General principles in irAE management in lung cancer treatment

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台中榮總 胸腔內科

曾政森 醫師

Jeng-Sen Tseng, M.D., Ph.D. (tzeng64@gmail.com)
Division of Chest Medicine, Taichung Veterans General Hospital
Faculty of Medicine, School of Medicine, National Yang-Ming University
Institute of Biomedical Sciences, National Chung Hsing University

“PRINCIPLES” of irAEs management

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General principles in irAE management

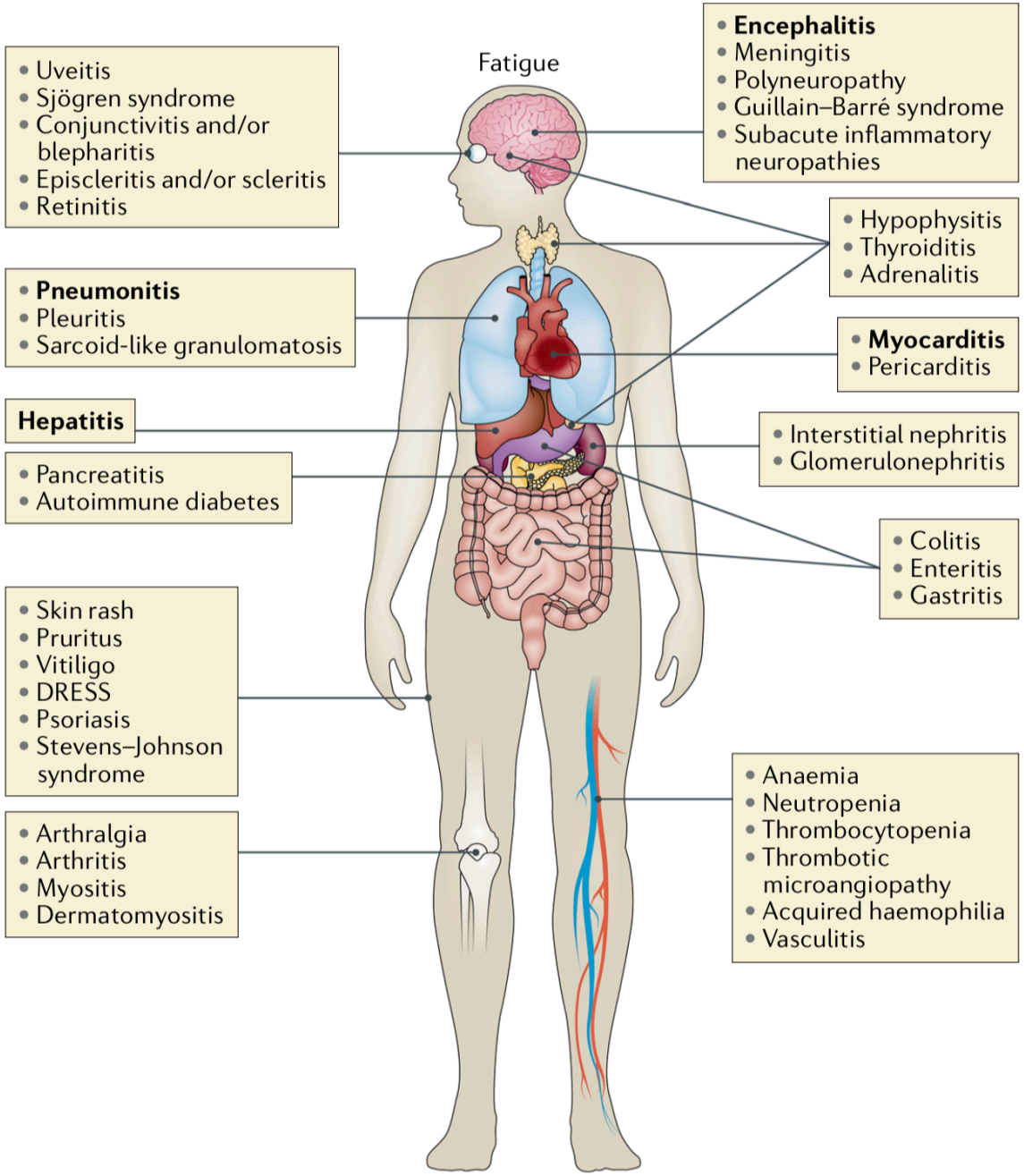
I. The incidence of irAE

Overall AEs as compared with CT

AE(s)	Pembrolizumab[1,2] (KN-024 & 042, n = 1555)		Nivolumab + Ipilimumab[3] (CM-227, n = 1146)		Atezolizumab[4] (IMPower110, n = 572)	
	IO	CT	IO + IO	CT	IO	CT
Any grade	512 (64.8)	688 (89.9)	442 (76.7)	467 (81.9)	258 (90.2)	249 (94.7)
Grade 3-5	154 (19.5)	331 (43.3)	189 (32.8)	205 (36.0)	97 (33.9)	149 (56.7)

Less all grade AEs and less grade 3-5 AEs as compared with chemotherapy

[1]Reck M et al. N Engl J Med 2016; 375:1823-33. [2]Mok T et al. Lancet 2019; 393:1819-30.
[3]Hellmann MD et al. N Engl J Med 2019; 381:2020-31. [4]Herbst RS et al. N Engl J Med 2020; 383:1328-39.



Spectrum of irAE

Almost whole body can be affected

Martins F et al. Nat Rev Clin Oncol 2019; 16:563-80.

Anti-PD-1: Pembrolizumab (1L)

KN-024 Pembrolizumab (n = 154)[1]

irAE(s)	Any Grade	Grade 3-5
Any	45 (29.2)	15 (9.7)
Hypothyroidism	14 (9.1)	0
Hyperthyroidism	12 (7.8)	0
Pneumonitis	9 (5.8)	**4 (2.6)**
Infusion reaction	7 (4.5)	0
Severe skin reaction	6 (3.9)	**6 (3.9)**
Thyroiditis	4 (2.6)	0
Colitis	3 (1.9)	2 (1.3)
Myositis	3 (1.9)	0
Hypophysitis	1 (0.6)	1 (0.6)
Nephritis	1 (0.6)	1 (0.6)
Pancreatitis	1 (0.6)	1 (0.6)
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)

*No grade 5 irAE.

KN-042 Pembrolizumab (n = 637)[2]

irAE(s)	Any Grade	Grade 3-5
Any	177 (28)	51 (8)
Hypothyroidism	77 (12)	1 (<1)
Pneumonitis	53 (8)	**22 (3)** → 1 died
Hyperthyroidism	39 (6)	1 (<1)
Severe skin reaction	15 (2)	**11 (2)**
Infusion reaction	10 (2)	1 (<1)
Thyroiditis	10 (2)	0
Hepatitis	9 (1)	7 (1)
Colitis	7 (1)	4 (<1)
Adrenal insufficiency	4 (<1)	2 (<1)
Hypophysitis	3 (<1)	3 (<1)
Nephritis	3 (<1)	1 (<1)
Myocarditis	1 (<1)	1 (<1)
Pancreatitis	1 (<1)	0

*Death due to pneumonitis 1/13 in experimental arm.

[1]Reck M et al. N Engl J Med 2016; 375:1823-33. [2]Mok T et al. Lancet 2019; 393:1819-30.

Anti-PD-1: Nivolumab (1L)

CM-227 Nivolumab (n = 576 and 391)[1]

irAE(s)	Nivolumab + Ipilimumab		Nivolumab	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Skin	196 (34.0)	24 (4.2)	83 (21.2)	4 (1.0)
Endocrine	137 (23.8)	24 (4.2)	51 (13.0)	2 (0.5)
Gastrointestinal	105 (18.2)	14 (2.4)	50 (12.8)	4 (1.0)
Hepatic	91 (15.8)	**47 (8.2)**	42 (10.7)	**15 (3.8)**
Pulmonary	48 (8.3)	19 (3.3)	30 (7.7)	6 (1.5) → 4&1 died
Renal	25 (4.3)	4 (0.7)	6 (1.5)	3 (0.8)
Infusion reaction	23 (4.0)	0	17 (4.3)	2 (0.5)

*Death due to pneumonitis 4/8 in Nivo/Ipi arm and 1/2 in Nivo arm.

CM-9LA Nivolumab (n = 358)[2]

irAE(s)	Nivolumab + Ipilimumab	
	Any grade	Grade 3-5
Skin	129 (36.0)	**16 (4.5)**
Endocrine	82 (22,9)	10 (2.8)
Gastrointestinal	62 (17.3)	**20 (5.6)**
Hepatic	35 (9.8)	**16 (4.5)**
Renal	18 (5.0)	7 (2.0)
Pulmonary	13 (3.6)	6 (1.7) → 1 died
Infusion reaction	16 (4.5)	2 (0.6)

*Death due to pneumonitis 1/7 in experimental arm.

[1]Hellmann MD et al. N Engl J Med 2019; 381:2020-31.
[2]Luis Paz-Ares et al. Lancet Oncol 2021; 22:198-211.

Anti-PD-L1: Atezolizumab (1L)

IMpower110: Atezolizumab (n = 286)[1]

irAE(s)	Any grade	Grade 3-5
Any	115 (40.2)	19 (6.6)
Hepatitis	46 (16.1)	**12 (4.2)**
Skin rash	44 (15.4)	**3 (1.0)**
Hypothyroidism	27 (9.4)	0
Hyperthyroidism	13 (4.5)	0
Pneumonitis	11 (3.8)	2 (0.7)
Infusion-related reaction	4 (1.4)	0
Colitis	3 (1.0)	2 (0.7)

*Grade 5 AE of any cause: 11 (no Grade 5 irAE).

[1]Herbst RS et al. N Engl J Med 2020; 383:1328-39.

Anti-PD-L1: Durvalumab (1L)

MYSTIC: Durvalumab (n = 369)[1]

irAE(s)	Any grade	Grade 3-5
Any	50 (13.6)	16 (4.3)
Hypothyroidism	21 (5.7)	2 (0.5)
Pneumonitis	8 (2.2)	**5 (1.4)** → 1 died
Diarrhea	7 (1.9)	1 (0.3)
Skin rash	5 (1.4)	**4 (1.1)**
Colitis	2 (0.5)	1 (0.3)
Adrenal insufficiency	1 (0.3)	1 (0.3)
Hyperthyroidism	4 (1.1)	0
Hepatitis	1 (0.3)	1 (0.3)
Pancreatic laboratory parameters	2 (0.5)	1 (0.3)
Dermatitis	2 (0.5)	0
Hepatic laboratory parameters	2 (0.5)	1 (0.3)
Hypophysitis	0	0
Nephritis	0	0
Thyroid laboratory parameters	2 (0.5)	0
Type 1 diabetes mellitus	0	0
Other rare	2 (0.5)	1 (0.3)

*Death due to pneumonitis 1/2 in experimental arm.

PACIFIC: Durvalumab (n = 475)[2]

irAE(s)	Any grade	Grade 3-5
Any	115 (24.2)	20 (4.2)
Pneumonitis	51 (10.7)	**8 (1.7)** → 4 died
Hypothyroidism	44 (9.3)	1 (0.2)
Hyperthyroidism	13 (2.7)	0
Skin rash	5 (1.1)	2 (0.4)
Dermatitis	5 (1.1)	0

*21 patients with Gr. 5 AE of any causes; 4 with pneumonitis.

[1]Rizvi NA et al. JAMA Oncol 2020; 6:661-74.
[2]Antonia SJ et al. N Engl J Med 2017; 337:1919-29.

