Not common but essential adverse events in patients being treated with ICIs

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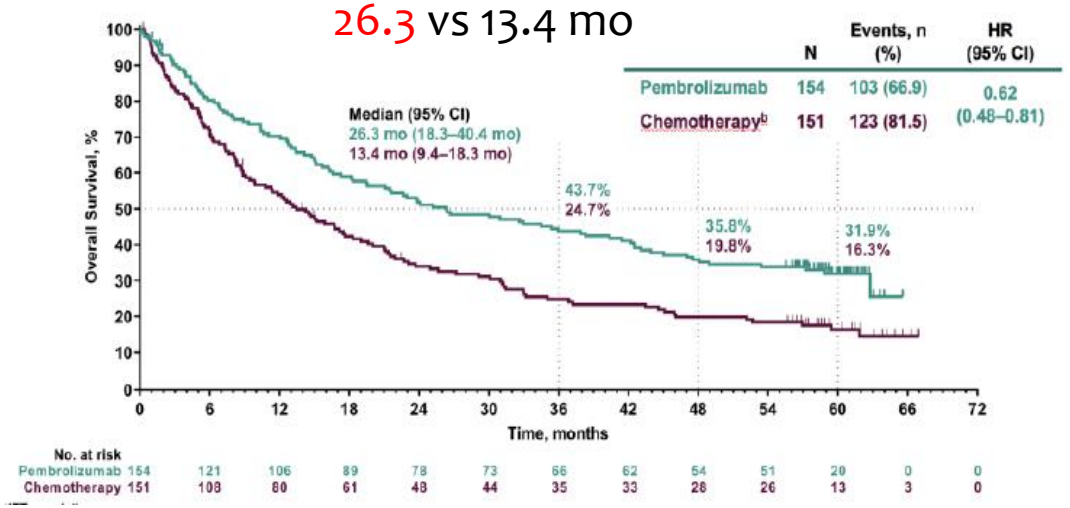
8th, Apr 2022 KATRD Spring Lung Cancer Symposium

OS benefit of 1st-line IO in NSCLC

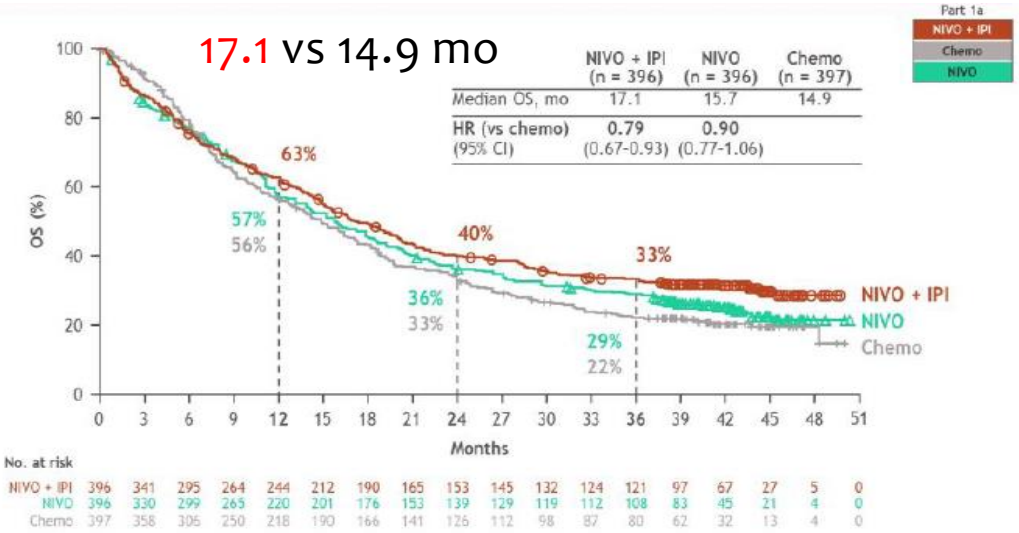
KEYNOTE-024 (PD-L1≥50%)

