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Network Respiratory Diseases (ERN-LUNG)

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8th International Meeting on PULMONARY RARE DISEASES AND ORPHAN DRUGS

Pulmonary complications of cancer immune therapy…

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Centre de Référence des Maladies Pulmonaires Rares

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i2B Immunopathology - Immunotherapy - Inflammation

I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:

Affiliation / financial interest	Nature of conflict / commercial company name
Tobacco-industry and tobacco corporate affiliate related conflict of interest	**NO**
Grants/research support (to myself, my institution or department):	Research supports in thoracic oncology from AZ, BI, Novartis, Pfizer for my institution
Honoraria or consultation fees:	AZ, BI, BMS, Lilly, MSD, Novartis, Pfizer, Roche
Participation in a company sponsored bureau:	**NO**
Stock shareholder:	**NO**
Spouse/partner:	**NO**
Other support or other potential conflict of interest:	**NO**

Immunotherapy(ies)

Active

Designed to act on the immune system itself

Antigen dependant

Therapeutic vaccine

GSK1572932A
TG4010
Belagenpumatucel-L
Racotumomab
Stimuvax
CIMAvax

Antigen independant

T-cell function modulation

CTAL-A4 inhibition
PD-1 inhibition
PD-L1 inhibition

Passive/adoptive

Designed to act at tumor Immune based mechanism

Anti-tumour mAbs

Bevacizumab
Ramucirumab
Cetuximab

Adoptive

IL-2-DC
Interferons
Cytokines

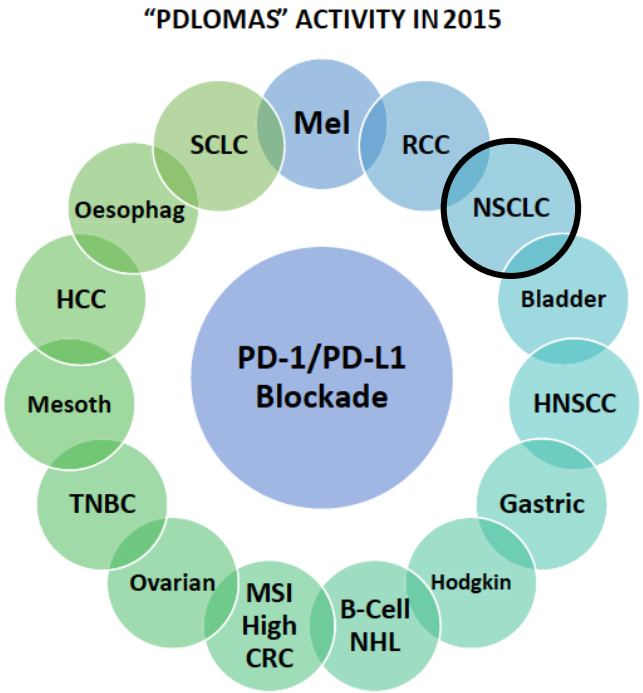
Immune system stimulation

Genetically modified T-cells (CAR/Ts)
TILS

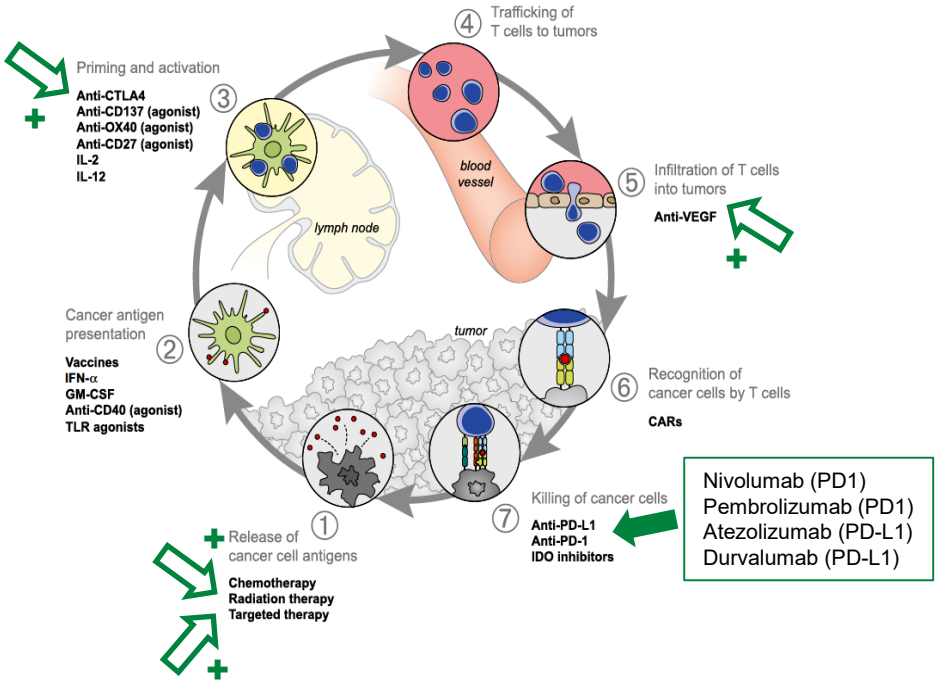
Houot R, Cancer Immunol Res 2015, 3:115; Zheng Y, PLoS One 2016, 11:e0162630; Zhu J, Cochrane Database Syst Rev 2016, CD01130012

Which cancer types and which drugs?

Which cancer types…



Which potential ICI mono- or combo-therapy …



Chen DS, Immunity 2013, 39:1; Michot JM, Eur J Cancer 2016, 54:139

When, who and which drugs for NSCLC today?

Summary of the main standard and option recommendations for the treatment of NSCLC by TNM stage

Treatment	Stage I-IIA	Stage IIB-IIIA	Stage IIIB	Stage IV		
Eligibility	**Age, PS, FEV1/DLCO, comorbidities**			**Age, PS, histology, comorbidities, "auto-immunity"**		
1st line	NA	NA	NA	**addiction (ADC)**	**PD-L1 ≥50%**	**PD-L1<50%**
Standard	Surgery	Surgery± peri-operative CT	Concomitant radio-CT± **Durvalumab**	Kinase inhibitor	**Pembrolizumab**	Doublet platinum± bevacizumab
Option	SBRT	Radio-CT	Sequential radiotherapy+CT	Doublet platinum ±bevacizumab	Doublet platinum ±bevacizumab	-
2nd line				**rebiopsy/ctDNA**	**1st line?/PD-L1**	
Standard	-	-	-	Kinase inhibitor, Doublet platinum ±bevacizumab	Doublet platinum ±bevacizumab **Immunotherapy***, mono-CT	**Immunotherapy**, mono-CT

*Atezolizumab or Nivolumab (PD-L1 0-100% or unknown) and Pembrolizumab (PD-L1 ≥1%)

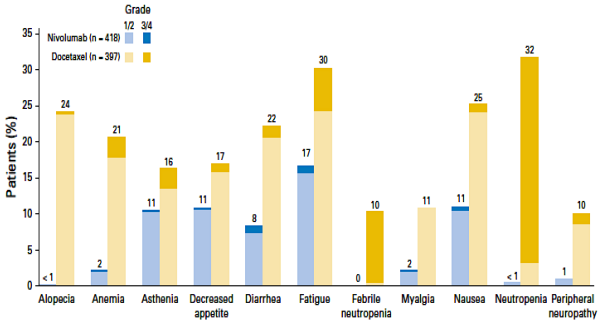
Planchard D, Ann Oncol 2018, 29:iv192

When, who and which drugs for NSCLC tomorrow?

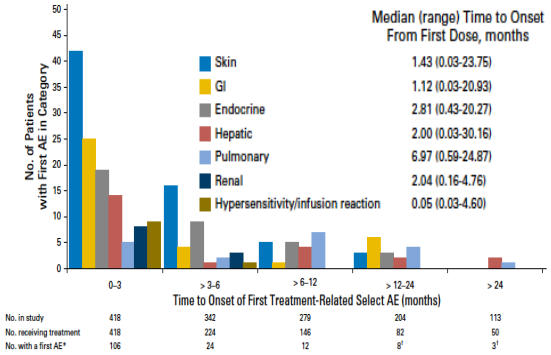
	Studies		PFS/OS (months)		Toxicities Grade 3-5, %
Mono Combo-ICI	**KN-024** NSCLC/PD-L1 ≥50%	Pembro	10.3 — 30.0	HR=0.60	27% Vs 53%
		Doublet platinum	6.0 — 14.2		
	KN-042 NSCLC/PD-L1 ≥1%	Pembro	5.4 — 16.7	HR=0.81	18% Vs 41%
		Doublet platinum	6.5 — 12.1		
	CM-227 NSCLC/TMB ≥10 mut/Mb	Nivo+ipi	7.2 — 23.0	HR=0.79 (NS) Not a Phase III trial	33% Vs 37%
		Doublet platinum	5.4 — 16.4		
Combo-CT	**KN-189** Non squamous	Pembro+Plat-pem	8.8 — 21.5	HR=0.49	67% Vs 66%
		Plat-pem	4.9 — 11.3		
	IMp-132 Non squamous	Atezo+Plat-pem	7.6 — 14.8	HR=0.81 (NS)	69% Vs 59%
		Plat-pem	5.2 — 11.7		
	IMp-150 Non squamous	Atezo+beva+Ca-pacli	8.3 — 19.2	HR=0.78 PD-L1 effect?	59% Vs 50%
		Beva+Ca-pacli	6.8 — 14.4		
Combo-CT	**KN-407** Epidermoid	Pembro+Ca-pacli/nab-pacli	6.4 — 15.9	HR=0.64	70% Vs 68%
		Ca-pacli/nab-pacli	4.8 — 11.3		
	IMp-131 Epidermoid	Atezo+Ca-nab-pacli	6.3 — 14.0	HR=0.96 (NS)	69% Vs 58%
		Ca-nab-pacli	5.6 — 13.9		

What did we learn about immune-related AEs?