General principles in irAE management

I. The incidence of irAE

- The overall AEs (any grade & grade 3-5) are less in IO than in chemotherapy.
- The incidence of irAE is approximately 25-40% with all grades and 5-10% with grade 3-5.
- The most common irAEs are endocrinopathy (esp. thyroid), pneumonitis, skin toxicity, and hepatitis.
- The most common grade 3-5 irAEs are pneumonitis, skin toxicity, and hepatitis.
- AE lead to death is rare; of them, pneumonitis is the most common cause (~20%).

General principles in irAE management

I. The incidence of irAE

All grade ~25-40%, grade 3-5 ~5-10%

II. Risk factors of irAE

Comparisons between regimens

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Nivolumab	**0.28 (0.13 to 0.59)**	**0.14 (0.03 to 0.59)**	0.61 (0.27 to 1.34)	1.00 (0.37 to 2.68)	**0.10 (0.03 to 0.29)**	**0.11 (0.05 to 0.24)**	**0.25 (0.15 to 0.42)**
0.49 (0.25 to 0.95)	Ipilimumab	0.48 (0.10 to 2.42)	2.17 (0.92 to 5.34)	**3.56 (1.20 to 10.99)**	**0.35 (0.13 to 0.95)**	**0.41 (0.17 to 1.00)**	0.89 (0.42 to 1.96)
0.18 (0.04 to 0.74)	0.36 (0.08 to 1.63)	Tremelimumab	4.49 (0.94 to 21.33)	**7.39 (1.43 to 38.18)**	0.73 (0.12 to 4.29)	0.84 (0.18 to 3.89)	1.85 (0.45 to 7.49)
0.84 (0.41 to 1.72)	1.69 (0.80 to 3.77)	**4.72 (1.06 to 21.27)**	Pembrolizumab	1.65 (0.57 to 4.76)	**0.16 (0.05 to 0.56)**	**0.19 (0.08 to 0.45)**	**0.41 (0.21 to 0.79)**
1.44 (0.60 to 3.35)	**2.90 (1.08 to 7.92)**	**8.08 (1.73 to 37.65)**	1.71 (0.66 to 4.41)	Atezolizumab	**0.10 (0.02 to 0.39)**	**0.11 (0.04 to 0.31)**	**0.25 (0.11 to 0.57)**
0.27 (0.09 to 0.80)	0.55 (0.21 to 1.56)	1.54 (0.26 to 9.21)	0.33 (0.10 to 1.08)	**0.19 (0.05 to 0.73)**	Two ICI drugs	1.15 (0.33 to 4.08)	2.52 (0.82 to 8.07)
0.22 (0.11 to 0.44)	**0.44 (0.20 to 1.00)**	1.23 (0.29 to 5.39)	**0.26 (0.12 to 0.57)**	**0.15 (0.06 to 0.38)**	0.79 (0.24 to 2.62)	One ICI drug with conventional therapy	**2.19 (1.23 to 3.95)**
0.40 (0.25 to 0.63)	0.81 (0.42 to 1.59)	2.26 (0.58 to 8.80)	**0.48 (0.26 to 0.88)**	**0.28 (0.14 to 0.59)**	1.48 (0.48 to 4.36)	**1.85 (1.07 to 3.10)**	Conventional therapy

Pooled incidence (%)

*		†	
n = 9	14.4 (11.9 to 17.3)	n = 11	14.1 (11.9 to 16.7)
n = 6	25.4 (16.6 to 36.9)	n = 8	28.6 (18.9 to 40.8)
n = 1	52.3	-	-
n = 5	20.8 (10.2 to 37.8)	n = 6	19.8 (10.6 to 33.9)
n = 3	15.7 (11.7 to 20.6)	n = 6	15.1 (12.7 to 17.9)
n = 2	57.7 (52.9 to 62.4)	-	-
n = 7	43.7 (38.4 to 49.2)	-	-
n = 22	36.2 (31.3 to 41.4)	-	-

Pooled incidence (%)

*

n = 9	n = 6	n = 1	n = 5	n = 3	n = 2	n = 7	n = 22
74.3 (67.4 to 80.2)	85.0 (73.2 to 92.2)	96.0	77.1 (68.1 to 84.2)	66.6 (62.8 to 70.3)	94.2 (88.6 to 97.2)	84.5 (80.0 to 88.1)	84.2 (79.1 to 88.2)

†

n = 11	n = 8	-	n = 6	n = 6	-	-	-
71.8 (63.0 to 79.2)	86.8 (76.7 to 93.0)	-	75.1 (66.9 to 81.8)	66.4 (64.4 to 68.4)	-	-	-

* Based on studies included in NMA

Grade 1-5 adverse events

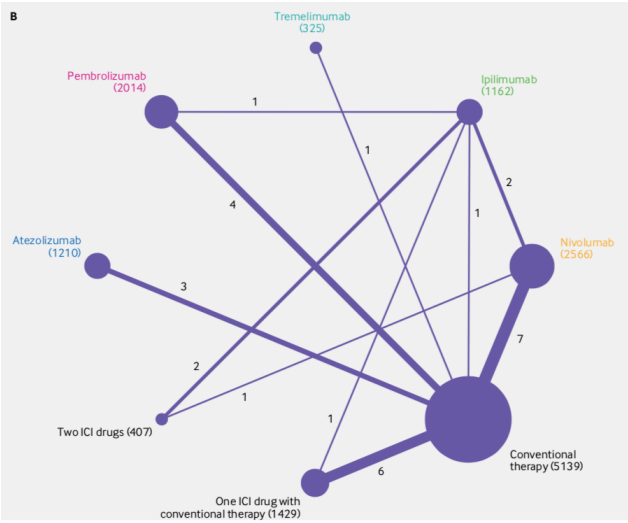
† Based on studies included in NMA and validation group

Grade 3 or 4 adverse events

Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis

Cheng Xu,[1] Yu-Pei Chen,[1] Xiao-Jing Du,[1] Jin-Qi Liu,[1] Cheng-Long Huang,[1] Lei Chen,[1] Guan-Qun Zhou,[1] Wen-Fei Li,[1] Yan-Ping Mao,[1] Chiun Hsu,[2] Qing Liu,[3] Ai-Hua Lin,[3] Ling-Long Tang,[1] Ying Sun,[1] Jun Ma[1]

Meta-analysis of 36 comparative phase II and III RCTs (n = 15,370)



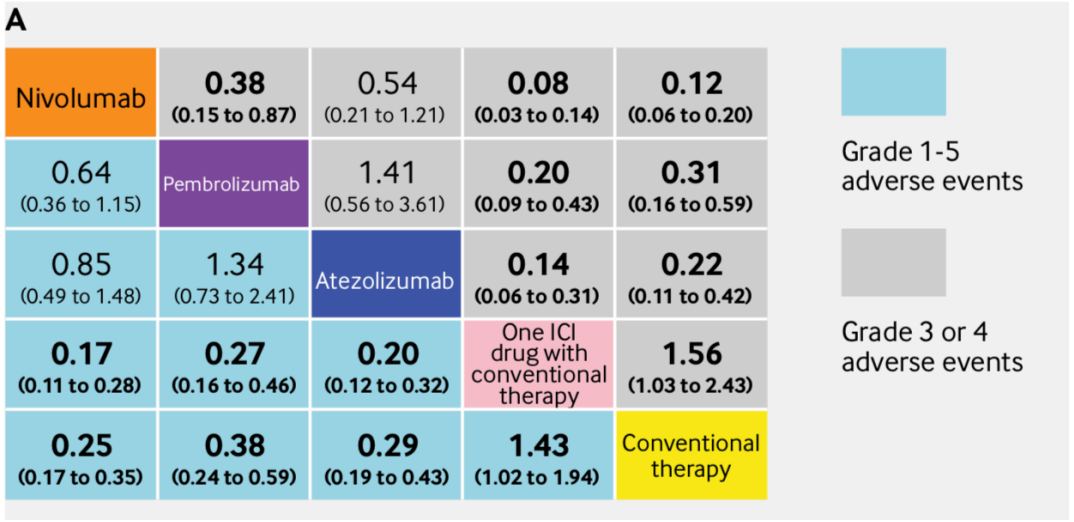
- The pooled odds ratios and 95% credibility intervals indicate the result of the top treatment compared with the bottom treatment.
- Conventional therapy: C/T, targeted therapy or combinations.
- network meta-analysis (NMA)

Xu C et al. BMJ 2018; 363:k4226.

Comparisons between regimens

First author, year	Study ID	Region	Trial phase	Total No	Safety analysis No	Arm	Treatment (median follow-up time, months)	CTCAE version	TrAE reporting rate*
Untreated stage IV/recurrent squamous non-small-cell lung cancer:									
Govindan, 2017[18]	CA184-104	MN	III	749	388	1	PTX, CBP, and IPI 10 mg/kg every 3 weeks (12.5	3.0	≥5
					361	2	PTX and CBP (11.8)		
Untreated PD-L1 positive stage IV/recurrent squamous/non-squamous non-small-cell lung cancer:									
Carbone, 2017[21]	CheckMate 026	MN	III	541	267	1	NIV 3 mg/kg every 2 weeks (13.5)	4.0	≥5
					263	2	ICC, Platinum base chemotherapy, 6 cycles (13.5)		
Reck (1), 2016[25]	Keynote 024	MN	III	305	154	1	PEM 200 mg every 3 weeks (11.2)	4.0	≥10
					150	2	ICC (CBP and pemetrexed, DDP and pemetrexed, CBP and GEM, DDP and GEM, CBP and PTX) (11.2)		
Untreated extensive-disease mall-cell lung cancer:									
Reck (2), 2016[26]	CA184-156	MN	III	954	478	1	IPI 10 mg/kg every 3 weeks, ETO, and DDP or CBP (10.5)	3.0	≥5
					476	2	ETO and DDP or CBP (10.2)		
Reck, 2013[38]	CA184-041	MN	II	130	42	1	CR (IPI 10 mg/kg every 2 weeks and ?TX 175 mg/m^{2}every 3 weeks or CBP AUC=6, followed by PTX or CBP) (min 11.1)	3.0	≥15
					42	2	PR (PTX 175 mg/m^2 every 3 weeks or CBP AUC=6, followed by IPI 10 mg/kg every 2 weeks and PTX or CBP) (min 11.1)		
					44	3	CR (PTX 175 mg/m^2 every 3 weeks or CBP AUC=6) (min 11.1)		
Untreated stage IIIB/IV non-squamous non-small-cell lung cancer:									
Langer, 2016[27]	Keynote 021	USA, Taiwan	II	123	59	1	PEM 200 mg every 3 weeks, CBP AUC=5, and pemetrexed 500 mg/m^2 every 3 weeks (10.6)	4.0	≥10
					62	2	CBP AUC=5 and pemetrexed 500 mg/m^2 every 3 weeks (10.6)		
Treated PD-L1 positive advanced squamous/non-squamous non-small-cell lung cancer:									
Herbst, 2016[30]	Keynote 010	MN	II/III	1034	339	1	PEM 2 mg/kg every 3 weeks (13.1)	4.0	≥10
					343	2	PEM 10 mg/kg every 3 weeks (13.1)		
					309	3	DOC 75 mg/m^2 every 3 weeks (13.1)		
Treated advanced/metastatic (stage IIIB/IV or recurrent) squamous non-small-cell lung cancer:									
Brahmer, 2015[34]	CheckMate 017	MN	III	272	131	1	NIV 3 mg/kg every 2 weeks (min 11.0)	4.0	≥5
					129	2	DOC 75 mg/m^2 every 3 weeks (min 11.0)		
Treated advanced/metastatic (stage IIIB/IV or recurrent) non-squamous non-small-cell lung cancer:									
Borghaei, 2015[35]	CheckMate 057	MN	III	582	287	1	NIV 3 mg/kg every 2 weeks (min 13.2)	4.0	≥5
					268	2	DOC 75 mg/m^2 every 3 weeks (min 13.2)		
Untreated stage IIIB/IV squamous/non-squamous non-small-cell lung cancer:									
Lynch, 2012[39]	CA184-041	MN	II	204	71	1	CR (IPI 10 mg/kg every 2 weeks and ?TX 175 mg/m^2 every 3 weeks or CBP AUC=6, followed by PTX or CBP) (NR)	3.0	≥15
					67	2	PR (PTX 175 mg/m^2 every 3 weeks or CBP AUC=6, followed by IPI 10 mg/kg every 2 weeks and PTX or CBP) (NR)		
					65	3	CR (PTX 175 mg/m^2 every 3 weeks or CBP AUC=6) (NR)		
Treated advanced/me astatic (stage IIIB/IV or recurrent) squamous/non-squamous non-small-cell lung cancer:									
Rittmeyer, 2017[12]	OAK	MN	III	1225	609	1	ATE 1200 mg every 3 weeks (21.0)	4.0	≥10
					578	2	DOC 75 mg/m^2 every 3 weeks (21.0)		
Fehrenbacher, 2016[31]	POPLAR	MN	II	287	142	1	ATE 1200 mg every 3 weeks (14.8)	4.0	≥5
					135	2	DOC 75 mg/m^2 every 3 weeks (15.7)		

Subgroup analysis: lung cancer



Xu C et al. BMJ 2018; 363:k4226.