26.3 vs 13.4 mo



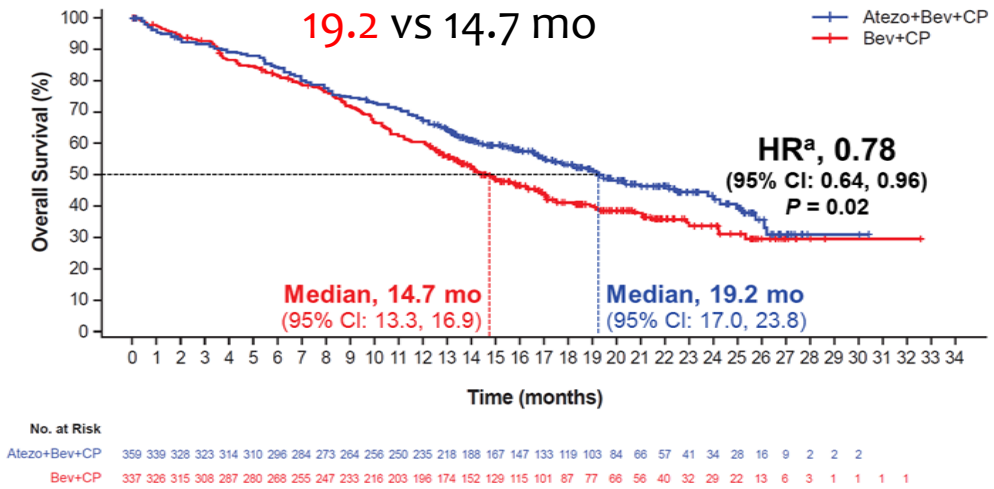
CHECKMATE-227

17.1 vs 14.9 mo



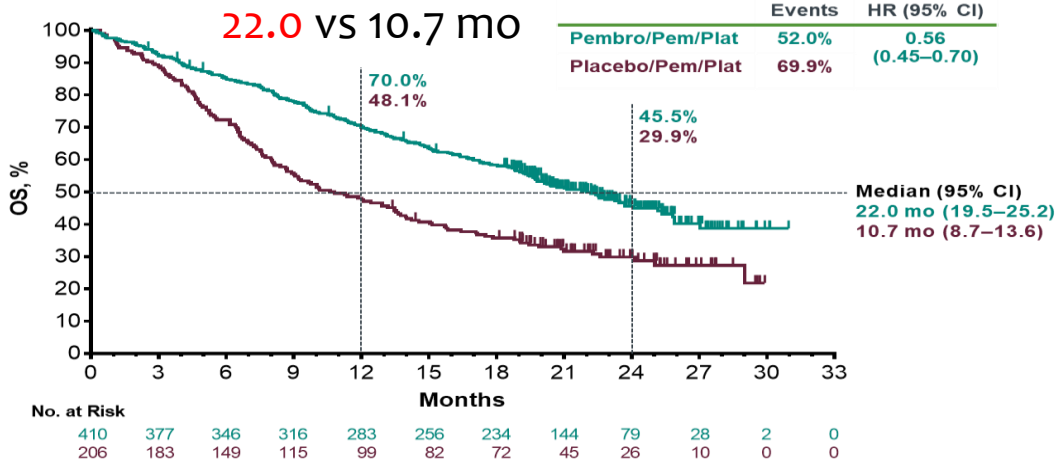
IMpower-150

19.2 vs 14.7 mo



KEYNOTE-189

22.0 vs 10.7 mo



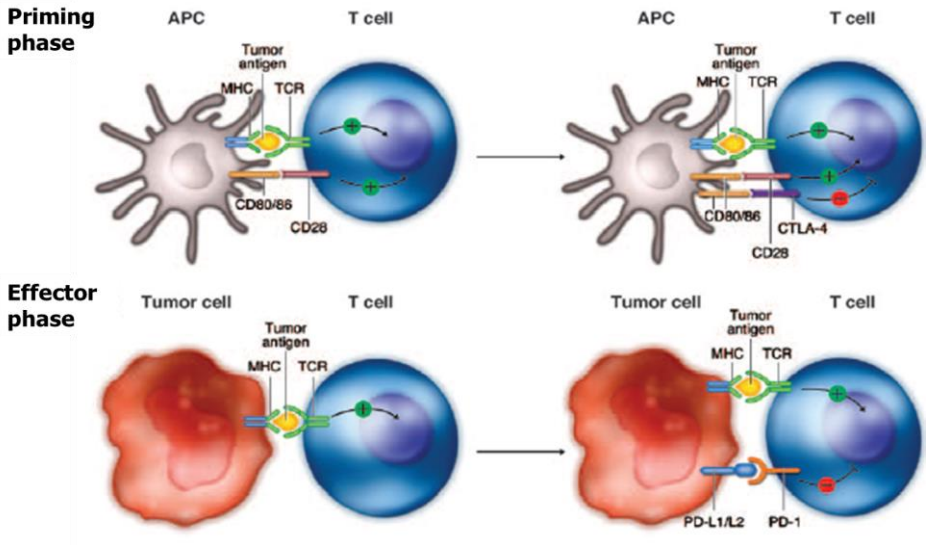
J Clin Oncol 2020; ASCO 2019 Annual Meeting; N Engl J Med 2018; 378:2288-2301; N Engl J Med 2020; 382:874-875