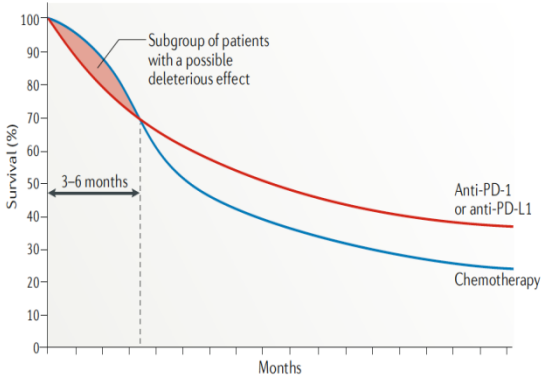
Less frequent and less severe AE with ICI…



…but description of immune related AE with ICI …including pseudo-progression



…and risk of hyperprogression

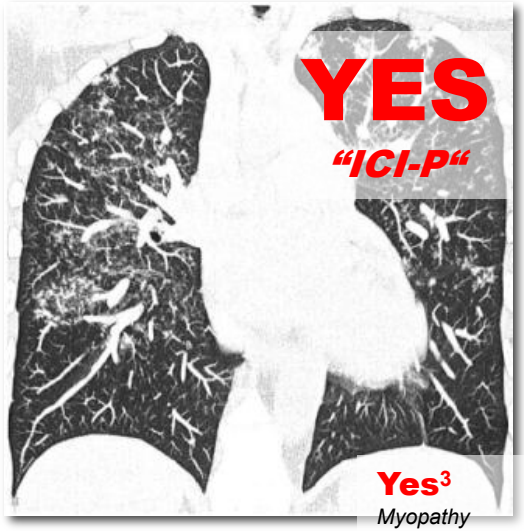


Horn L, J Clin Oncol 2017, 35:3924; Champiat S, Nature Rev Clin Oncol 2018, 15:748

Immune-related respiratory AEs observed with ICIs

Lower-respiratory tract

Lung parenchyma



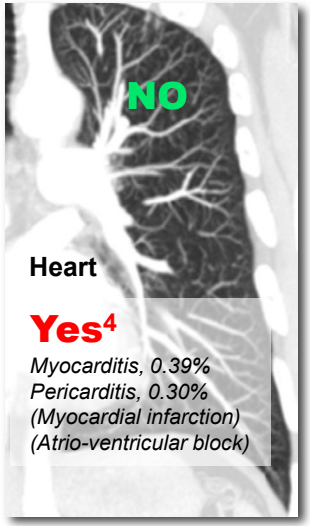
Pleura

Yes[2]
(2 cases)

Yes[3]
Myopathy
Myasthenia gravis
Guillain-Barré syndrome

Neuro-muscular

Pulmonary vessels



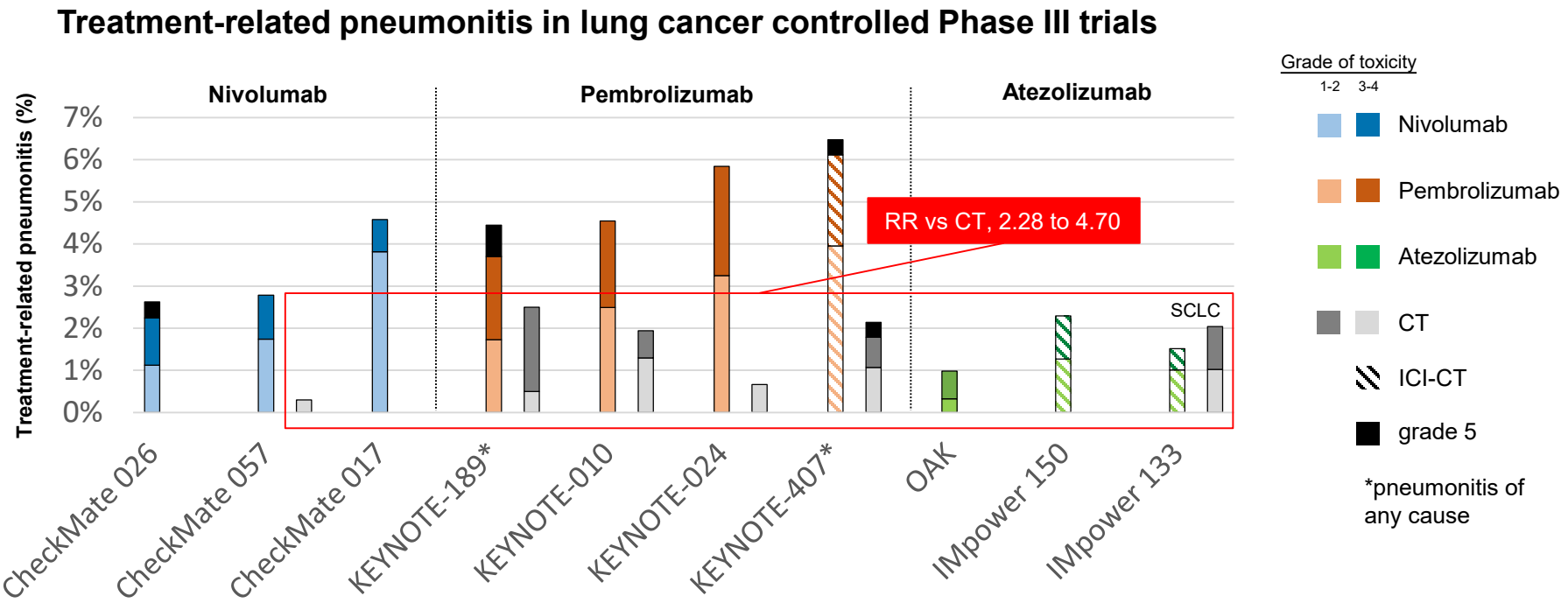
Heart

Yes[4]
Myocarditis, 0.39%
Pericarditis, 0.30%
(Myocardial infarction)
(Atrio-ventricular block)

1. *Pradere A, Eur J Cancer 2017, 75:308; Maeno K, Ann Oncol 2017, 28:2891*
2. *Yanaghiara T, Ann Oncol 2017, 28:20383; Ide M, Thoracic Cancer 2018, 9:1519*
3. *Makarious D, Eur J Cancer 2017, 82:128; Touat M, Neurology 2018, 91:e985;*

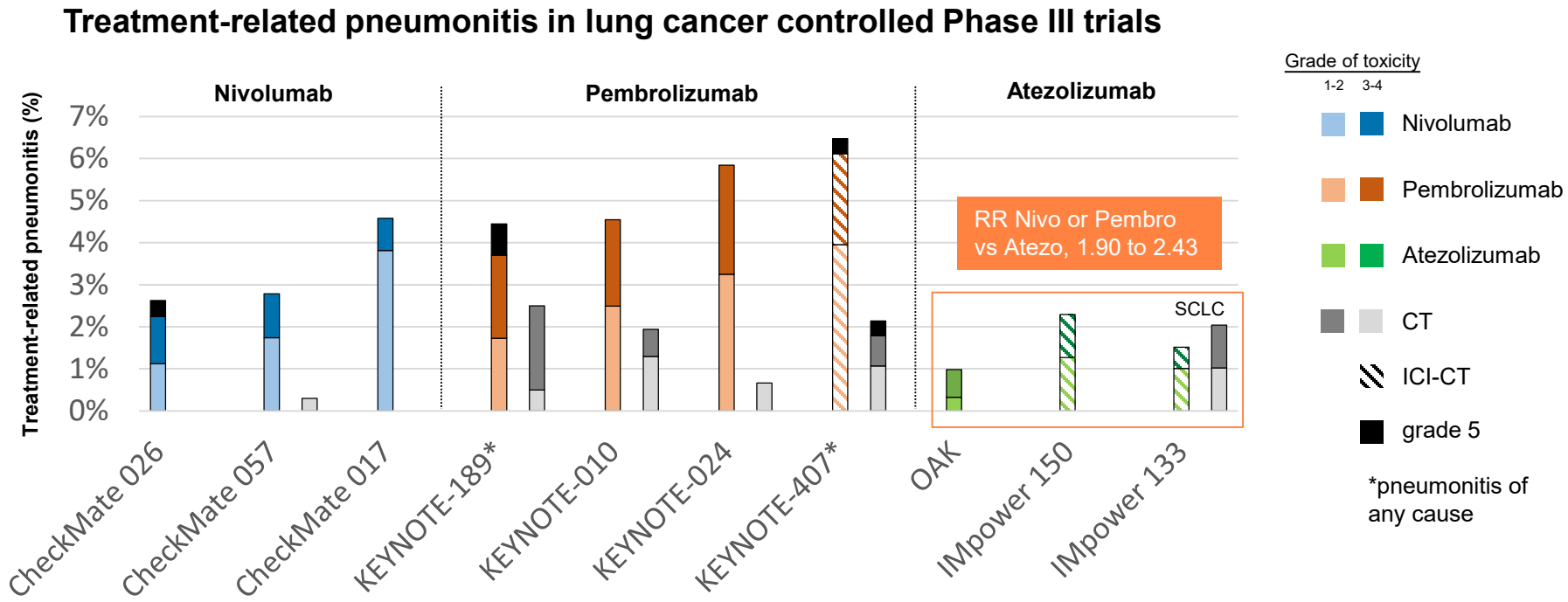
3. Jonhson DB, N Engl J Med 2016, 375:1749; Lyon A, Lancet Oncol 2018, 19:e447; Salem JO, Lancet Oncol 2018, 19:1579