Comparisons between regimens

Higher risks of certain AE profiles of IO regimens

Atezolizumab: hypothyroidism, nausea, and vomiting.

Pembrolizumab: arthralgia, pneumonitis, and hepatic toxicities.

Nivolumab: endocrine toxicities.

Ipilimumab: skin, gastrointestinal, and renal toxicities.

Xu C et al. BMJ 2018; 363:k4226.

Risk factors for irAEs: retrospective study

Patients who received **pembrolizumab** at Samsung Medical Center (2015-2917), n = 391
54% of patients were lung cancer

67 (**17.1%**) with clinically significant irAEs

	Odds ratio	95% CI	*p*
BMI	1.08	1.01–1.16	0.036
Number of pembrolizumab cycle	1.15	1.08–1.22	<0.001
dNLR ≥ 3	0.37	0.17–0.81	0.012

Eun Y et al. Sci Rep 2019; 9:14039.

Risk factors for irAEs: retrospective study

- N = 75 patients: lung cancer (***70%***), urothelial cancer (12%), HCC (6%), and RCC (5%)
- 31 patients (**42%**) had irAE

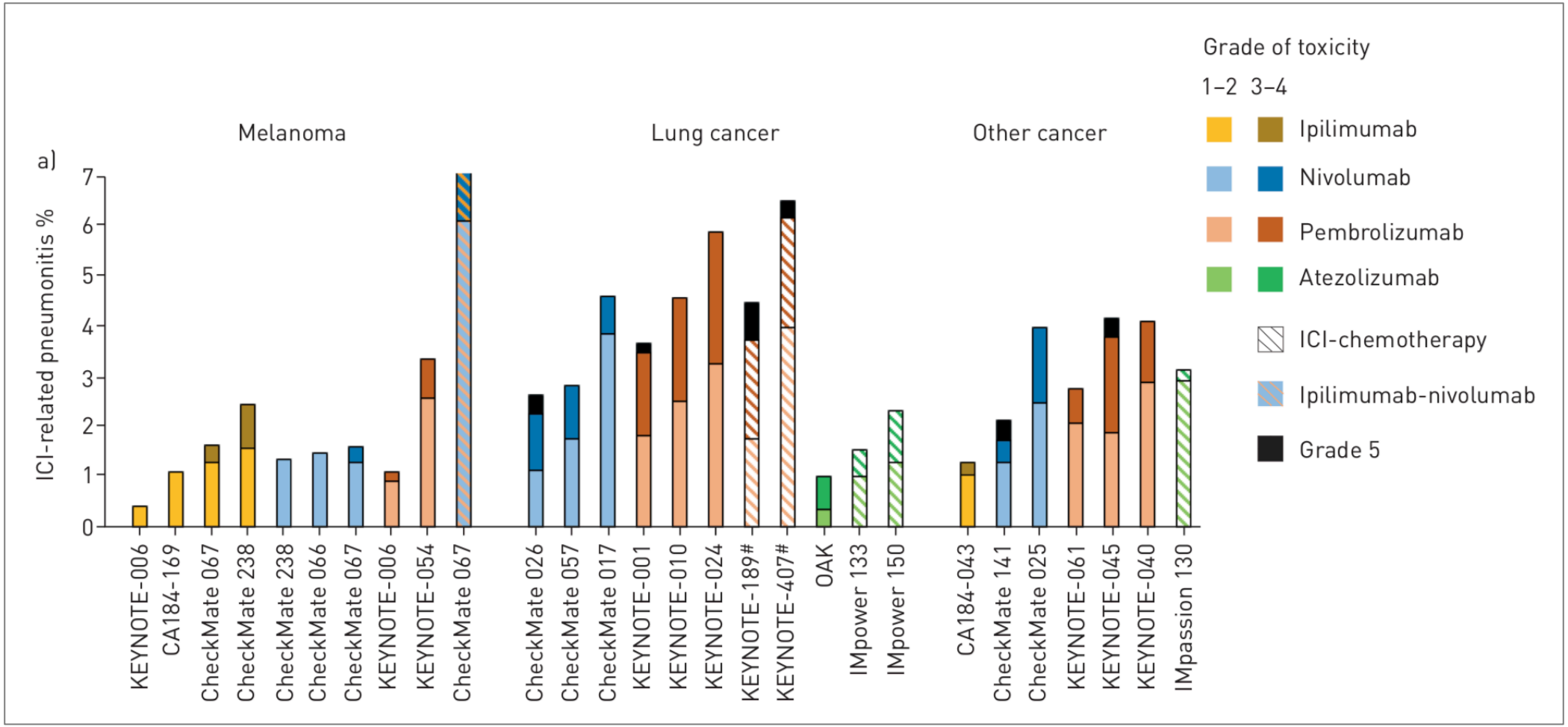
- Most common irAE: endocrine dysfunction, skin toxicity, and pneumonitis

Factor	aOR	95% CI	P value
Female	3.72	1.15-12.83	0.037
Lung adenocarcinoma	3.94	1.12-13.79	0.032
Allergy history	17.04	1.57-191.55	0.022
Autoimmune disease	16.88	2.75-103.48	0.002

Parmanande AQ et al. Ann Oncol 2019; 30:Suppl 11, X121.

Risk factors of pneumonitis

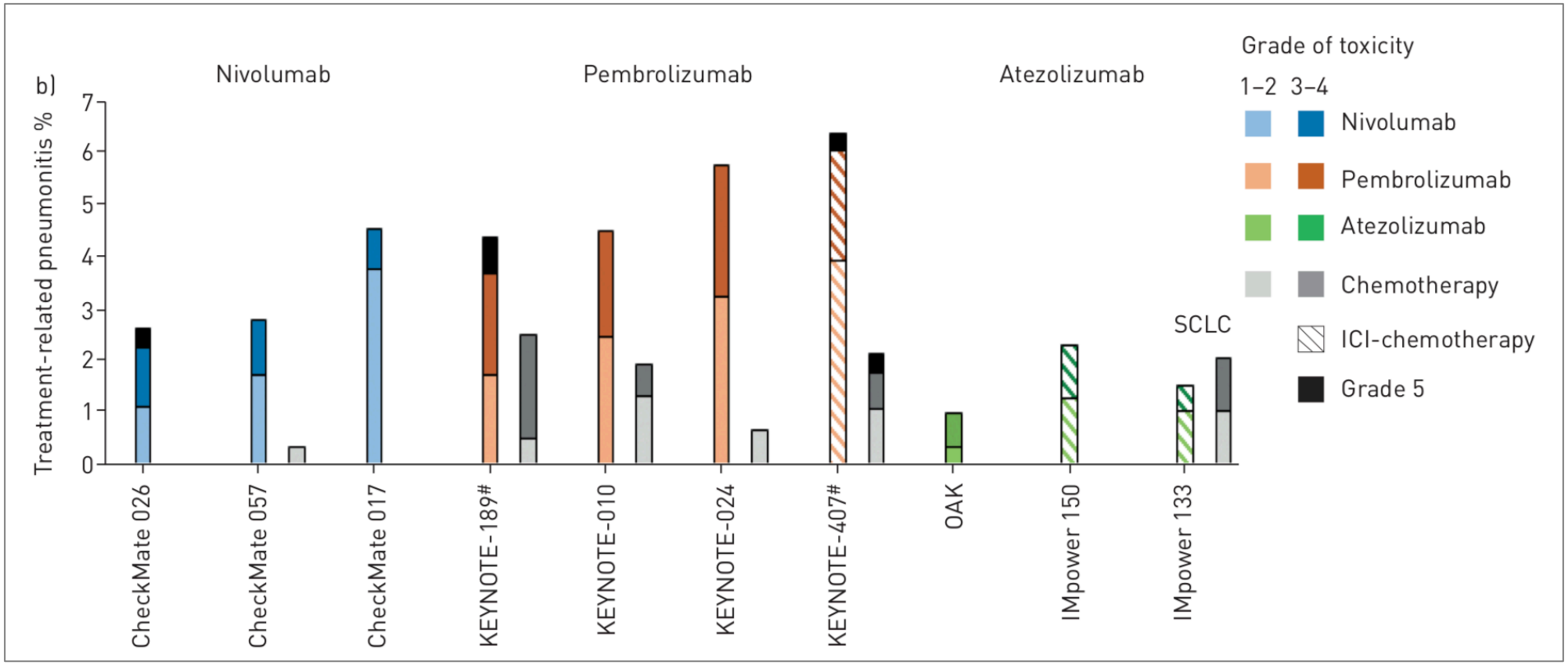
ICI-P in phase-III trials



Cadranel J et al. Eur Respir Rev 2019; 28:190058.

Risk factors of pneumonitis

ICI-P in phase-III lung cancer trials



Cadranel J et al. Eur Respir Rev 2019; 28:190058.

Risk factors of pneumonitis

Immune checkpoint inhibitor-related pneumonitis (ICI-P)

Characteristics	Comments
Frequency of ICI-P	5th cause of irAEs after skin toxicities, hepatitis, thyroiditis, and colitis 2.6-4.8% all grade; 0.6-2.0% for grades ≥ 3
Increased risk of pneumonitis in NSCLC	Relative risk all grades: 1.33-1.43
Increased risk of pneumonitis compared to CT	Relative risk all grades: 2.35-5.17 Relative risk grades ≥ 3: 1-4.19
Increased risk of ICI-P with anti-PD-1/PD-L1 versus anti-CTLA-4 inhibitors	Relative risk all grades: 3.47-6.4
Increased risk of ICI-P with ICI/ICI combotherapy versus ICI monotherapy	Relative risk all grades: 3.48-3.68
Fatal ICI-P	Primary cause of lethal irAEs: 35% of deaths 13% fatality rate
Other reported risk factors	Age, prior ILD, SqCC, male

Cadranel J et al. Eur Respir Rev 2019; 28:190058.