KFDA-approved ICIs for lung cancer (Mar. 2022)

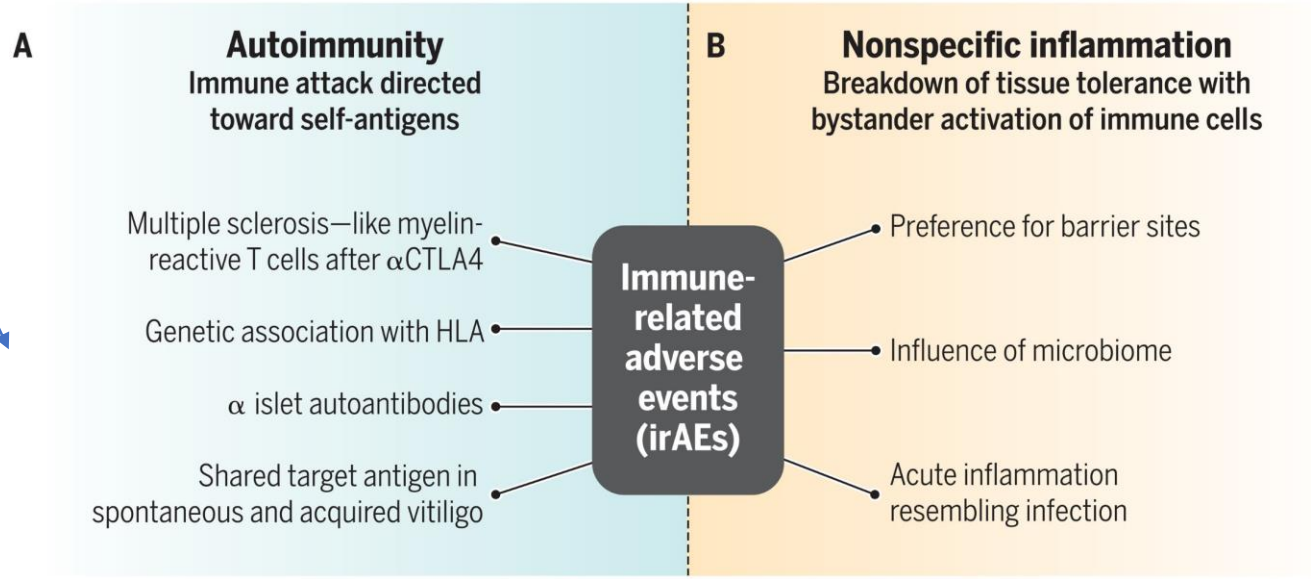
PD-(L)1 inhibitors

CTLA-4 inhibitor

Immune checkpoint inhibition: "Double-edged sword"



Anti-tumor effects



J Thorac Oncol. 2015 Jul;10(7):974-84; Science Immunology 2021 Nov:6(65)

Content

I. **General concepts and key questions**

- Difference among different class of drugs?
- Contraindicated in patients with autoimmune dz?
- Association b/w irAEs and clinical outcome?
- Interaction with sequential treatment?