Epidemiology of Ir-pneumonitis – *phase III trials and meta-analyses*



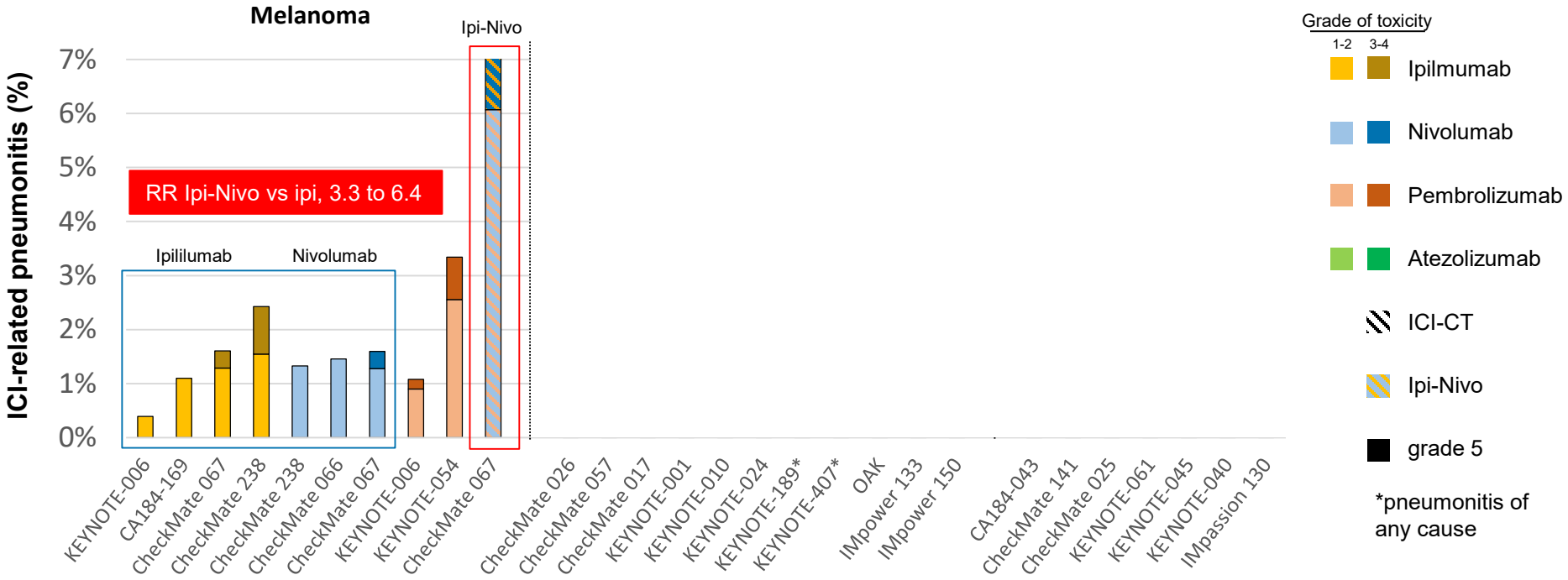
Abdel–Rahman O, Therap Advanced Respir Dis 2016, 10:183; Costa R, Oncotarget 2017, 8:8910; Hu YB, Trans Lung Cancer Res 2017, 6:S8; Ma K, Frontiers Pharm 2018, 9:1430

Epidemiology of Ir-pneumonitis – *phase III trials and meta-analyses*



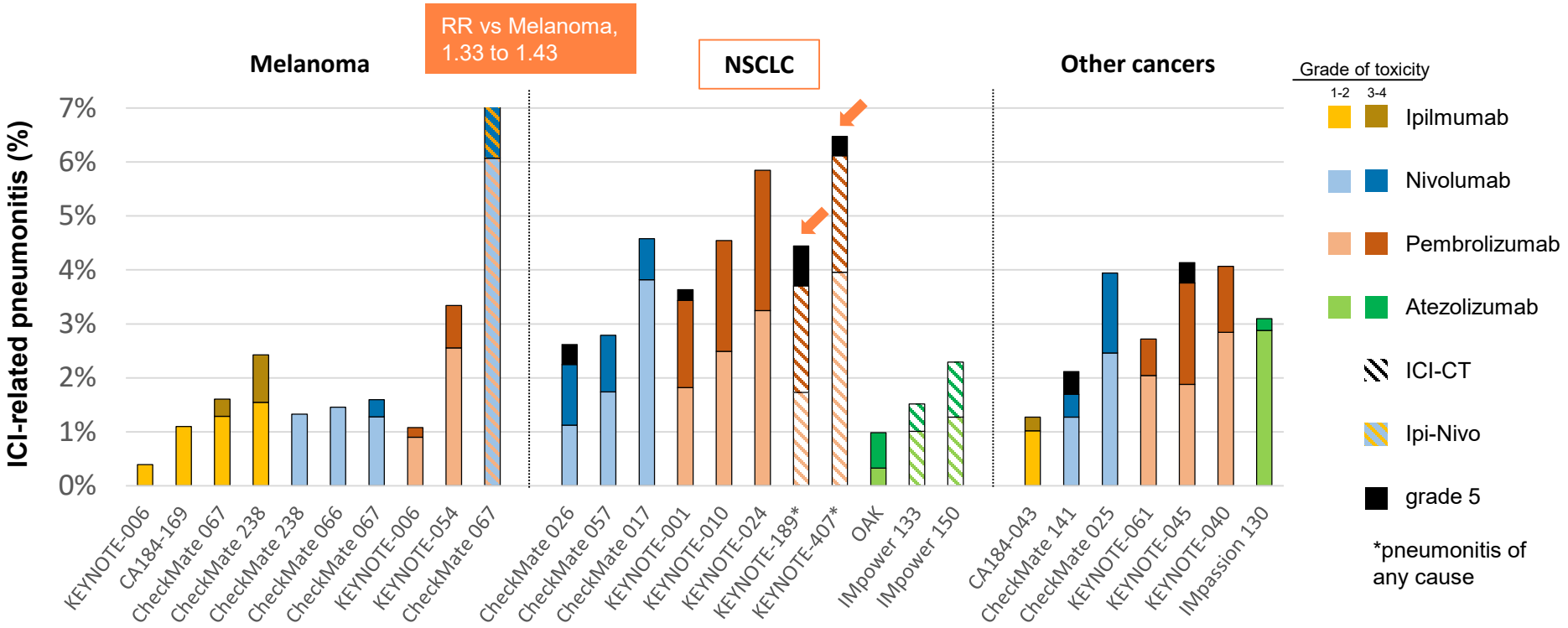
Ma K, Frontiers Pharm 2018, 9:1430

Epidemiology of Ir-pneumonitis – *phase III trials and meta-analyses*



Abdel–Rahman O, Therap Advanced Respir Dis 2016, 10:183; Nishino M, JAMA Oncol 2016, 2:1607

Epidemiology of Ir-pneumonitis – *phase III trials and meta-analyses*



Nishino M, JAMA Oncol 2016, 2:1607; Ma K, Frontiers Pharm 2018, 9:1430

Fatal Ir-pneumonitis – *pharmacovigilance database*

Vigilyse - Vigibase pharmacovigilance database

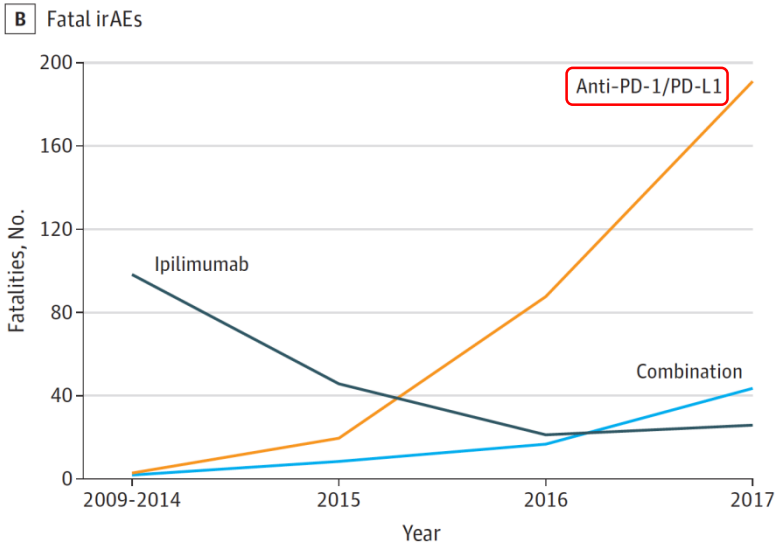
613 (1.9%) deaths reported among 31,059 irAEs since 2014

Table 1. Spectrum of Fatal Immune-Related Adverse Events in Vigilyze

Variable	No. (%) Ipilimumab (n = 193)	Anti-PD-1/PD-L1 (n = 333)	Combination (n = 87)	*P* Value
Types of cancer[a]				<.001
Melanoma	136 (96)	50 (18)		
Lung cancer	0	152 (54)	17 (23)	
Other	5 (4)	78 (28)	8 (11)	
Type of fatal irAE				
Colitis	135 (70)	58 (17)	32 (37)	<.001
Pneumonitis	15 (8)	115 (35)	12 (14)	<.001
Hepatitis	31 (16)	74 (22)	19 (22)	.23
Hypophysitis	10 (5)	3 (1)	2 (2)	.01
Cardiac	3 (2)	27 (8)	22 (25)	<.001
Myositis	1 (0.5)	22 (7)	11 (13)	<.001
Nephritis	1 (0.5)	7 (2)	3 (4)	.19
Adrenal	8 (4)	6 (2)	3 (4)	.26
Neurologic	11 (6)	50 (15)	7 (8)	.003
Hematologic	3 (2)	14 (4)	2 (2)	.22
Other (skin, thyroid, diabetes, other gastrointestinal)	13 (7)	24 (8)	7 (8)	.93