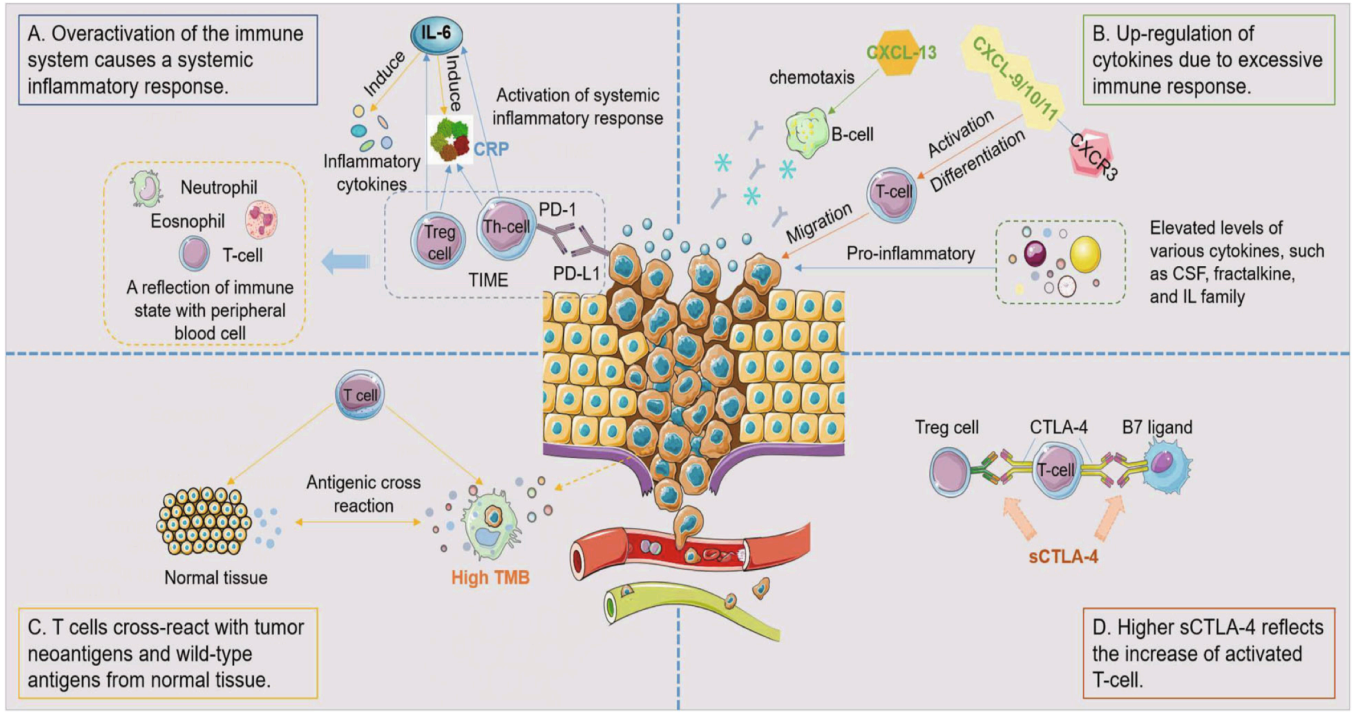
Biomarkers of irAEs

Table 1 Nonspecific biomarker of irAEs

Biomarker	Author	Year	Cancer type	Patient number	Treatment	Correlation between biomarker and irAEs	Possible hypothesis
CRP	Abolhassani AR [18]	2019	MM	37	Anti-PD-1 Anti-CTLA-4	CRP elevation can predict the onset of irAEs in patients treated with ICIs in the absence of infectious disease.	Tumor-promoting inflammation could cause a systemic inflammatory response;CRP level was positively associated with the infiltration of CD8 + T cell and Treg cell which could activate the systemic inflammatory response.
IL-6	Okiyama N [19]	2017	MM	22	Anti-PD-1	The IL-6 level was significantly increased in the patients with psoriasiform dermatitis after nivolumab treatment.	Overactivation of the immune system;Excessive release of inflammatory cytokines.
	Valpione S [15]	2018	MM	140	Anti-CTLA 4	A lower baseline level of IL-6 was strongly associated with the development of irAEs.	
Blood cell count	Fujisawa Y [20]	2017	MM	101	Anti-PD-1	The increase of WBC counts and the decrease of relative lymphocyte counts were closely related to the incidence of grade 3–4 irAEs.	Conventional blood cell counts could be a crude reflection of the body's immune state, but the mechanism is unclear.
	Diehl A [21]	2017	Multiple solid tumors (lung cancer, MM, RCC, urothelial, HNSCC, Merkel cell carcinoma, colon cancer)	167	Anti-PD-1	Higher baseline and increase of absolute lymphocyte and eosinophil counts after ICIs treatment were strongly associated with the development of irAEs.	
	Nakamura Y [22]	2019	MM	45	Anti-PD-1	The elevation of absolute eosinophil count at baseline and relative eosinophil count at 1 month might be valuable biomarkers to predicte endocrine irAEs.	
Cytokines	Khan S [23]	2019	Multiple solid tumors (lung cancer, kidney cancer, MM, head/neck cancer, liver cancer, bladder cancer)	65	Anti-PD-1/L1 Anti-CTLA 4	The up-regulation of various cytokines after ICIs treatment was closely related to the occurrence of irAEs, especially the induced CXCL9, 10, 11 and 13.	Activate T cell;Excessive release of cytokines;Various cytokines have powerful pro-inflammatory activities, including stimulating immune cell recruitment, proliferation, survival, differentiation, and effector functions, and many of these cytokines (such as IL-1A, IL-1B, IL-2, IFN 2, and IL-12P70) are associated with inflammation, which is the basis of autoimmune diseases.
	Lim SY [24]	2019	MM	98	Anti-PD-1 Anti-CTLA 4	Eleven cytokines, including G-CSF, GMCSF, Fractalkine, FGF-2, IFN-2, IL-12p70, IL-1a, IL-3 1B, IL-1RA, IL-2, IL-13, were significantly upregulated in patients with severe irAEs at baseline and early during treatment.	
TMB	Bomze D [25]	2019	Multiple solid tumors	16,397	Anti-PD-1	There is a significant positive correlation between high TMB and irAEs during anti-PD-1 therapy in a variety of solid tumors	While fighting against neoantigens, T cells could also cross-react with the corresponding wild-type antigens in normal tissues, resulting in damage to normal tissues.
sCLTA-4	Pistillo MP [26]	2018	MM	113	Anti-CTLA-4	Higher baseline levels of sCTLA-4 were closely associated with irAEs, especially the gastrointestinal adverse events.	Elevated levels of sCTLA-4 might block the interactions between full-length CTLA-4 expressed by autoreactive T cells and Tregs as well as B7 ligands, thus enhance the cytotoxicity of T cells and reduce the immunosuppression function of Treg cell.

irAEs immune related adverse events, *ICIs* immune checkpoint inhibitors, *CRP* C reactive protein, *MM* malignant melanoma, *Anti-PD-1/L1* anti-programmed cell death protein 1/ligand 1, *Anti-CTLA-4* anti-cytotoxic T lymphocyte associated antigen-4, *IL-6* interleukin 6, *RCC* renal cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *WBC* white blood cell, *NLR* neutrophil-lymphocyte ratio, *TMB* tumor mutation burden, *sCLTA-4* soluble CTLA-4, *flCTLA-4* full-length CTLA-4

Possible mechanisms of nonspecific biomarkers of irAEs.



- Majorities with small case numbers
- Reality & underlying mechanisms are not yet confirmed
- Useful in clinical practice ??

Xia XH et al. J Exp Clin Cancer Res 2020; 39:284.

PD-L1 expression and AEs

CM-227 study (Nivolumab + Ipilimumab)[1]

PD-L1 ≥ 1%		PD-L1 < 1%	
N = 391		N = 185	
Any Grade	Grade 3-4	Any Grade	Grade 3-4
302 (77.2)	139 (35.5)	140 (75.7)	50 (27.0)

The AEs according to PD-L1 expression level were **similar** to that in overall population.

Cho JY et al. Risk factors of ICI-P (Korea, all NSCLC)[2]

	Without ICI-P (n = 145)	With ICI-P (n = 22)	P value
PD-L1 > 0% (22C3)	35/46 (76.1%)	5/6 (83.3%)	1.000
PD-L1 > 0% (SP263)	17/22 (77.3%)	5/6 (83.3%)	1.000

[1]Hellmann MD et al. N Engl J Med 2019; 381:2020-31.
[2]Cho JY et al. Lung Cancer 2018; 125:150-6.

General principles in irAE management

I. The incidence of irAE

All grade ~25-40%, grade 3-5 ~5-10%

II. Risk factors of irAE

- Different IO regimens may have various risks and preferred types of irAEs; Combo > Mono.
- Overall AE: anti-CTLA4 > anti-PD-1/PD-L1 (Pembrolizumab, Nivolumab, Atezolizumab).
- Other factors: BMI, IO cycles, NLR, female, lung cancer, allergy, autoimmune disease. (!?)
- Other biomarkers: not yet conclusive and clinically useful. (!?)
- Pneumonitis: lung cancer & IO *per se*, anti-PD-1/PD-L1 > anti-CTLA4, combotherapy.

General principles in irAE management

I. The incidence of irAE

All grade ~25-40%, grade 3-5 ~5-10%

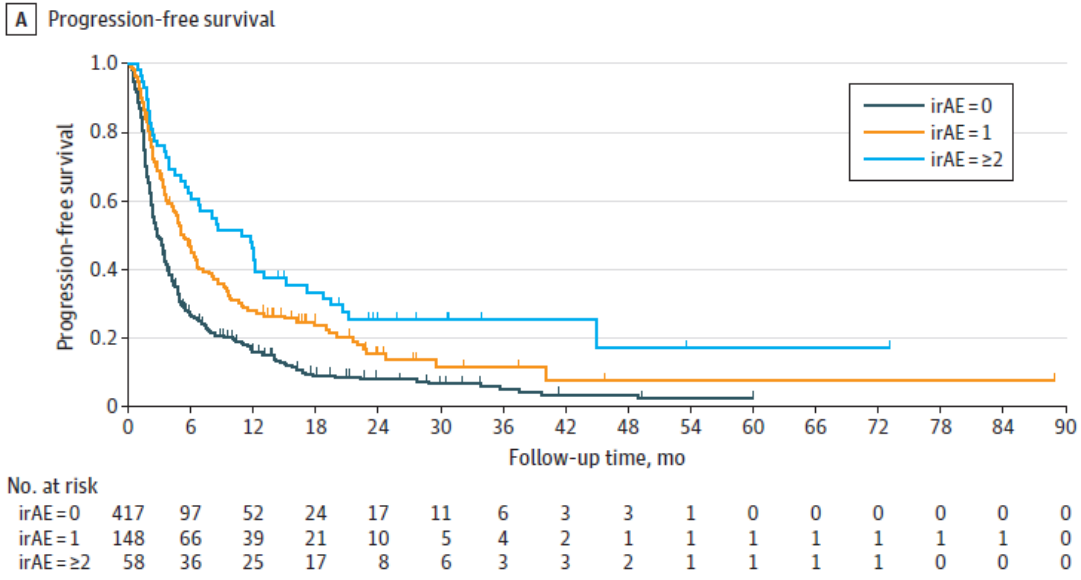
II. Risk factors of irAE

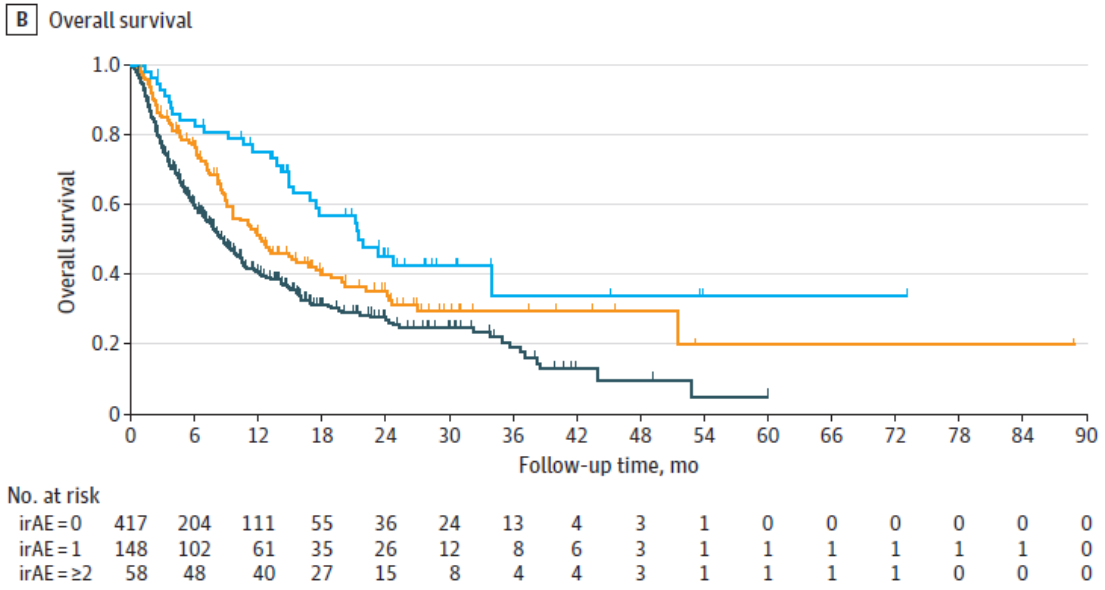
Some factors had been reported but few would impact the practice