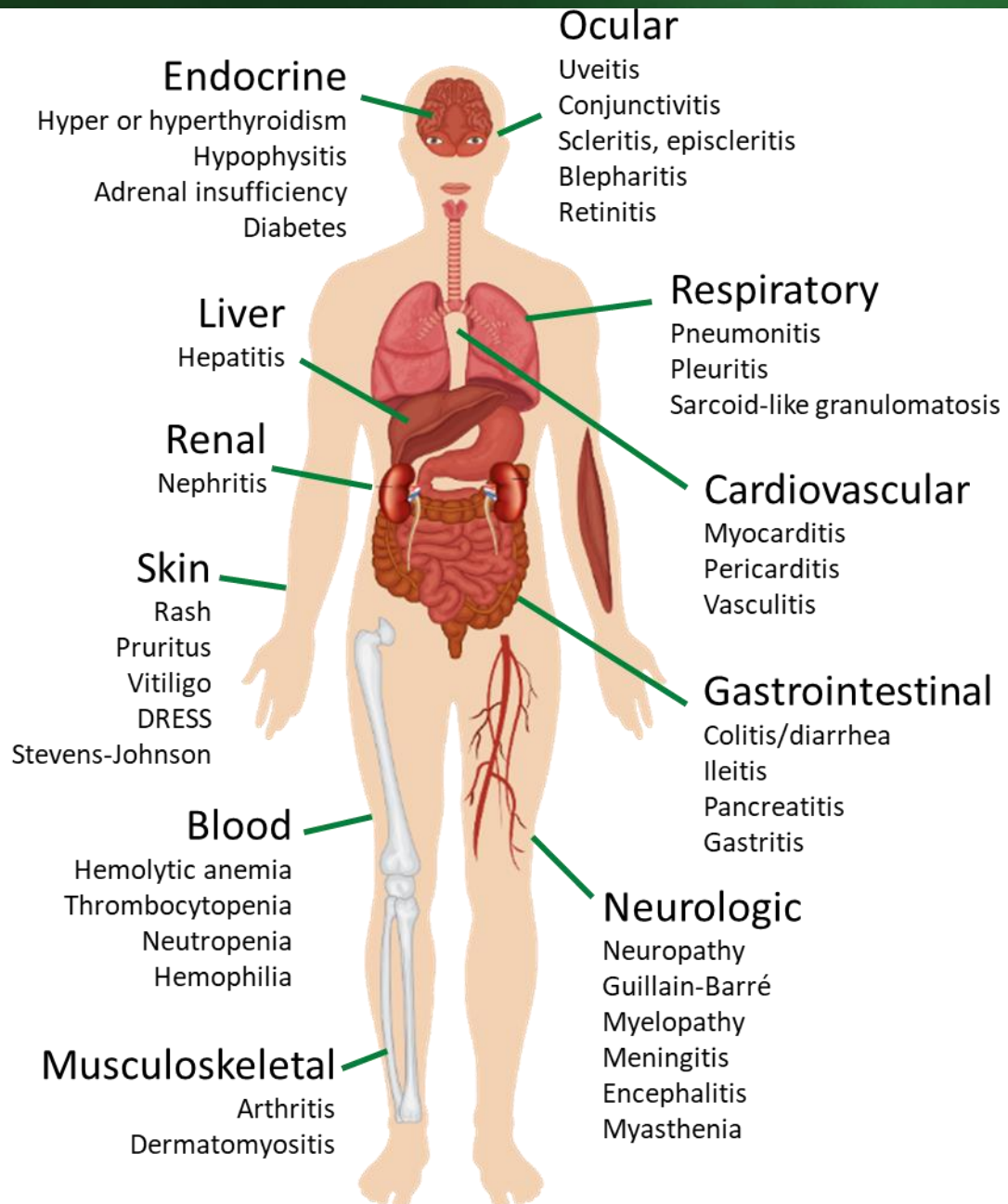
II. **Organ-specific toxicities**

- Dermatologic
- Endocrine
- Pulmonary
- Hepatitis
- Neuro-muscular

III. **Take-home messages**

I. General concepts and key questions

Immune-related AEs (irAEs) can occur any organ system



irAEs: basic concepts

- Distinctive from CTx- or TKI-related AEs
- Most of irAEs occur typically weeks to months following the initiation of ICIs.
- Can occur within days after the first dose and even after discontinuation.