81% with monotherapy
35% cause of death

23% cause of death



Wang DY, JAMA Oncol 2018, 4:1721

Fatal Ir-pneumonitis – *pharmacovigilance database and meta-analysis*

Vigilyse - Vigibase pharmacovigilance database

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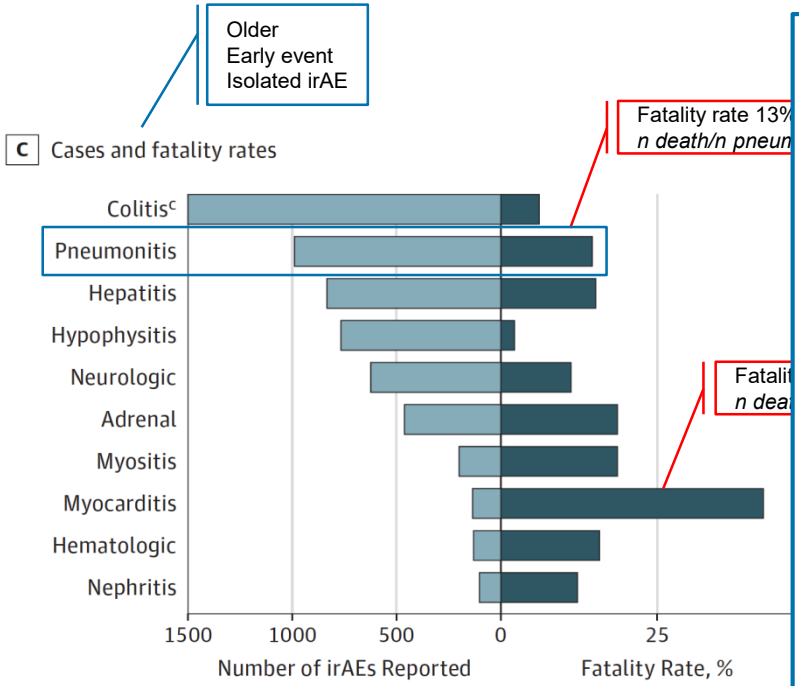


Systematic review and meta-analysis

Table 2. 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 1	23 (40)	2 (6)	0	2 (11)
Pneumonitis 1	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 DY, JAMA Oncol 2018, 4:1721

Epidemiology of Ir-pneumonitis – *associated treatments at risk*

Research

JAMA Oncology | Brief Report

EGFR-TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With Non-Small Cell Lung Cancer

Yasuo Oshima, MD, PhD; Tetsuya Tanimoto, MD; Koichiro Yuji, MD, PhD; Arinobu Tojo, MD, PhD

Table 2. Proportion of Interstitial Pneumonitis in 20 516 Patients With Non-Small Cell Lung Cancer

Variable	Cases, No. (n = 20 516)	IP (n = 985)	Point Estimate (95% CI)		*P* Value (Wald Test)
			Proportion of IP	Adjusted[a] Odds Ratio	
Age, mean (SD), y			65.5 (11.5)	1.01 (1.00-1.02	.003
Sex					
Female	8618	315	3.7 (3.3-4.1)	1 [Reference]	
Male	9351	534	5.7 (5.2-6.2)	1.56 (1.34-1.83)	<.001
Not reported	2547	136	5.3 (4.5-6.3)	0.79 (0.44-1.43)	.43
Nivolumab	5178	330	6.4 (5.7-7.1)	1.79 (1.50-2.13)	<.001
EGFR-TKI	5777	265	4.6 (4.1-5.2)	1.21 (1.00-1.47)	.05
Afatinib	1358	86	6.3 (5.1-7.8)		
Erlotinib	3195	67	2.1 (1.6-2.7)		
Gefitinib	678	47	6.9 (5.1-9.1)		
Osimertinib	702	75	10.7 (8.5-13.2)		
Nivolumab plus EGFR-TKI[b]	70	18	25.7 (16.0-37.6)	4.31 (2.37-7.86)	<.001

Oshima Y, JAMA Oncol 2018, 4:1112;

ANTICANCER RESEARCH *37*: 5199-5205 (2017)
doi:10.21873/anticanres.11943

Correlation of Radiation Pneumonitis History Before Nivolumab with Onset of Interstitial Lung Disease and Progression-free Survival of Patients with Pre-treated Advanced Non-small Cell Lung Cancer

AKIHIRO TAMIYA[1], MOTOHIRO TAMIYA[2], KENJI NAKAHAMA[1], YOSHIHIKO TANIGUCHI[1], TAKAYUKI SHIROYAMA[3], SHUN-ICHI ISA[4], TAKAKO INOUE[2], KYOICHI OKISHIO[4], KAZUMI NISHINO[2], TORU KUMAGAI[2], HIDEKAZU SUZUKI[3], TOMONORI HIRASHIMA[3], FUMIO IMAMURA[2] and SHINJI ATAGI[4]

Retrospective cohort, Japan 2015/2016 *(n=201)*

Factor	N	ILD incidence (%)	Relative risk ratio (95% CI)	*p*-Value
All patients	201	24 (12.4)		-
Gender				
Male	135	14.1		
Female	66	9.1	0.65 (0.27-1.54)	0.37
PS				
0-1	153	13.1		
2-4	48	10.4	0.80 (0.32-2.01)	0.80
Smoking history				
Yes	157	13.4		
No	44	9.1	0.68 (0.25-1.88)	0.61
History of RT to chest field				
No	151	9.3		
Yes	50	22.0	2.37 (1.15-4.88)	0.03
History of radiation pneumonitis				
No	167	9.6		
Yes	34	26.5	2.76 (1.33-5.73)	0.018

Tamiya A, Anticancer Res 2017, 37:5199

Epidemiology of Ir-pneumonitis – *populations at risk*

Review Article

Immunotherapy in the Asiatic population: any differences from Caucasian population?

Lunxi Peng[1,2], Yi-Long Wu[1,2]

- Higher frequency of respiratory AEs in Pacific trial (durvalumab after radio-CT) any grades in Asian (73.6%) vs non Asian (33.9%)
- Higher frequency of respiratory AEs (38%) in TATON trial (durvalumab plus osimertinib) in EGFR NSCLC

Annals of Internal Medicine — REVIEW

Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease

A Systematic Review

Noha Abdel-Wahab, MD, PhD; Mohsin Shah, MD; Maria A. Lopez-Olivo, MD, PhD; and Maria E. Suarez-Almazor, MD, PhD

- 75% of patients with preexisting autoimmune present irAE when receiving ICI including a disease recurrence in 41% of cases and a de novo irAE in 42%.
- Respiratory AEs are not particularly frequent; 3 out of 5 sarcoidosis relapsed.
- No less effective…

Thoracic Cancer — Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease

Osamu Kanai[1,2], Young Hak Kim[2], Yoshiki Demura[3], Makiko Kanai[1,4], Tsuyoshi Ito[5], Kohei Fujita[1],

- Higher frequency of respiratory AEs in patients with ILD (31%) receiving nivolumab for advanced NSCLC compared with others (12%); higher in patients with UIP (36%) than NSIP pattern (25%); higher severety and early onset in patients with UIP
- No less effective…

IASLC

BRIEF REPORT

Check for updates

Safety and Efficacy of PD-1 Inhibitors Among HIV-Positive Patients With Non-Small Cell Lung Cancer

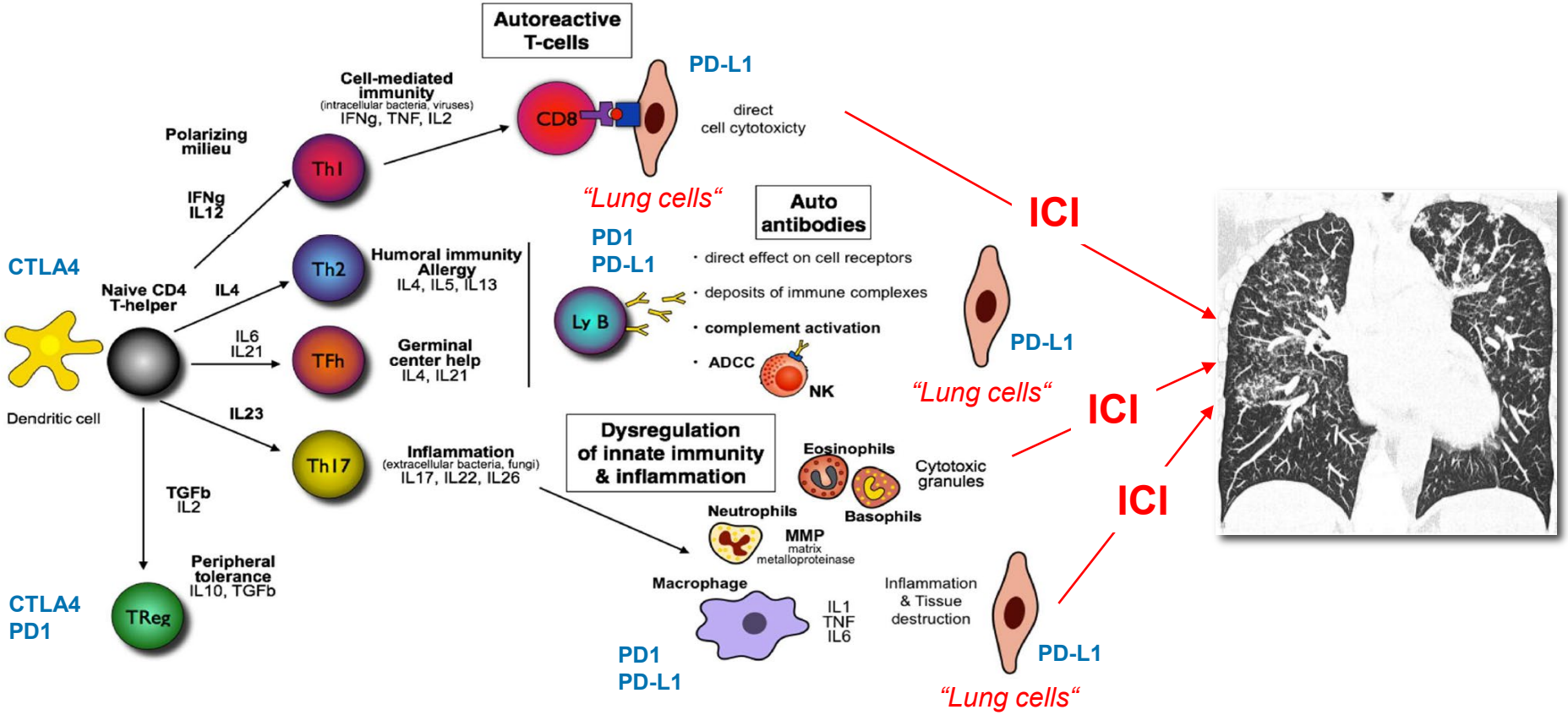
Lorena Ostios-Garcia, MD,[a] Jennifer Faig, MD,[b] Giulia C. Leonardi, MD,[a]