III. Prognostic role of irAE

Prognostic role of irAEs: positive

N = 623 NSCLC patients receiving IO
Multi-system irAEs: pneumonitis/thyroiditis (14%), hepatitis/thyroiditis (10%), dermatitis/pneumonitis (10%)





JAMA Oncology | Brief Report

Multisystem Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors for Treatment of Non–Small Cell Lung Cancer

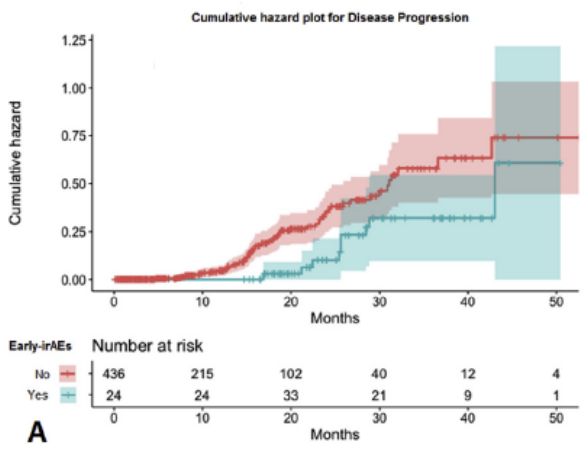
Bairavi Shankar, BA; Jiajia Zhang, MD, MPH; Abdul Rafeh Naqash, MD; Patrick M. Forde, MBBCh; Josephine L. Feliciano, MD; Kristen A. Marrone, MD; David S. Ettinger, MD; Christine L. Hann, MD, PhD; Julie R. Brahmer, MD; Biagio Ricciuti, MD; Dwight Owen, MD, MS; Yukihiro Toi, MD; Paul Walker, MD; Gregory A. Otterson, MD; Sandip H. Patel, MBBS; Shunichi Sugawara, MD; Jarushka Naidoo, MBBCH, MHS

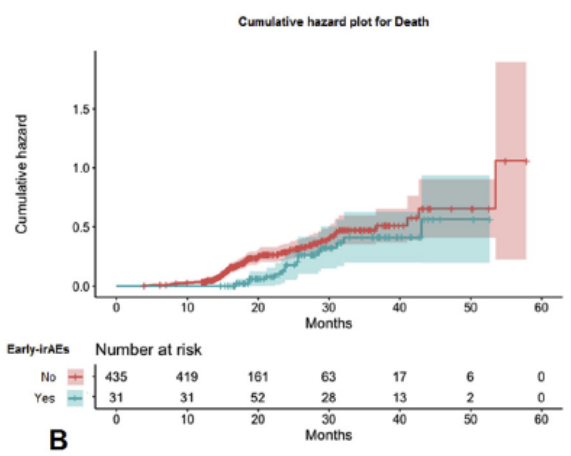
Shankar B et al. JAMA Oncol 2020; 6:1952-6.

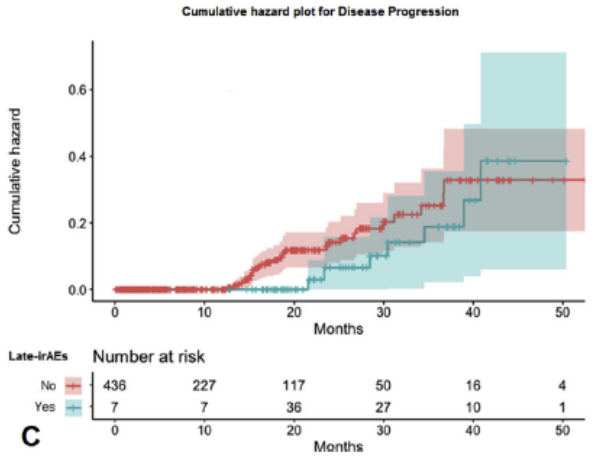
Prognostic role of irAEs: negative

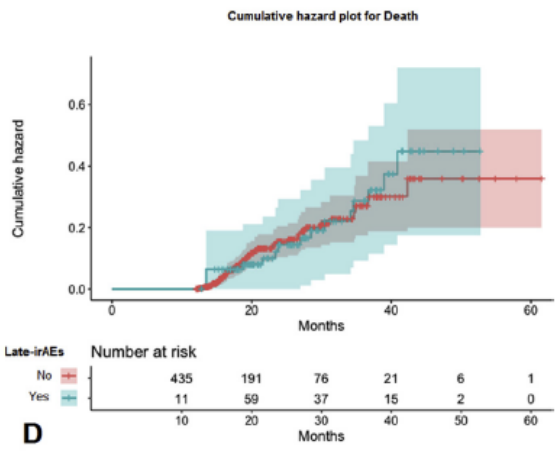
N = 436 cancer patients receiving anti-PD1/PD-L1 treatment (49.1% with lung cancer)
Early irAEs (≤ 12 months); late irAEs (> 12 months).

Time-adjusted cumulative hazard plot over time









PD based on **early** irAEs

0.63 (95% CI 0.30-1.29)

Death based on **early** irAEs

0.79 (95% CI 0.34-1.86)

PD based on **late** irAEs

0.75 (95% CI 0.37-1.56)

Death based on **late** irAEs

0.92 (95% CI 0.49-1.74)

Nigro O et al. Eur J Cancer 2020; 134:19-28.

General principles in irAE management

I. The incidence of irAE

All grade ~25-40%, grade 3-5 ~5-10%

II. Risk factors of irAE

Some factors had been reported but few would impact the practice

III. Prognostic role of irAE

- Many studies suggested that the presence of irAEs was associated with a better outcome.
- But some studies reported that no significant prognostic role or irAEs.
- Currently, it is still not conclusive and we would not look forward the irAEs developing in our patients.

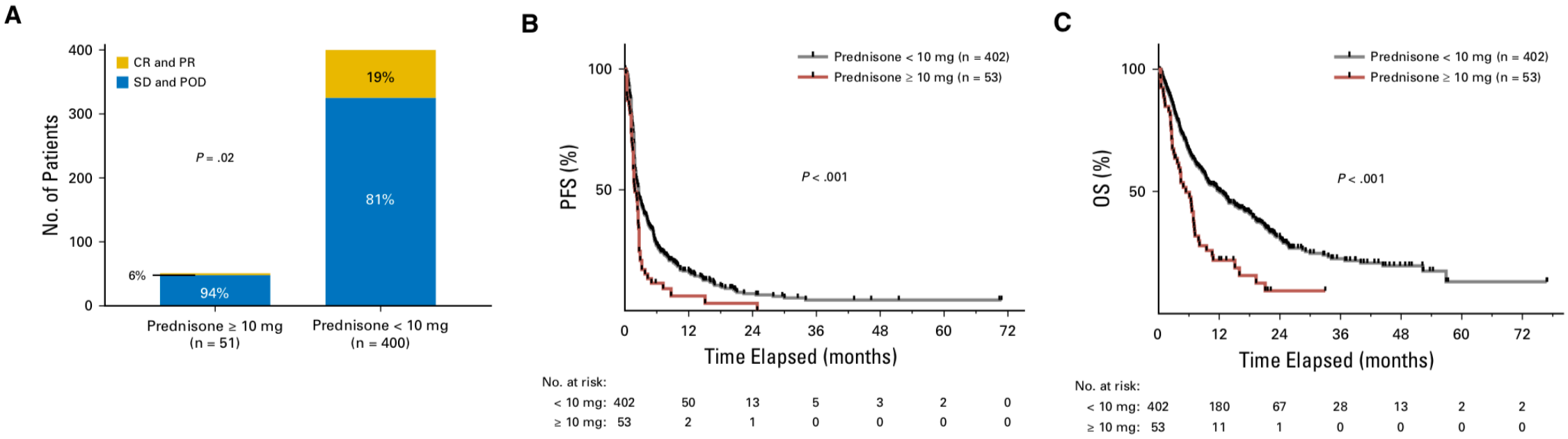
General principles in irAE management

I. The incidence of irAE	All grade ~25-40%, grade 3-5 ~5-10%
II. Risk factors of irAE	Some factors had been reported but few would impact the practice
III. Prognostic role of irAE	Some studies showed positive correlation of irAEs with outcome
IV. Diagnosis of irAE	

As you decide to prescribe IO, the risks exist

Currently, **NO** documented strategy to prevent irAEs

Premedication with corticosteroid is **NOT** feasible!



Efficacy of PD-(L)1 blockade in patients on baseline steroids

N = 455 NSCLC patients at Memorial Sloan Kettering Cancer Center & Gustave Roussy Cancer Center.

Arbour KC et al. J Clin Oncol 2018; 36:2872-8.

Pre-IO therapy assessment (NCCN)

Pre-Therapy Assessment[a]
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening (HIV; hepatitis A, B, C) as indicated
Imaging • Cross-sectional imaging • Brain MRI if indicated
General bloodwork • CBC (with differential if indicated) • Comprehensive metabolic panel
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder
Pancreatic (ICI_ENDO-1) • Baseline testing is not required.
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)[c]
Pituitary/Adrenal (ICI_ENDO-3) • Consider serum cortisol (morning preferred) and thyroid function as above
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for high-risk patients (eg, interstitial lung disease on imaging, COPD, previous suspected treatment-related lung toxicity)
Cardiovascular (ICI_CARDIO-1) • Consider baseline ECG • Individualized assessment in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease

Clinical

- Review of symptoms and physical examination
- Oxygen saturation

Laboratory tests

- CBC with differential
- Infectious disease screen (HIV, hepatitis)
- Thyroid function
- Serum cortisol

Images

- Cross-sectional imaging
- Brain MRI (if indicated)

Other tests

- PFT with DLCO for high risk patients
- Baseline ECG

Pre-IO therapy assessment (SITC)

Routine pre-treatment screening

History
- ♦ Detailed questioning for autoimmune, infectious disease, endocrine and organ-specific disease history
- ♦ History of base line bowel habit (frequency of bowel movements, usual stool consistency)

Blood tests
- ♦ CBC
- ♦ CMP
- ♦ TSH
- ♦ HbA1c
- ♦ Free T4
- ♦ Total CK
- ♦ Infectious disease screen: HBsAg, HBsAb, HBcAb, hCAb, CMV antibody, T-spot test, HIV antibody, HIV antigen (p24)[a]
- ♦ Fasting lipid profile

Dermatologic examination
- ♦ Full skin and mucosal exam, taking note of the extent and type of lesions present

Pulmonary tests
- ♦ Baseline oxygen saturation on room air and during ambulation

Cardiac tests
- ♦ ECG
- ♦ Troponin I or T: baseline and weekly for 6 weeks[b]

Additional screening tests recommended in patients with pre-existing organ disease/at risk of organ-specific toxicity

Endocrine tests
- ♦ 8 am cortisol
- ♦ 8 am ACTH

Cardiac tests
- ♦ Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)

Pulmonary tests
- ♦ PFTs[c]
- ♦ 6MWT[c]

sitc Cancer Immunotherapy CONNECT

What's more than NCCN suggestions?

