du temps réversible après corticothérapie et ne génèrent pas de toxicité au long terme.

4. Ces toxicités immunologiques sont doses dépendantes avec les anti-CTLA4 et doses indépendantes avec les autres checkpoint inhibiteurs.

5. Les corticoides (en situation métastatiques) pour la gestion d'un irAEs n'affectent pas la réponse à l'immunotherapie.

6. Pour les situations complexes, maladies auto-immunes préexistantes, ne pas contre indiquer l'immunothérapie mais encadrer la prescription.

7. Possibilité de rechallenge ouverte au delà du grade 3 avec une approche bénéfice risque.

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Drug Development Department

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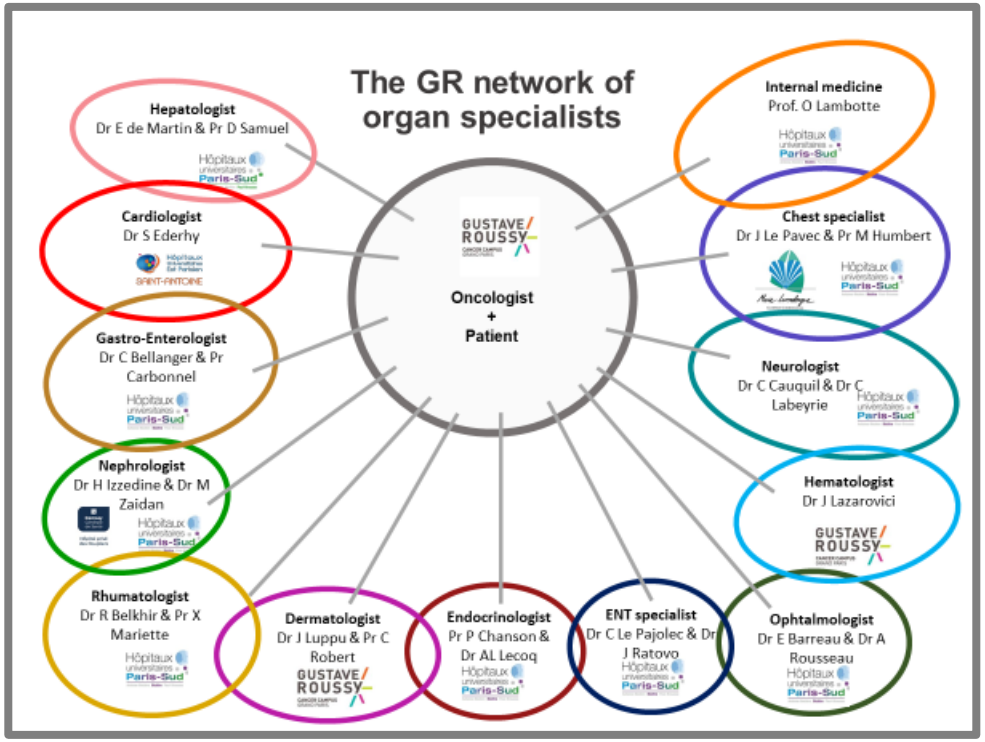

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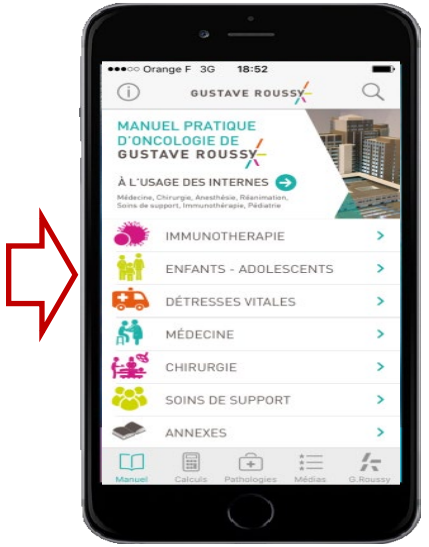
Thanks for your attention

To manage iTOX use the Gustave Roussy app!



Disponible sur App Store

Available on the Android App Store

Accepted Manuscript

First-line Pembrolizumab *vs.* Pembrolizumab plus Chemotherapy *vs.* Chemotherapy alone in Non-Small Cell Lung Cancer: A Systematic Review and Network Meta-analysis