- No increased toxicity in HIV patients receiving anti-PD1 inhibitors for advanced NSCLC
- No less effective…

[b]Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
[c]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
[d]Division of Infectious Disease, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Peng L, J Thoracic Dis 2018, 10:S1482; Ostios-Garcia L, J Thorac Oncol 2018, 13:1037; Tamiya A, Anticancer Res 2017, 37:5199; Abdel-Wahab N, Ann Intern Med 2018, 168:121; Kanai O, Thoracic Cancer 2018,9:847

Pathophysiology of Ir-pneumonitis – *who knows?*



Ir-pneumonitis in clinical series – *tumors, drugs and incidence*

Series	Cancer	Incidence, ICI-P	ICI	Patients	Time to onset
Abdel-Wahab (n=251) All ir-AEs	Melanoma, 95.6% NSCLC, 1.2%	10 (4%)	Ipi, 60% Nivo, 30% Pem, 10%	*Male, 63% (all pop)* *Age, 60 yrs (all pop)* *Smokers?*	*53% during 2nd and 3rd injection (all pop)*
Naidoo (n=915)	Melanoma, 60% NSCLC, 20% Others, 17%	43 (5%)	aPD1, 93% aPD-L1, 7% Combo, 44%	Male? Age, 67 yrs Smokers, 67%	12 weeks (1.3-82) Mono: 19.7 weeks Combo: 11.6 weeks
Delaunay (n=1828)	NSCLC, 75% Melanoma, 20.3% Others, 4.7%	64 (3.5%)	Ipi, 6.9% aPD1, 79% aPD-L1, 14% Trials, 9.4%	Male, 84.4% Age, 59 yrs Smokers, 83%	9.9 weeks (1-117)
Kato (n=111)	NSCLC, 100%	8 (7.2%)	Nivo, 100%	Male, 100% Age, 65 yrs Smokers, 100%	5.3 weeks (2.3-24)
Suresh (n=205)	NSCLC, 100%	39 (19%)	Nivo, 92% Combo, 21%	Male, 82% Age, 68 years Smokers, 95%	2.9 weeks (3-26)
Cho (n=167)	NSCLC, 100%	22 (13%)	Nivo, 59% Pembro, 32% Nivo-Ipi, 9%	Male, 76% Age ≥70 years, 30% Smokers, 70%	7.7 weeks (2.9-139)

Abdel-Wahab N, PLoS One 2016, 11:e160221; Naidoo J, J Clin Oncol 2017, 35:709; Delaunay M, Eur Respir J 2017, 50:1; Kato T, Lung Cancer 2017, 104:111; Suresh K, J Thorac Oncol 2018, 13:1930; Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *risk factors case vs controls*

ICI-P *(n=39)* **vs non-ICI-P** *(n=166)*

Table 2. Risk Factors for Development of CIP at 1 Year

Risk Factor	OR	CI	*p* Value
Univariate analysis			
Demographics			
Female Sex	1.12	(0.53-2.35)	0.75
Smoking	0.86	(0.41-1.82)	0.70
Age	1	(0.96-1.04)	0.69
Race (vs. white)			
Black	1.08	(0.37-2.72)	0.87
Asian/other	2.09	(0.28-10.2)	0.39
Tumor characteristics			
Adenocarcinoma	0.42	(0.19-0.89)	0.02
Initial stage (vs. stage IV)			
I	0.33	(0.01-1.83)	0.30
II	1.24	(0.26-4.39)	0.74
III	1.44	(0.62-3.26)	0.38
Therapy-related factors			
Chemotherapy	0.86	(0.38- 2.0)	0.72
Surgery	0.53	(0.17-1.37)	0.22
ICI therapy (vs. nivolumab therapy)			
Pembrolizumab	0.39	(0.06-1.44)	0.22
Other	0.19	(0.01-1.00)	0.11
Combination ICI	1.72	(0.80-3.67)	0.16
Multivariate analysis[a]			
Adenocarcinoma	0.38	(0.17-0.82)	0.01

Patient characteristics.

Variable	Without pneumonitis (n = 145)	With pneumonitis (n = 22)	P
Age ≥ 70 years	44 (30.3)	12 (54.5)	0.025
Male sex	110 (75.9)	18 (81.8)	0.538
Former/Current smoker	102 (70.3)	18 (81.8)	0.265
ECOG ≥ 2	16 (11.0)	4 (18.2)	0.336
COPD	19 (13.1)	6 (27.3)	0.083
Bronchiectasis	7 (4.8)	1 (4.5)	0.954
Interstitial lung disease[a]	4 (2.8)	4 (18.2)	0.002
Postoperative recurrence	31 (21.4)	6 (27.3)	0.535
Pathology			0.060
Adenocarcinoma	96 (66.2)	10 (45.5)	
Non-adenocarcinoma	49 (33.8)	12 (54.5)	
Extrathoracic metastasis	85 (58.6)	7 (31.8)	0.019
Observation period[d], day	140.0 (3–1511)	145.5 (40–1379)	0.533
ICI exposures, n	5 (1–63)	5 (1–68)	0.627

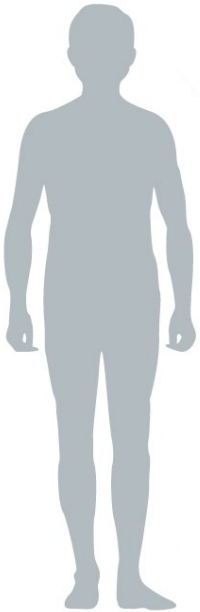
Risk factors of ICI-related pneumonitis.

Variable	Univariate		Multivariate		
	OR	95% CI	OR	95% CI	P
Age ≥ 70 years	2.76	1.11–6.85	1.87	0.69–5.05	0.218
Interstitial lung disease	7.83	1.80–34.08	6.03	1.19–30.45	0.030
Extrathoracic metastasis	0.33	0.13–0.86	0.34	0.13–0.92	0.034

Suresh K, J Thorac Oncol 2018, 13:1930; Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *symptoms and severity*

Asymptomatic
7%[c], 23%[f], 33%[b]

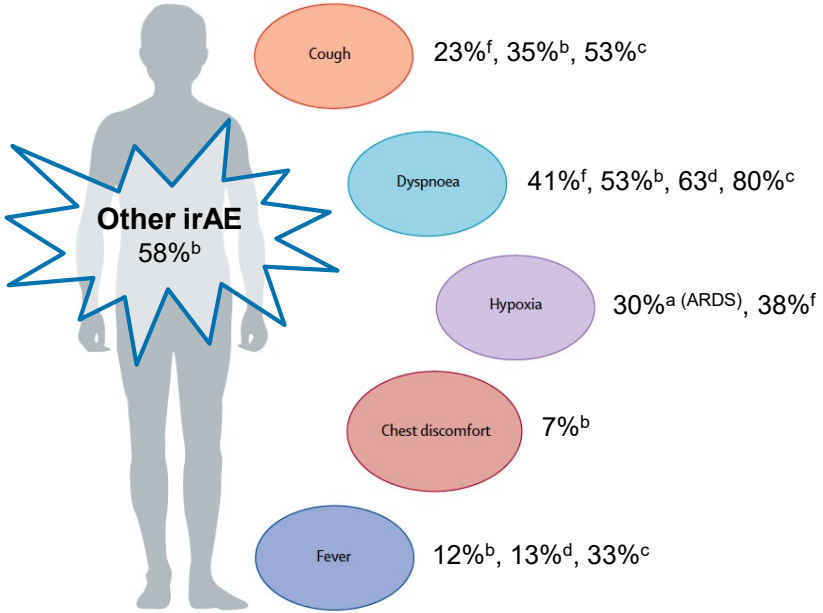


a) Abdel-Wahab N, PLoS One 2016, 11:e160221; b) Naidoo J, J Clin Oncol 2017, 35:709; c) Delaunay M, Eur Respir J 2017, 50:1; d) Kato T, Lung Cancer 2017, 104:111; e) Suresh K, J Thorac Oncol 2018, 13:1930; f) Cho JY, Lung Cancer 2018, 125:2018

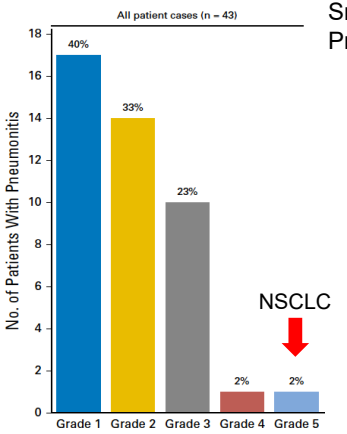
Ir-pneumonitis in clinical series – *symptoms and severity*

Asymptomatic
7%[c], 23%[f], 33%[b]

Respiratory symptoms

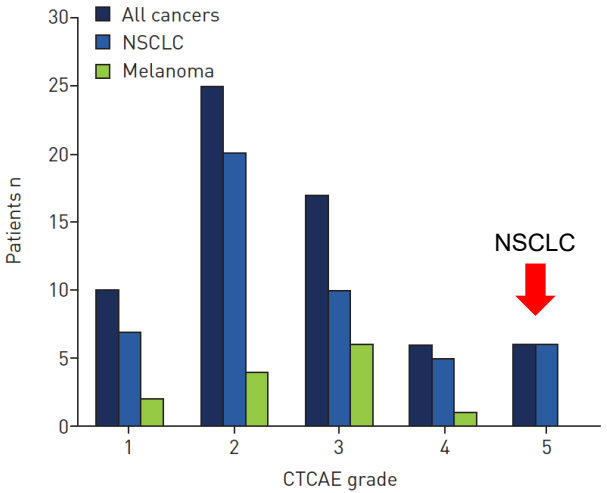


Naidoo J et al.