- HbA1c
- CK
- CMV Ab, T-spot test
- Fasting lipid profile
- Troponin I or T

- (ACTH)
- (BNP or NT pro-BNP)
- (6MWT)

***( ): additional tests in patients with pre-existing diseases/risks**

Puzanov I et al. J ImmunoThera Cancer 2017:5:95.

Monitoring frequency (NCCN)

	Monitoring Frequency[b]
Clinical	Clinical exam at each visit with adverse event (AE) symptom assessment
Imaging	Periodic imaging as indicated
General bloodwork	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated
Dermatologic	Conduct/repeat as needed based on symptoms
Pancreatic	No routine monitoring needed if asymptomatic
Thyroid	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated
Pituitary/Adrenal	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6–12 weeks as indicated
Pulmonary	Repeat oxygen saturation tests based on symptoms
Cardiovascular	Consider periodic testing for those with abnormal baseline or symptoms
Musculoskeletal	No routine monitoring needed if asymptomatic

- Clinical exam/symptom assessment play the main role during F/U
- Images: periodic follow up
- General bloodwork: prior to each Tx. or every 4 weeks
- Hormones: every 4-6 weeks during IO treatment
- Closer monitoring may be required for patients with **combotherapy**

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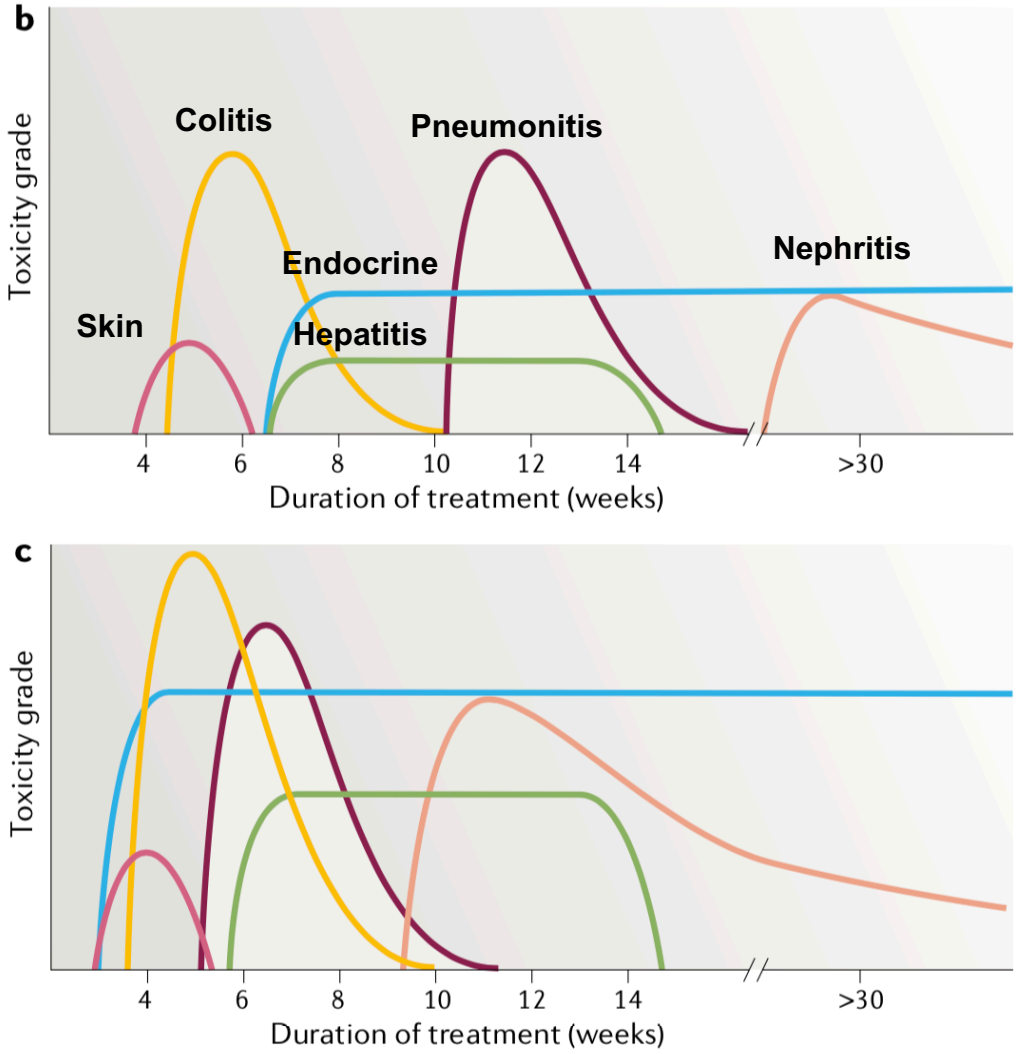
NCCN Guidelines Version 1.2021
Management of Immune Checkpoint Inhibitor-Related Toxicities

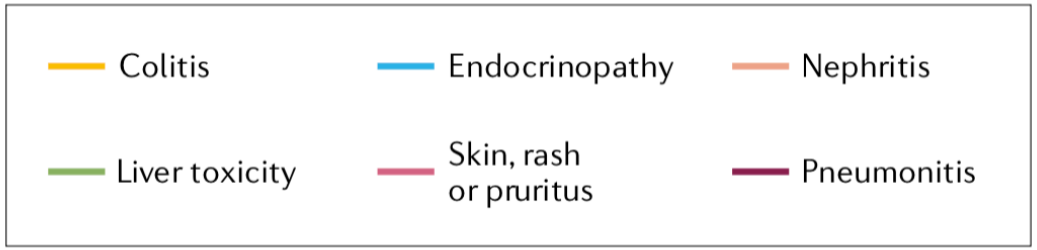
How to make the irAEs diagnosis ?

History of IO Treatment

Possible kinetics of major irAE(s)



Anti-PD-1 or Anti-PD-L1 treatment



Ipilimumab plus anti-PD-1 treatment

Martins F et al. Nat Rev Clin Oncol 2019; 16:563-80.

irAEs may develop late in the course of Tx.

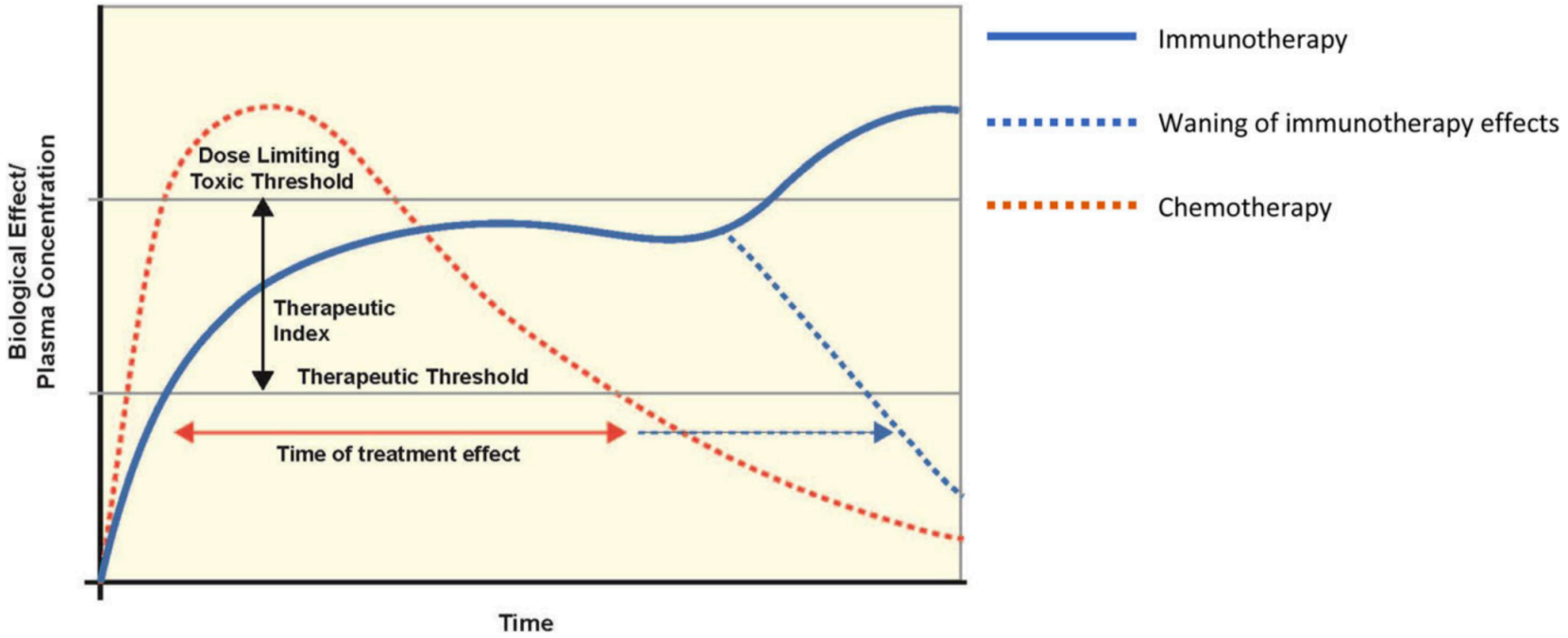


Fig. 2 Pharmacokinetic/pharmacodynamic differences between chemotherapy and immunotherapy. Reproduced with permission from [25]. Dotted blue line represents waning of the biological effects of immunotherapy over time, and solid blue line represents early or late toxic effects. Horizontal dotted blue arrow therefore represents duration of immunotherapy treatment benefit

irAEs: even months or years after discontinuation of treatment (SITC guideline)

Ernstoff M et al. Future Oncol 2017; 153:1162-5.
Puzanov I et al. J ImmunoThera Cancer 2017:5:95.

How to make the irAEs diagnosis ?

History of IO Treatment

Symptoms/Signs of irAEs

Possible symptoms/signs of irAEs

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE 1 or MORE)
CARDIO: Myocarditis	Chest pain, shortness of breath, fatigue, irregular heart beat (arrhythmia), syncope.
DERM: Bullous dermatitis	Inflammation of the skin and the presence of bullae, which are filled with fluid. The most common irAE reported is bullous pemphigoid. May be intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
DERM: Maculopapular rash (morbilliform rash)	Macules (flat) and papules (elevated)
DERM: Pruritis	Itching sensation, with or without rash
DERM: Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN)	SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively
ENDO: Hyperglycemia-related diabetic ketoacidosis (DKA)	Excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath
ENDO: Asymptomatic/ subclinical hypothyroidism	Elevated TSH with normal free T4. Usually asymptomatic, may consider with increased fatigue
ENDO: Clinical (overt) primary hypothyroidism	Fatigue, lethargy, sensation of being cold, possible constipation
ENDO: Thyrotoxicosis due to thyroiditis	Tachycardia, tremor, anxiety *Note: most patients with thyrotoxicosis due to thyroiditis have minimal, if any symptoms
ENDO: Hypophysitis	Acute onset headache, photophobia, nausea/emesis, fatigue, may have low blood pressure
ENDO: Primary adrenal insufficiency	High ACTH with low morninig cortisol, abnormal cosyntropin stimulation test. This is a rare diagnosis not usually associatedwith checkpoint immunotherapy.
GI: Colitis	Watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
GI: Pancreatitis	Acute pancreatitis: epigastric pain, nausea, possible vomiting. Chronic pancreatitis: chronic abdominal pain, deficiency in pancreatic enzyme production with possible malabsorption
GI: Transaminitis	Elevated alanine transaminase (ALT) and aspartate transaminase (AST).