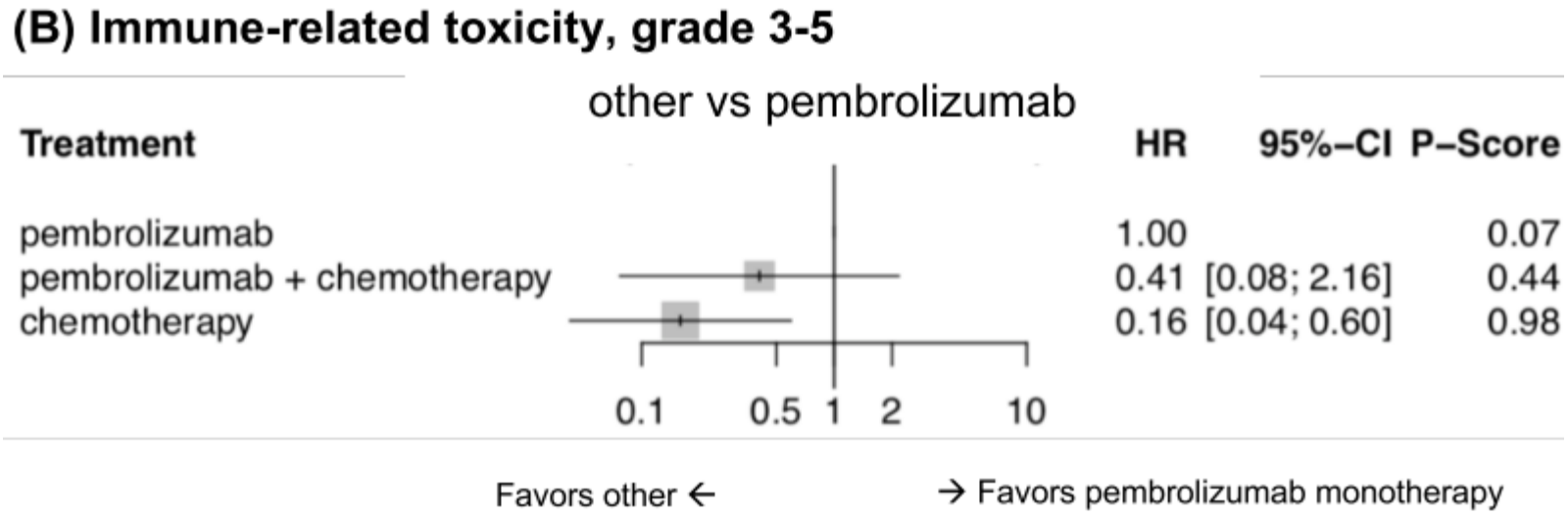
Ryul Kim, MD, Bhumsuk Keam, MD, PhD, Seokyung Hahn, PhD, Chan-Young Ock, MD, PhD, Miso Kim, MD, Tae Min Kim, MD, PhD, Dong-Wan Kim, MD, PhD, Dae Seog Heo, MD, PhD

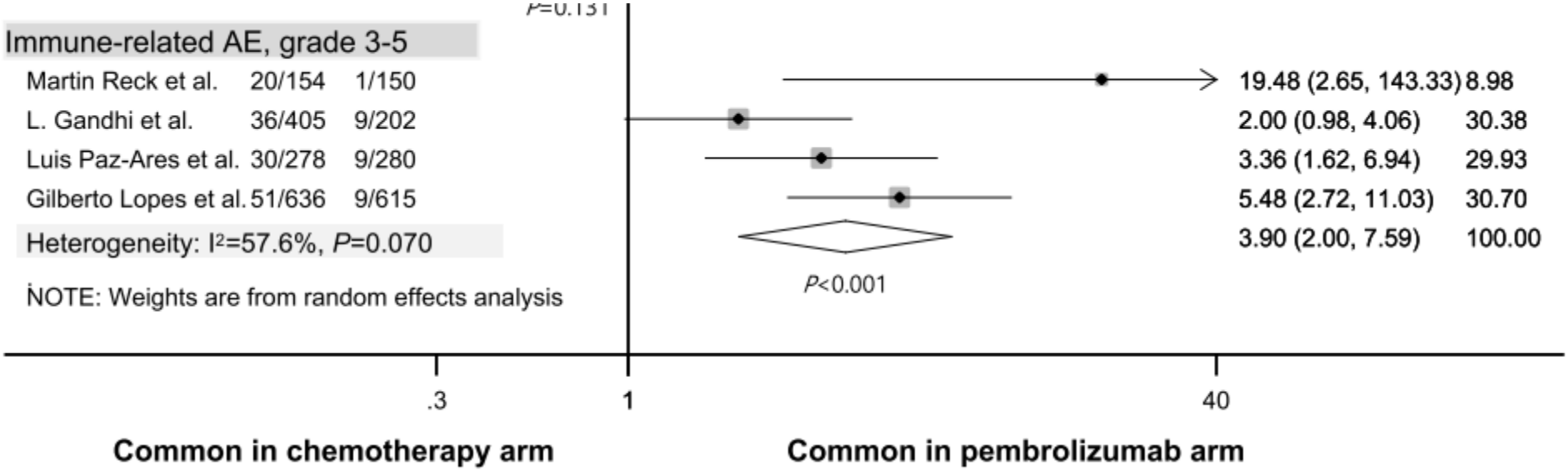
PII: S1525-7304(19)30113-5

DOI: https://doi.org/10.1016/j.cllc.2019.05.009

Reference: CLLC 966

To appear in: *Clinical Lung Cancer*




P=0.131
Immune-related AE, grade 3-5
Martin Reck et al. 20/154 1/150
L. Gandhi et al. 36/405 9/202
Luis Paz-Ares et al. 30/278 9/280
Gilberto Lopes et al. 51/636 9/615
Heterogeneity: I²=57.6%, P=0.070
NOTE: Weights are from random effects analysis
19.48 (2.65, 143.33) 8.98
2.00 (0.98, 4.06) 30.38
3.36 (1.62, 6.94) 29.93
5.48 (2.72, 11.03) 30.70
3.90 (2.00, 7.59) 100.00
P<0.001
.3
1
40
Common in chemotherapy arm
Common in pembrolizumab arm