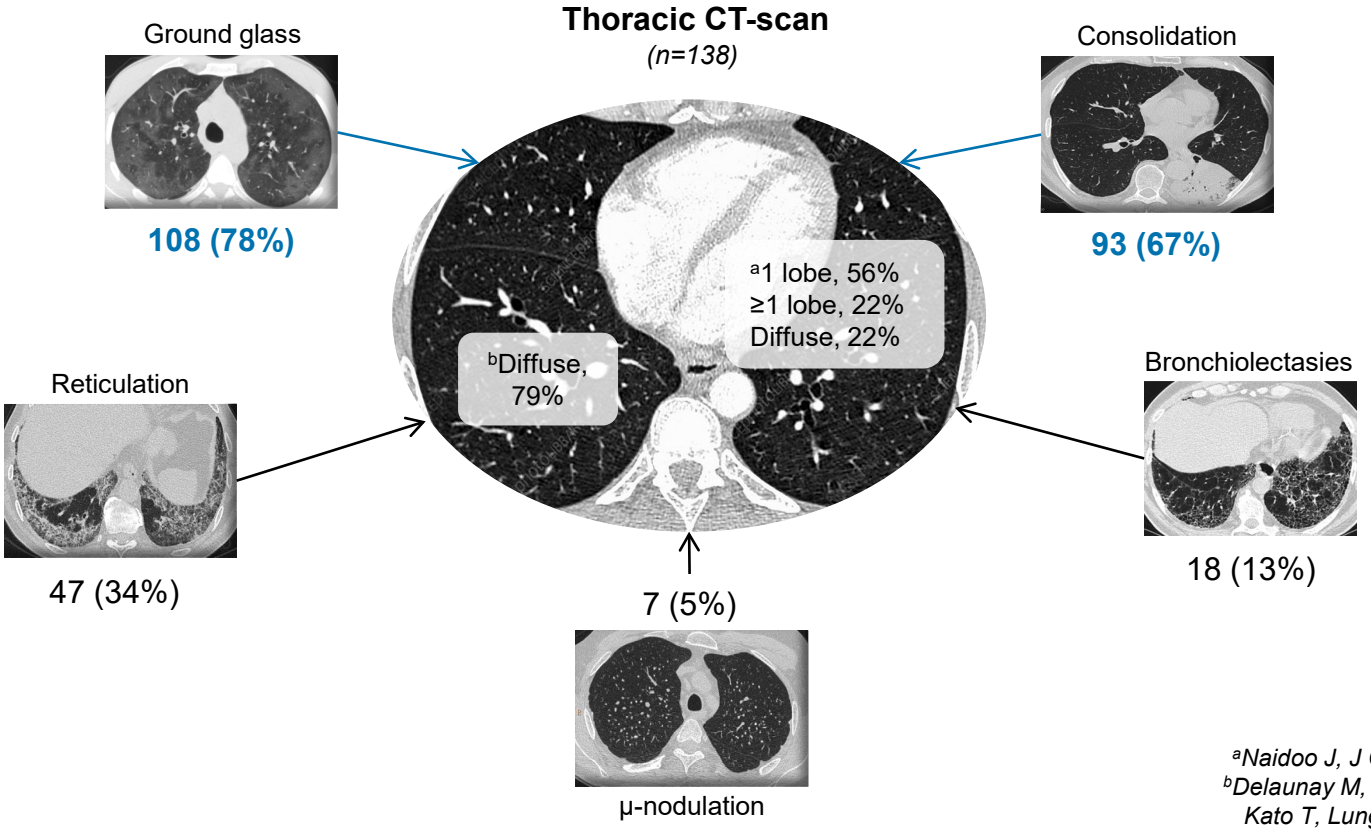
Smokers vs non-smokers (p=0.05)
Prior vs non prior respiratory disease (p=0.05)

Delaunay M et al.



a) Abdel-Wahab N, PLoS One 2016, 11:e160221; b) Naidoo J, J Clin Oncol 2017, 35:709; c) Delaunay M, Eur Respir J 2017, 50:1; d) Kato T, Lung Cancer 2017, 104:111; e) Suresh K, J Thorac Oncol 2018, 13:1930; f) Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *radiological findings*



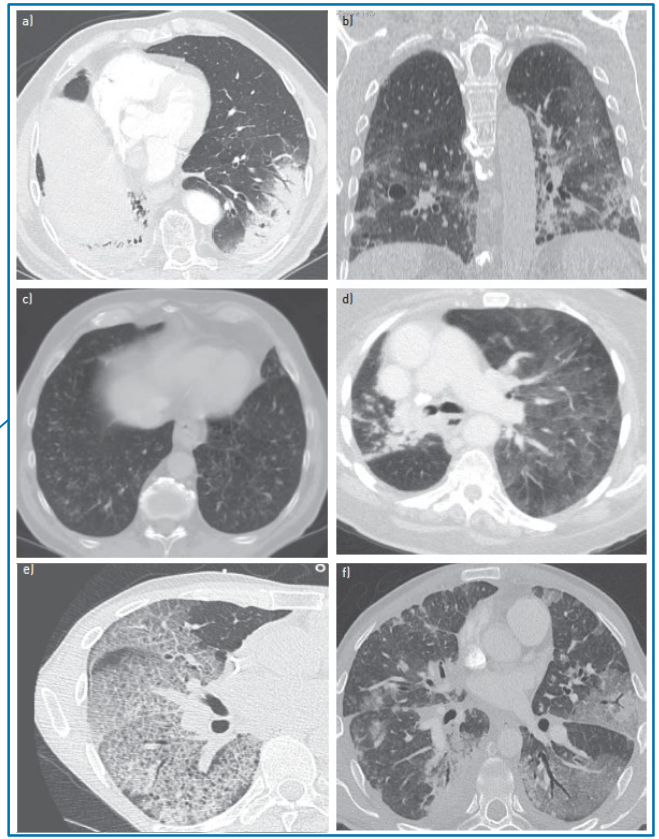
Hansell DM, Radiology 2008, 246:697 35:709; Travis WD, Am J Resp Crit Care Med 2013:188, 733

[a]Naidoo J, J Clin Oncol 2017, 35:709;
[b]Delaunay M, Eur Respir J 2017, 50:1;
Kato T, Lung Cancer 2017, 104:111;
Suresh K, J Thorac Oncol 2018, 13:1930

Ir-pneumonitis in clinical series – *radiological findings*

Delaunay M et al.
(CT-scan, n=64)

Radiological features	
Lesions	
GGO	52 (81.3)
Consolidations	34 (53.1)
Intralobular lines	14 (21.9)
Interlobular septal thickening	10 (15.6)
Traction bronchectasis	11 (17.2)
Extent (lobes) n	3 (1–5)
Pattern	
Organising pneumonia	15 (23.4)
Hypersensitivity pneumonia	10 (15.6)
NSIP and organising pneumonia	6 (9.4)
NSIP	5 (7.8)
Bronchiolitis	4 (6.3)
NSIP and bronchiolitis	1 (1.6)
No classification	23 (35.9)

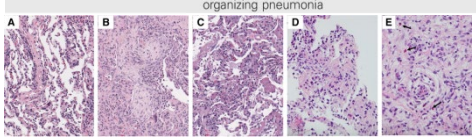


Delaunay M, Eur Respir J 2017, 50:1; Suresh K, J Thorac Oncol 2018, 13:1930; Naidoo J, J Clin Oncol 2017, 35:709; Cho JY, Lung Cancer 2018, 125:2018

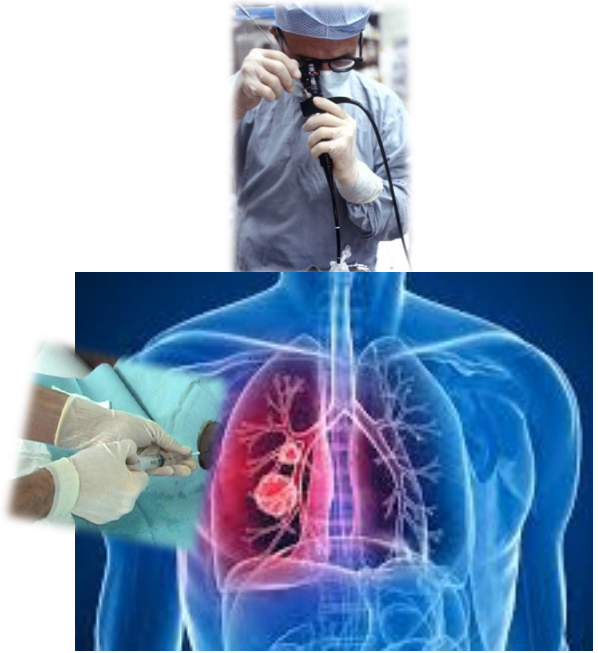
Ir-pneumonitis in clinical series – *BAL and pathological findings*

Naidoo J et al. *(n=11)*

Specimen Type	Main Pathologic Finding	Radiologic Subtype
Transbronchial biopsy	Nondiagnostic (mild chronic inflammation)	COP-like
Transbronchial and endobronchial biopsies	Organizing pneumonia, CIP	COP-like
Transbronchial and endobronchial biopsies	CIP, granulomas	NOS
Bronchoscopic biopsy	CIP with focal fibrin (focal acute lung injury)	GGO
Transthoracic core biopsy	CIP, granulomas	Hypersensitivity
Transbronchial biopsy	Nondiagnostic (benign bronchial mucosa)	COP-like
Transbronchial biopsy	Nondiagnostic (benign bronchial mucosa)	COP-like
Transbronchial biopsy	Diffuse alveolar damage	GGO
Transthoracic core biopsy and transthoracic fine-needle aspiration	Organizing pneumonia, CIP, eosinophils, vessels with recanalized thrombi	NOS
Transbronchial biopsy	CIP, eosinophils	GGO
Wedge resection	Granulomatous inflammation, organizing pneumonia	Interstitial



NSIP DAD eosinophil
OP granuloma



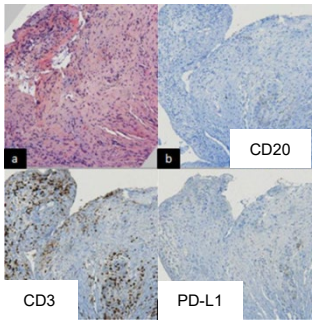
Delaunay M et al.