***Majorities are non-specific !!!!**

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NCCN Guidelines Version 1.2021
Management of Immune Checkpoint Inhibitor-Related Toxicities

How to make the irAEs diagnosis ?

History of IO Treatment

Symptoms/Signs of irAEs

Diagnostic workup (Lab., images, Bx.)

Role of biopsy in irAEs management

- Possible sites of biopsy: skin, bowel, liver, lung, muscle, temporal artery, kidney, bone marrow, endomyocardium.
- Majorities are optional.

- Help in confirming the diagnosis.
- To rule out other differential diagnosis.
- Predict the treatment outcome (e.g. the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab).

- Careful benefit-risk analysis: **will it lead to a change of management** ???

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American Society of Clinical Oncology

Brahmer JR et al. J Clin Oncol 2018; 36:1714-68.

How to make the irAEs diagnosis ?

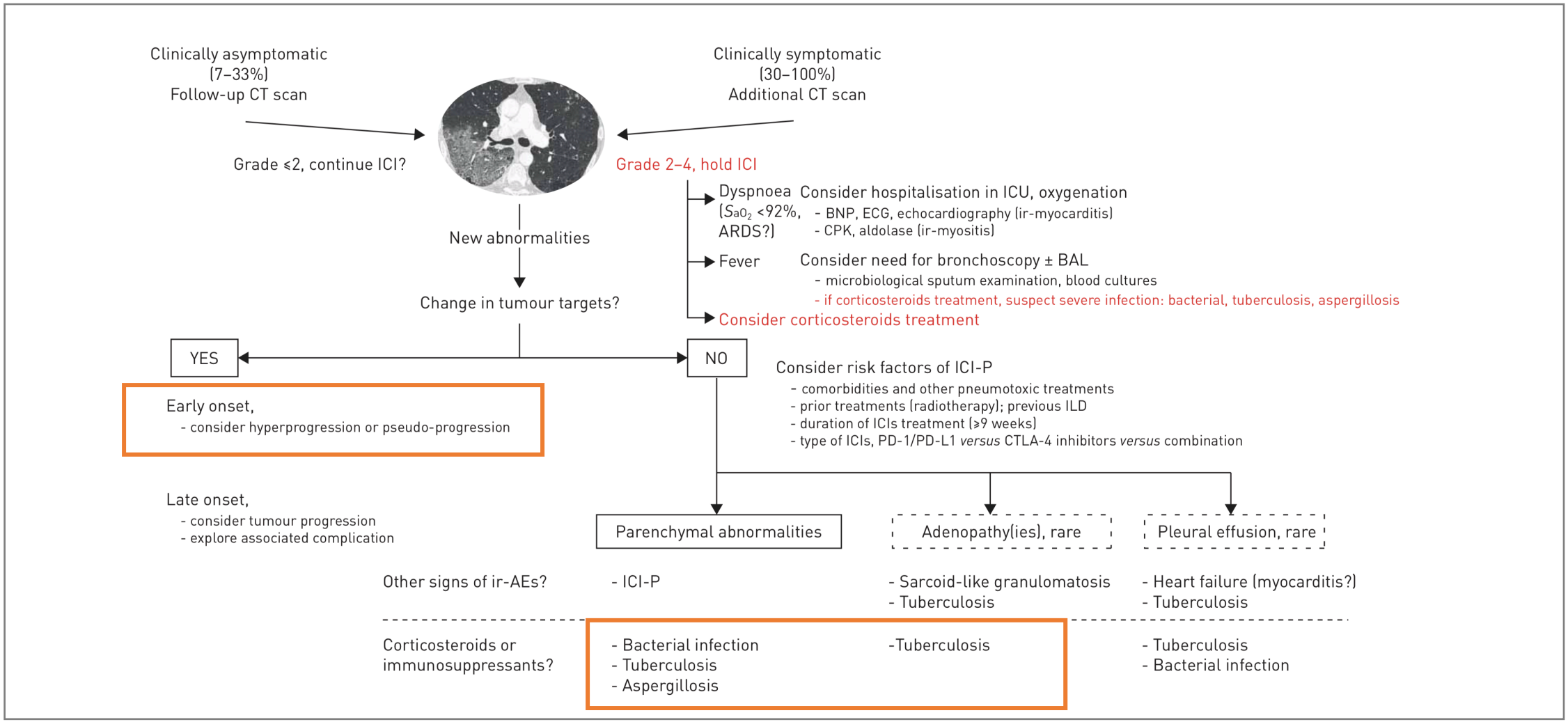
History of IO Treatment

Symptoms/Signs of irAEs

Diagnostic workup (Lab., images, Bx.)

EXCLUSION of other possibilities

Algorithm for management of suspected ICI-P



Cadranel J et al. Eur Respir Rev 2019; 28:190058.

General principles in irAE management

I. The incidence of irAE	All grade ~25-40%, grade 3-5 ~5-10%
II. Risk factors of irAE	Some factors had been reported but few would impact the practice
III. Prognostic role of irAE	Some studies showed positive correlation of irAEs with outcome
IV. Diagnosis of irAE	

- No definite prevention strategy; corticosteroid premedication is not suitable.
- The kinetics of irAEs may provide a clue for clinicians to expect the presence of the illness.
- Diagnosis is made based on history of IO treatment, presence of S/Ss, diagnostic workup and, mostly importantly, exclusion of other possibilities.

General principles in irAE management

I. The incidence of irAE	All grade ~25-40%, grade 3-5 ~5-10%
II. Risk factors of irAE	Some factors had been reported but few would impact the practice
III. Prognostic role of irAE	Some studies showed positive correlation of irAEs with outcome
IV. Diagnosis of irAE	IO exposure – S/Ss – Diagnostic workup – Exclusion of D.D.
V. Treatment of irAE	

Guidelines of irAEs management

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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

ABSTRACT

Purpose
To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events in patients treated with immune checkpoint inhibitor (ICPi) therapy.

Methods
A multidisciplinary, multi-organizational panel of experts in medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, urology, neurology, hematology, emergency medicine, nursing, trialist, and advocacy was convened to develop the clinical practice guideline. Guideline development involved a systematic review of the literature and an informal consensus process. The systematic review focused on guidelines, systematic reviews and meta-analyses, randomized controlled trials, and case series published from 2000 through 2017.

Results
The systematic review identified 204 eligible publications. Much of the evidence consisted of systematic reviews of observational data, consensus guidelines, case series, and case reports. Due to the paucity of high-quality evidence on management of immune-related adverse events, recommendations are based on expert consensus.

Recommendations
Recommendations for specific organ system–based toxicity diagnosis and management are presented. While management varies according to organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert to grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. Additional information is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

J Clin Oncol 36:1714-1768. © 2018 American Society of Clinical Oncology and National Comprehensive Cancer Network

INTRODUCTION

Immune checkpoint inhibitors (ICPis) have revolutionized the treatment of many different types of cancers. These inhibitors work by blocking pathways called checkpoints. These checkpoint pathways are mechanisms for the human immune system to control the immune response. The immune checkpoint proteins cytotoxic T-lymphocyte–associated-4 (CTLA-4) and programmed cell death protein 1 (PD-1) are

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2021 — February 1, 2021

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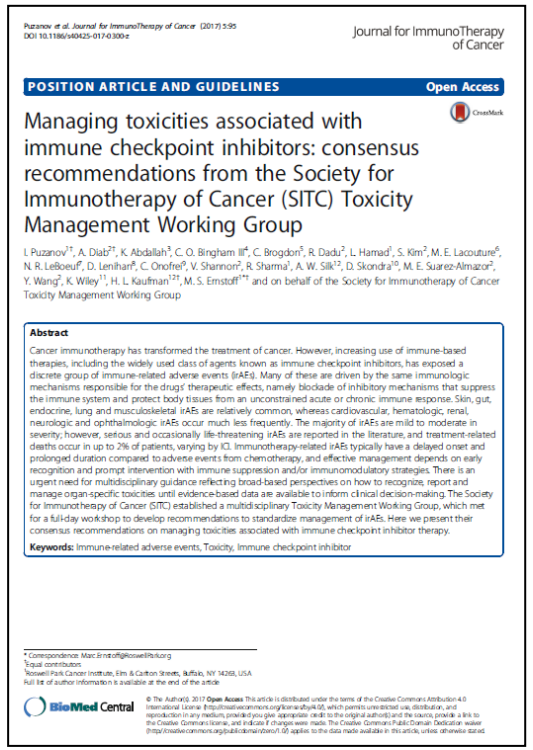

Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES | Open Access

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[†1], A. Diab[†2], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12*], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Abstract

Cancer immunotherapy has transformed the treatment of cancer. However, increasing use of immune-based therapies, including the widely used class of agents known as immune checkpoint inhibitors, has exposed a discrete group of immune-related adverse events (irAEs). Many of these are driven by the same immunologic mechanisms responsible for the drugs' therapeutic effects, namely blockade of inhibitory mechanisms that suppress the immune system and protect body tissues from an unconstrained acute or chronic immune response. Skin, gut, endocrine, lung and musculoskeletal irAEs are relatively common, whereas cardiovascular, hematologic, renal, neurologic and ophthalmologic irAEs occur much less frequently. The majority of irAEs are mild to moderate in severity; however, serious and occasionally life-threatening irAEs are reported in the literature, and treatment-related deaths occur in up to 2% of patients, varying by ICI. Immunotherapy-related irAEs typically have a delayed onset and prolonged duration compared to adverse events from chemotherapy, and effective management depends on early recognition and prompt intervention with immune suppression and/or immunomodulatory strategies. There is an urgent need for multidisciplinary guidance reflecting broad-based perspectives on how to recognize, report and manage organ-specific toxicities until evidence-based data are available to inform clinical decision-making. The Society for Immunotherapy of Cancer (SITC) established a multidisciplinary Toxicity Management Working Group, which met for a full-day workshop to develop recommendations to standardize management of irAEs. Here we present their consensus recommendations on managing toxicities associated with immune checkpoint inhibitor therapy.

Keywords: Immune-related adverse events, Toxicity, Immune checkpoint inhibitor

* Correspondence: Marc.Ernstoff@RoswellPark.org
† Equal contributors
[1]Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA
Full list of author information is available at the end of the article

BioMed Central

ESMO

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

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

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee May 2017.

General aspects of immune checkpoints blockade

Incidence and epidemiology

Immunotherapy with monoclonal antibodies (MoAbs) targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) and its ligand PD-L1 has become standard of care for an increasing number of indications (Table 1). Therefore, an increasing number of patients will be exposed to these drugs with a chance of developing toxicities from these treatments. Depending on the immune checkpoint that is targeted, the incidence of toxicity varies. Toxicities from immune checkpoint inhibitors (ICPis) can be divided into infusion reactions and immune-related adverse events (irAEs) or adverse events of special interest (AEoSI). The latter will be the subject of these Clinical Practice Guidelines. Any organ or tissue can be involved, although some irAEs occur much more commonly than others. The most frequently occurring irAEs affect skin, colon, endocrine organs, liver and lungs. Others are very infrequent, but may be very serious, even lethal, such as neurological disorders and myocarditis.