BAL[#] *(n=30)*

Yes	35 (55.6)
No	28 (44.4)
Unknown	1
Lymphocytes[¶]	33.5 (1.0–70.0)
⩽15	6 (20.0)
>15	24 (80.0)
Unknown	5

TBB *(n=5)*

Lymphocytic infiltration



Naidoo J, J Clin Oncol 2017, 35:709; Delaunay M, Eur Respir J 2017, 50:1; Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *grades of toxicity and management*

Series	ICI-P	Grades	Response	ICI	Corticosteroids	ATB	Evolution	Other treatment
Naidoo (n=915)	n=43 melanoma Ipi, 60%	Grade 1-2, **71%** Grade ≥3, 29% **Grade 5, 2.3%**	CR+PR, 61% SD, 34% PD, 5%	Pursued, 48% Suspended, 28% **Stopped, 24%**	**51.6%** 50 mg (20-80) 68 dys (20-154)	ND	**Resolved, 74.4%** **Improved, 11.6%** **Worsened, 11.6%**	**Yes** *Infliximab, CPM (n=5)*
Delaunay (n=1828)	n=64	Grade 1-2, **55%** Grade ≥3 45% **Grade 5, 17%**	CR+PR, 36% SD, 33% PD, 11% UK, 20%	Pursued, 8% Suspended, 17% **Stopped, 75%**	**86.9%** 80 mg (20-240) 27 dys (4-251)	66.1%	**Resolved, 28.6%** **Improved, 39.7%** Stable, 20.6%	No
Kato (n=111)	n=8	Grade 1-2, **75%** Grade ≥3, 25% **Grade 5, 13%**	ND	ND	**87.5%** ND ND	ND	**Resolved, 87.5**	**Yes** *CPM (n=1)*
Suresh (n=205)	n=39	Grade 1-2, **36%** Grade ≥3, 64% **Grade 5, 13%**	ND	ND	**100%** 1 mg/kg/dy ND	ND	**Resolved, 5.1%** **Improved, 64%** **Worsened, 17.9%**	**Yes** *2/2 MMF improved* *2/3 Infliximab improved*
Cho (n=167)	n=22	Grade 1-2, **68%** Grade ≥3, 32% **Grade 5, 18%**	CR+PR, 23% SD, 45% PD, 32%	Pursued, 5% Suspended, 32% **Stopped, 63%**	**77%** 0.8 mg/kg (0.4-11.7) 27 dys (2-269)	59%	**Resolved, 22.7%** **Improved, 27.3%** Stable, 4.5%	No

Naidoo J, J Clin Oncol 2017, 35:709; Delaunay M, Eur Respir J 2017, 50:1; Kato T, Lung Cancer 2017, 104:111; Suresh K, J Thorac Oncol 2018, 13:1930; Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *grades of toxicity and management*

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Kato (n=111)	n=8	Grade 1-2, **75%** Grade ≥3, 25% **Grade 5, 13%**	ND	ND	**87.5%** ND ND	ND	**Resolved, 87.5**	**Yes** *CPM (n=1)*
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Naidoo J, J Clin Oncol 2017, 35:709; Delaunay M, Eur Respir J 2017, 50:1; Kato T, Lung Cancer 2017, 104:111; Suresh K, J Thorac Oncol 2018, 13:1930; Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *grades of toxicity and management*

Series	ICI-P	Grades	Response	ICI	Corticosteroids	ATB	Evolution	Other treatment
Naidoo (n=915)	n=43 melanoma Ipi, 60%	Grade 1-2, **71%** Grade ≥3, 29% **Grade 5, 2.3%**	CR+PR, 61% SD, 34% PD, 5%	Pursued, 48% Suspended, 28% **Stopped, 24%**	**51.6%** 50 mg (20-80) 68 dys (20-154)	ND	**Resolved, 74.4%** **Improved, 11.6%** **Worsened, 11.6%**	**Yes** *Infliximab, CPM (n=5)*
Delaunay (n=1828)	n=64	Grade 1-2, **55%** Grade ≥3 45% **Grade 5, 17%**	CR+PR, 36% SD, 33% PD, 11% UK, 20%	Pursued, 8% Suspended, 17% **Stopped, 75%**	**86.9%** 80 mg (20-240) 27 dys (4-251)	66.1%	**Resolved, 28.6%** **Improved, 39.7%** Stable, 20.6%	No
Kato (n=111)	n=8	Grade 1-2, **75%** Grade ≥3, 25% **Grade 5, 13%**	ND	ND	**87.5%** ND ND	ND	**Resolved, 87.5**	**Yes** *CPM (n=1)*
Suresh (n=205)	n=39	Grade 1-2, **36%** Grade ≥3, 64% **Grade 5, 13%**	ND	ND	**100%** 1 mg/kg/dy ND	ND	**Resolved, 5.1%** **Improved, 64%** **Worsened, 17.9%**	**Yes** *2/2 MMF improved* *2/3 Infliximab improved*
Cho (n=167)	n=22	Grade 1-2, **68%** Grade ≥3, 32% **Grade 5, 18%**	CR+PR, 23% SD, 45% PD, 32%	Pursued, 5% Suspended, 32% **Stopped, 63%**	**77%** 0.8 mg/kg (0.4-11.7) 27 dys (2-269)	59%	**Resolved, 22.7%** **Improved, 27.3%** Stable, 4.5%	No

Naidoo J, J Clin Oncol 2017, 35:709; Delaunay M, Eur Respir J 2017, 50:1; Kato T, Lung Cancer 2017, 104:111; Suresh K, J Thorac Oncol 2018, 13:1930; Cho JY, Lung Cancer 2018, 125:2018

Ir-pneumonitis in clinical series – *is rechallenge feasible?*

Series	ICI-P	Grades	Response	ICI	Corti		ution	Other treatment
Naidoo (n=915)	n=43 melanoma Ipi, 60%	Grade 1-2, 71% Grade ≥3, 29% Grade 5, 2.3%	CR+PR, 61% SD, 34% PD, 5%	Pursued, 48% **Suspended** Stopped, 24%	51.6% 50 mg (20-80) 68 dys (20-154)	ND	Resolved, 74.4% Improved, 11.6% Worsened, 11.6%	Yes *Infliximab, CPM (n=5)*
Delaunay (n=1828)	n=64	Grade 1-2, 55% Grade ≥3 45% Grade 5, 17%	CR+PR, 36% SD, 33% PD, 11% UK, 20%	Pursued, 8% **Suspended** Stopped, 75%	86.9% 80 mg (20-240) 27 dy	66.1%	Resolved, 28.6% Improved, 39.7%	No
Kato (n=111)	n=8	Grade 1-2, 75% Grade ≥3, 25% Grade 5, 13%	ND	ND	87.5% ND ND			**es** *PM (n=1)*
Suresh (n=205)	n=39	Grade 1-2, 36% Grade ≥3, 64% Grade 5, 13%	ND	ND	100% 1 mg/ ND		5.1% 64% d, 17.9%	Yes *2/2 MMF improved* *2/3 Infliximab improved*
Cho (n=167)	n=22	Grade 1-2, 68% Grade ≥3, 32% Grade 5, 18%	CR+PR, 23% SD, 45% PD, 32%	Pursued, 5% **Suspended** Stopped, 63%	77% 0.8 mg/kg (0.4-11.7) 27 dys (2-269)	59%	Resolved, 22.7% Improved, 27.3% Stable, 4.5%	No

Rechallenge:
- **12/43 (28%)**, all grades 1-2
- 9/12 (75%), no recurrence

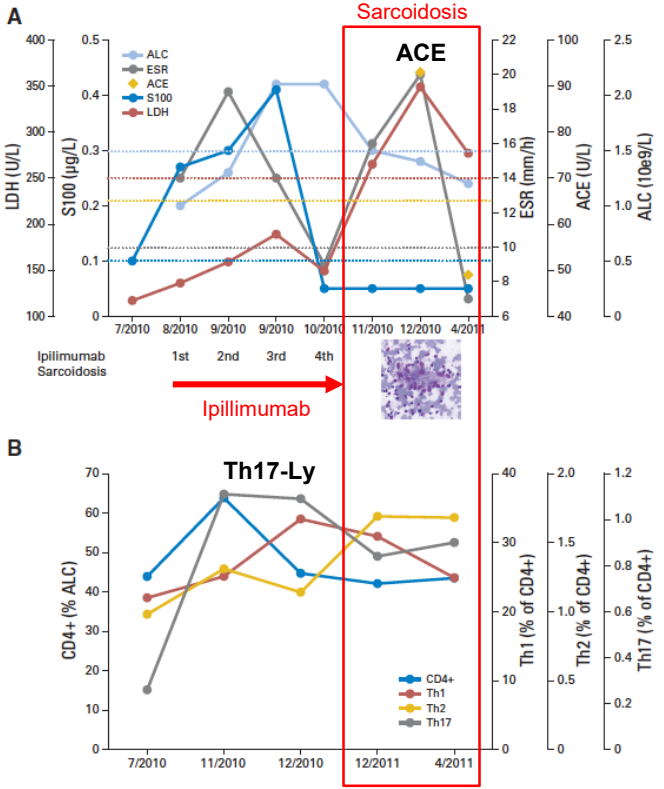
Rechallenge:
- **10/64 (17%)**, all except one grades 1-2
- 7/10 (70%), no recurrence

Rechallenge:
- **7/22 (32%)**, grades?
- 7/7 (100%), no recurrence

Naidoo J, J Clin Oncol 2017, 35:709; Delaunay M, Eur Respir J 2017, 50:1; Kato T, Lung Cancer 2017, 104:111; Suresh K, J Thorac Oncol 2018, 13:1930; Cho JY, Lung Cancer 2018, 125:2018

Ir-“sarcoid-like“ granulomatosis – *case reports*

Characteristics *(n=19)*	
Cancer • Melanoma • NSCLC/SCLC • Others	 **13 (72%)** 3/1 (22%) 2 (6%)
Age, median **Sex ratio,** male:female	54 years (35-80) 2:1
ICI • Ipilimumab/ipi+nivo • Nivo/pembro/atezo/durvalumab	 **7/5 (67%)** 3/2/1/1 (23%)
Delay, median	**12 weeks** (4-40)
Stage I/II/III/IV	**4/10**/5/0
Extra-thoracic involvement	skin, n=5; spleen, n=3; parotid/eyes, n=1; brain, n=1
Histology	**BB/TBB, n=7; EBUS, n=10**; skin, n=5; others, n=3
ICI interruption / corticosteroids	**13 (68%) / 9 (47%)**
Sarcoidosis follow-up	**16 (84%) improvement**, no deterioration
Cancer follow-up	DCR, n=12; PD, n=4; unknown, n=3