Ipilimumab-associated immune-related toxicities

irAEs from ipilimumab, anti-CTLA4, at a dose of 3 mg/kg, have been documented to occur in 60%–85% of patients [1, 2], mostly grades 1 and 2, but between 10% and 27% of patients develop grade 3 to 4 toxicities, and 2.1% ipilimumab-related deaths have been reported in the first phase III trial [1]. The onset of these toxicities varies but usually starts within the first 8 to 12 weeks of initiation of treatment [an example of onset of adverse events (AEs) upon ipilimumab treatment is depicted in Figure 1], with skin toxicities often being the first to develop. These toxicities are dose-dependent as no grade 3 to 4 AEs were observed at a dose of 0.3 mg/kg ipilimumab, whereas these toxicities increased to 30% with a dose of 10 mg/kg [3]. In the adjuvant setting with ipilimumab 10 mg/kg followed by a maintenance dose, the recorded grade 3 to 4 irAE rate was 41.6%, and the grade 5 irAE rate 1.1% [4].

PD-1/PD-L1 blockade immune-related toxicities

The most frequently reported AE with anti-PD-1/PD-L1 is fatigue. Incidence of fatigue, of which the pathogenesis is poorly understood, across single drug studies, is 16%–37% for anti-PD-1 and 12%–24% for anti-PD-L1 [5]. Only in a minority of patients fatigue can be attributed to hypothyroidism. High-grade toxicities from anti-PD-1 (either nivolumab or pembrolizumab) are less common than for the CTLA4 blocking agent ipilimumab. For nivolumab, any treatment-related AE was documented in 74%–85% of patients, with 12%–20% being grade 3 and 4 [2, 6, 7] for metastatic melanoma patients, 58% and 7%, respectively, for advanced cisplatin refractory squamous non-small-cell lung cancer (NSCLC) [8], 69% and 10%, respectively, for metastatic cisplatin refractory non-squamous NSCLC [9] and 79% and

ASCO 2018 | **NCCN 2021** | **SITC 2017** | **ESMO 2017**

Principle of irAEs treatment

- Inform possible irAEs before treatment
- Prompt recognition and diagnostic workups
- Discontinue IO treatment in patients with severe irAEs
- Management of irAEs relies heavily on **corticosteroids**
- Other immunomodulatory agents may be needed
- Steroid taper: **longer steroid taper** (> 4wks, sometimes 6-8wks or longer)
- Potential short and long-term complications of treatment (**infection**)
- Treatment should be individualized
- Additional considerations: PJP prophylaxis, PPI, calcium/vitamin D, fluconazole

General guidance of corticosteroid use in irAEs (STIC)

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

Puzanov I et al. J ImmunoThera Cancer 2017:5:95.

General principles in irAE management

I. The incidence of irAE	All grade ~25-40%, grade 3-5 ~5-10%
II. Risk factors of irAE	Some factors had been reported but few would impact the practice
III. Prognostic role of irAE	Some studies showed positive correlation of irAEs with outcome
IV. Diagnosis of irAE	IO exposure – S/Ss – Diagnostic workup – Exclusion of D.D.
V. Treatment of irAE	Hold IO, corticosteroid, taper slowly, F/U other complications

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VI. Re-challenge of IO	

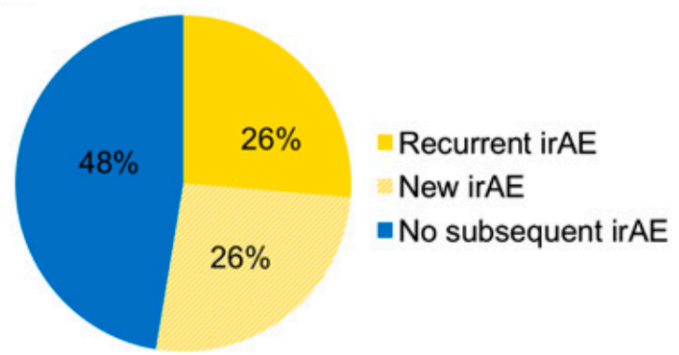
Safety and outcome of IO resumption

482 NSCLC patients
Anti-PD-(L)1 therapy
68 (14%) with serious irAE
(MSKCC)

Table 1. Characteristics of patients who experienced serious irAEs requiring treatment delay

	Retreatment	Discontinuation	*P*
No. of patients; *N* (%)	38	30	
Median age, years (range)	64 (49–83)	66 (42–84)	0.59
Sex, female; *N* (%)	18 (47)	11 (37)	0.46
Smoking history, *N* (%)			0.51
Yes	33 (87)	24 (80)	
No	5 (13)	6 (20)	
Histology, *N* (%)			0.06
Adenocarcinoma	23 (61)	26 (87)	
Squamous	11 (29)	4 (13)	
LCNEC or NOS	4 (10)	0 (0)	
Immunotherapy treatment data, *N* (%)			0.18
Anti–PD-1 or Anti–PD-L1	24 (63)	24 (80)	
Combination w/anti–CTLA4	14 (37)	6 (20)	
Line of therapy, *N* (%)			0.007
First	25 (66)	9 (30)	
Second and beyond	13 (34)	21 (70)	
Best overall response, *N* (%)			0.62
CR or PR	18 (47)	12 (40)	
SD or PD	20 (53)	18 (60)	

Abbreviations: LCNEC, large-cell neuroendocrine cancer; NOS, not otherwise specified carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; CR, complete response; SD, stable disease; PD, progressive disease.



60% of recurrent irAEs ≤ Gr. 2
85% improved to Gr. 1 after Tx.
Tx.-related death n = 2

For patients with PR prior to initial irAE (n = 20), resumption or not did not matter the PFS/OS

Santini FC et al. Cancer Immunol Res 2018; 6:1093.

Principle of immunotherapy rechallenge

- Consider permanent discontinuation in the setting of severe irAEs (e.g. Gr. 3 or more).
- Resumption of IO following Gr. 2 irAEs can be considered upon resolution to ≤ Gr. 1.
- More closer follow up while resuming IO.
- If toxicity returns, permanently discontinue the class of IO.
- **Assess patient's tumor status before rechallenge** (objective response → risk of toxicity recurrence).
- Shift to another class of IO (e.g. change from anti-CTLA4 to anti-PD(L)-1).
- Consult with organ-specific specialists.
- Resumption may not be advisable: e.g. GBS, transverse myelitis.
- Dose reductions of IO are **NOT** recommended.

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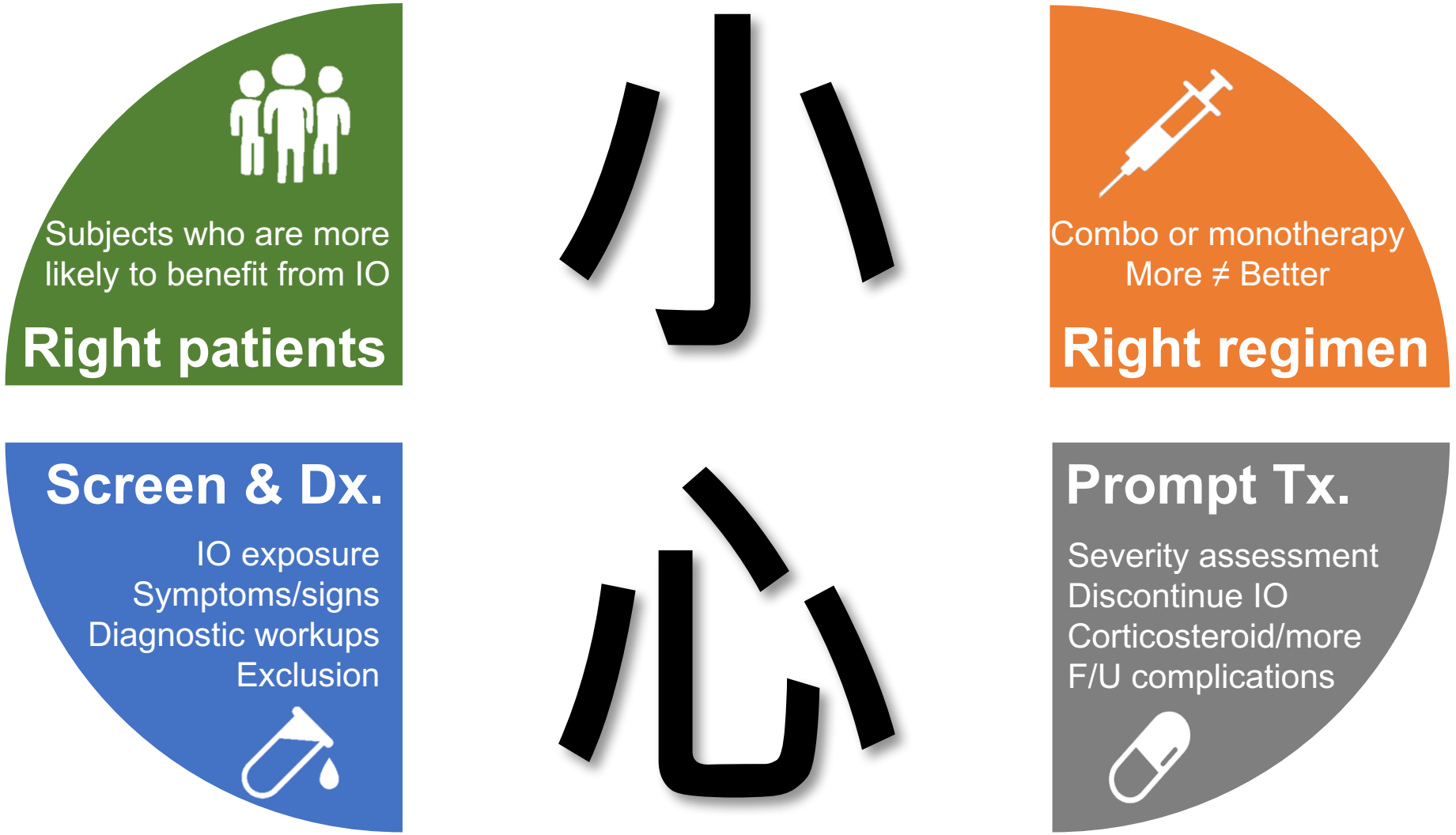
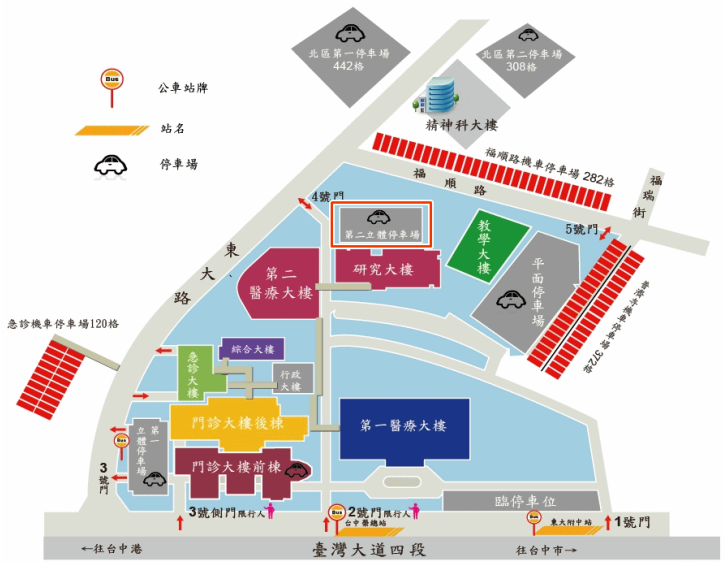
V. Treatment of irAE	Hold IO, corticosteroid, taper slowly, F/U other complications
VI. Re-challenge of IO	In some condition, IO resumption may be offered but be cautious

Conclusion: “PRINCIPLES” of irAE management





Thanks for your attention!

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Jeng-Sen Tseng, M.D., Ph.D. (tzeng64@gmail.com)
Division of Chest Medicine, Taichung Veterans General Hospital
Faculty of Medicine, School of Medicine, National Yang-Ming University
Institute of Biomedical Sciences, National Chung Hsing University