Wogel W, J Clin Oncol 2012, 30:a7; Broos E, Am J Respir Crit Care Med 2015, 192:764; Miedema J, J Autoimmunity 2018, 87:82

Ir-tuberculosis – *case reports*

Characteristics *(n=9)*	
Cancer • NSCLC • Melanoma • Others	 **5 (56%)** 2 (22%) 2 (22%)
Age, median **Sex ratio,** male:female	65 years (59-85) 8:1
ICI, nivo/pembrolizumab	5/4
Delay, median	**15 weeks** (4-33)
Symptoms	**no, n=4 (44%)**; fever and cough, n=3 (33%); others, n=3 (33%)
Thoracic CT	lung, n=5 (56%); pleural effusion, n=2 (22%)
Extra-thoracic involvement	spinal cord compression only, n=1
BAAR/histology	**9 (100%)/6 (75%)**, granuloma ± necrosis
ICI interruption / anti-TB drugs	**8 (89%) / 9 (100%)**
Tuberculosis follow-up	**8 cured (89%)** among whom **1 paradoxical aggravation (11%)** ; **2 died (22%)**
Cancer follow-up	DCR, n=7; unknown, n=2

- TB occurred in 2 of 908 patients treated by ICI for cancer for 4 years in France
- TB estimate incidence is 1/1000 treated patients/year in France
- TB occurs in absence of other immunosuppression except cancer *itself*
- TB occurs early after ICI introduction, suggesting TB reactivation rather than *de novo* TB infection
- Should IGRA test be performed before ICI introduction?
- PD-1 inhibition could favour exaggerated immune response against latent TB

Picchi H, Clin Mic Inf 2018, 24:216; Sakai S, PloS Pathogen 2016, May 31:1; Del Castillo M, Clin Infect Dis 2016, 63:1490

Ir-severe pulmonary infection – *does it exist?*

Retrospective cohort of severe infections in melanoma patients treated by ICI at the MSKCC between 2010 and 2014

7.3% Serious Infection?

Characteristic (n = 740 Patients)	Overall	Yes (n = 54)	No (n = 686)
Age, y, mean (range)	63 (4–93)	61.6 ± 2.0	63.0 ± 0.5
Male sex	469 (63)	40 (74)	430 (63)
Prior chemotherapy	229 (31)	20 (37)	209 (30)
Prior temozolomide	142 (19)	12 (22)	130 (19)
Corticosteroid use (≥10 mg/dy; ≥10 dys)	339 (46)	46 (85)	293 (43)
Infliximab use	54 (7)	13 (24)	41 (6)

Serious Infection?

Treatment (n = 898 Treatment Courses)	Overall	Yes (n = 54)	Yes (n = 844)
Ipilimumab	658 (73)	40 (74)	618 (73)
Nivolumab	52 (5.7)	1 (1.9)	51 (6)
Pembrolizumab	83 (9.2)	0 (0)	83 (9.8)
Ipilimumab + nivolumab	80 (8.9)	12 (22)	68 (8)

Table 2. Specific Infection Types

Infection Type	No. of Cases
Bacterial	46
Pneumonia	13
Intra-abdominal infection	7
Craniofacial infection	3
Bacterial bloodstream infection	13
Clostridium difficile–associated diarrhea	10
Fungal	6
Invasive pulmonary aspergillosis	2
Pneumocystis pneumonia	3
Candida bloodstream infection	1
Viral	5
Zoster (disseminated or facial)	3
CMV enterocolitis	1
EBV reactivation causing facial nerve paralysis	1
Parasitic	1
Strongyloides hyperinfection	1
Total[a]	58

Mortality 13%

Del Castillo M, Clin Infect Dis 2016, 63:1490

Ir-severe pulmonary infection – *does it exist?*

Retrospective cohort of severe infections in melanoma patients treated by ICI at the MSKCC between 2010 and 2014

Characteristic (n = 740 Patients)	Overall	7.3% Serious Infection? Yes (n = 54)	No (n = 686)	*P* Value	OR (95% CI)
Age, y, mean (range)	63 (4–93)	61.6 ± 2.0	63.0 ± 0.5	.47	
Male sex	470 (63)	40 (74)	430 (63)	.11	1.70 (.90–3.09)
Prior chemotherapy	229 (31)	20 (37)	209 (30)	.36	1.34 (.76–2.39)
Prior temozolomide	142 (19)	12 (22)	130 (19)	.59	1.22 (.64–2.36)
Corticosteroid use (≥10 mg/dy; ≥10 dys)	339 (46)	46 (85)	293 (43)	<.0001	7.71 (3.71–16.18)
Infliximab use	54 (7)	13 (24)	41 (6)	<.0001	4.74 (2.27–9.45)

Steroids: median dose, 40 mg; median duration, 60 days

Treatment (n = 898 Treatment Courses)	Overall	Serious Infection? Yes (n = 54)	Yes (n = 844)	*P* Value	OR (95% CI)
Ipilimumab	658 (73)	40 (74)	618 (73)	.99	1.05 (.55–1.90)
Nivolumab	52 (5.7)	1 (1.9)	51 (6)	.36	0.29 (.03–1.68)
Pembrolizumab	83 (9.2)	0 (0)	83 (9.8)	.0069	0 (0–.63)
Ipilimumab + nivolumab	80 (8.9)	12 (22)	68 (8)	.0017	3.26 (1.70–6.27)

Del Castillo M, Clin Infect Dis 2016, 63:1490

Diagnostic strategy of Ir-respiratory AEs – *in advanced NSCLC*

Clinically asymptomatic
(7-33%)

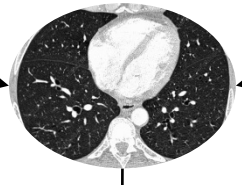
Follow-up CT-scan

Grade ≤ 2, continue ICI?

Clinically symptomatic
(30-100%)

Additional CT-scan

Grade 2-4, hold ICI



New abnormalities

Dyspnea
(SaO2 <92%, ARDS?)
→ Consider hospitalization in ICU, oxygenation
- *BNP, EKG, echocardiography (ir-myocarditis)*
- *CPK, aldolase (ir-myositis)*

Fever
→ Consider need for bronchoscopy ± BAL
- *microbiological sputum examination, blood cultures, LP/SP antigens…*
- *if corticosteroids treatment, suspect severe infection: bacterial, tuberculosis, PcJ pneumonia, aspergillosis*

Consider risk factors of Ir-AEs
- *comorbidities and other pneumotoxic treatments*
- *prior treatments: TKIs, radiotherapy*
- *duration of ICIs treatment (≥ 9 weeks)*
- *type of ICIs, PD-1/PD-L1 vs CTLA-4 inhibitors*
- ***other signs of ir-AEs***
- ***corticosteroids for previous irAE treatment***

Change in tumor targets

YES

- early onset,
  - consider **hyperprogression** or **pseudo-progression**
- late onset,
  - consider **tumor progression**
  - explore associated complication

NO

Pleural effusion
- **infection; TB;** progression; heart failure

Adenopathy(ies)
- **sarcoidose-like; TB;** progression

Parenchymal abnormalities
- **GGO, condensation**
  - **ICI-P**; **infection**
- **nodules, µnodules, bronchiolitis**
  - **infection; TB;**
  ICI-P; sarcoidose-like

Therapeutic strategy of Ir-pneumonitis – *international recommendations*

	ASCO	ESMO	SITC
Grade 1	*ICI management:* **hold ICI** *Treatment:* no specific treatment *Drug rechallenge:* Yes, **if** radiographic evidence of improvement	*ICI management:* **consider delay of treatment** *Treatment:* no specific treatment *Drug rechallenge:* unspecified	*ICI management:* **hold ICI** *Treatment:* no specific treatment *Drug rechallenge:* Yes, **if** chest imaging abnormalities resolve
Grade 2	*ICI management:* **hold ICI** *Treatment:* **prednisone 1-2 mg/kg/d orally** and taper over **4-6 weeks** *Drug rechallenge:* Yes, **if** resolution to G1 or less.	*ICI management:* **hold ICI** *Treatment* : **prednisolone 1 mg/kg/d orally** and taper over **at least 6 weeks** *Drug rechallenge* : unspecified	*ICI management :* **hold ICI** *Treatment*: **methylprednisolone 1 mg/kg/d (IV or oral** equivalent) and taper **at least 4 weeks** *Drug rechallenge :* Yes, **if** symptoms and imaging abnormalities resolve
Grade 3/4	*ICI management:* **stop ICI** *Treatment*: **empirical ATB / (methyl)prednisolone IV 1-2 mg/kg/d**; taper corticosteroids **over 4-6 weeks** If no improvement after 48h, may add infliximab 5 mg/kg or MMF or IVIG or cyclophosphamide; *Drug rechallenge:* No	*ICI management:* **stop ICI** *Treatment:* **empirical ATB / (methyl)prednisolone IV 2-4 mg/kg/d**; taper corticosteroids **at least 8 weeks** If no improvement after 48h, add infliximab 5 mg/kg or MMF *Drug rechallenge:* unspecified	*ICI management*: **stop ICI** *Treatment*: **methylprednisolone IV, 2 mg/kg/d**; taper corticosteroids **at least 8 weeks** If no improvement, add infliximab or cyclophosphamide, or MMF or IVIG *Drug rechallenge:* Grade 4: No **Grade 3 : case-by-case ; only if symptoms and imaging abnormalities resolve**

Brahmer J, J Clin Oncol 2018, 36:1714; Haanen J, Ann Oncol 2017, 28:iv119; Puzanov I, J ImmunoTherapy of Cancer 2017,5:95

Immune related-pneumonitis – *it is not about the frequency, but about diversity !*