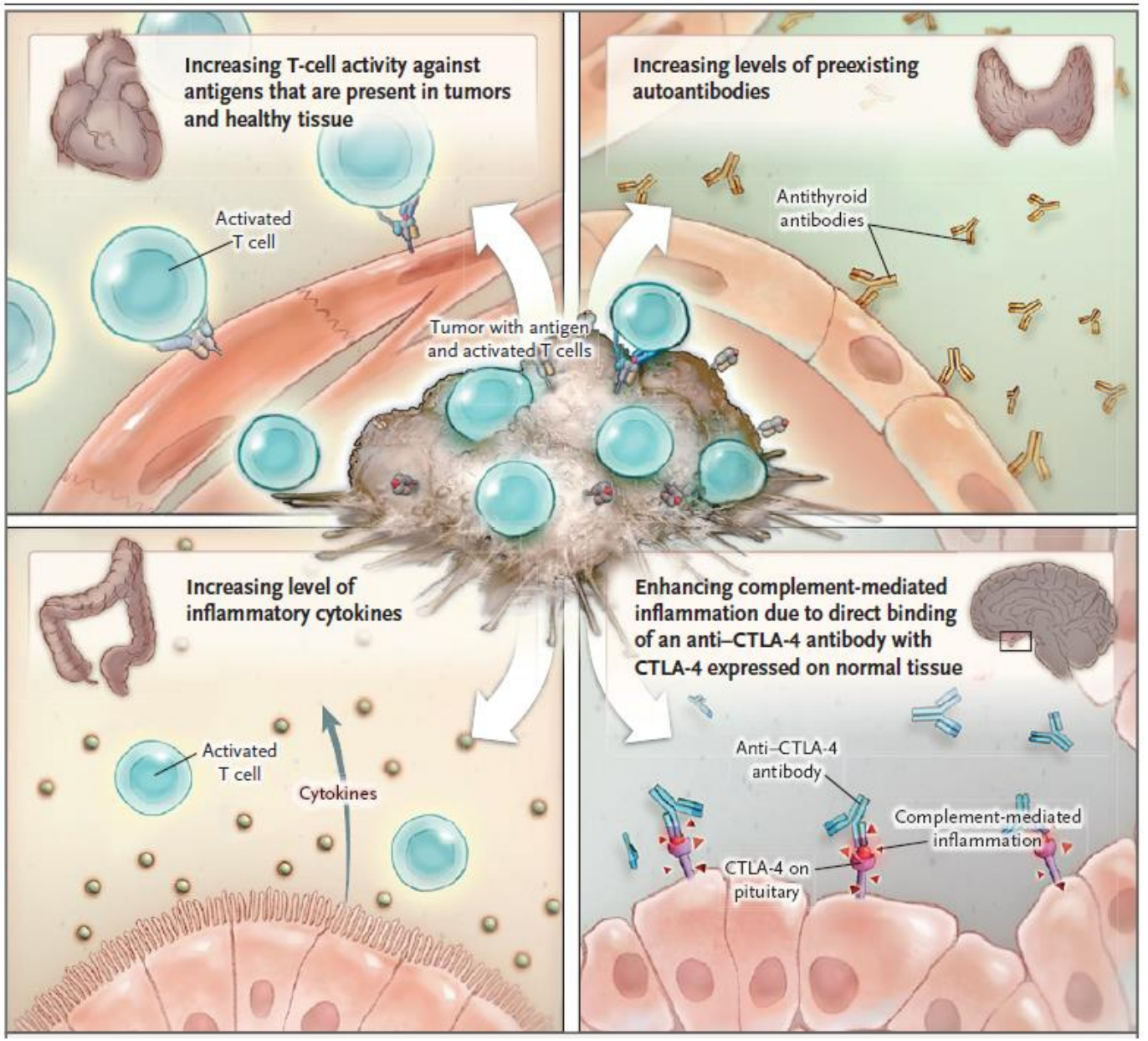
- Most are reversible, however, certain types of irAEs including endocrinopathy, pph neuropathy, and vitiligo can be chronic.
- Myocarditis, pneumonitis, colitis, and neurologic events are more relevant to mortality.
- Steroids is still the backbone of management of almost all serious irAEs.

Immunotargets Ther. 2017;6:51; Allergol Int. 2022 Jan 28;S1323-8930(22)00002-8, Nat Rev Clin Oncol. 2019 Sep;16(9):563-580

Possible mechanisms underlying irAEs

Increased T-cell activity

Inflammatory cytokines

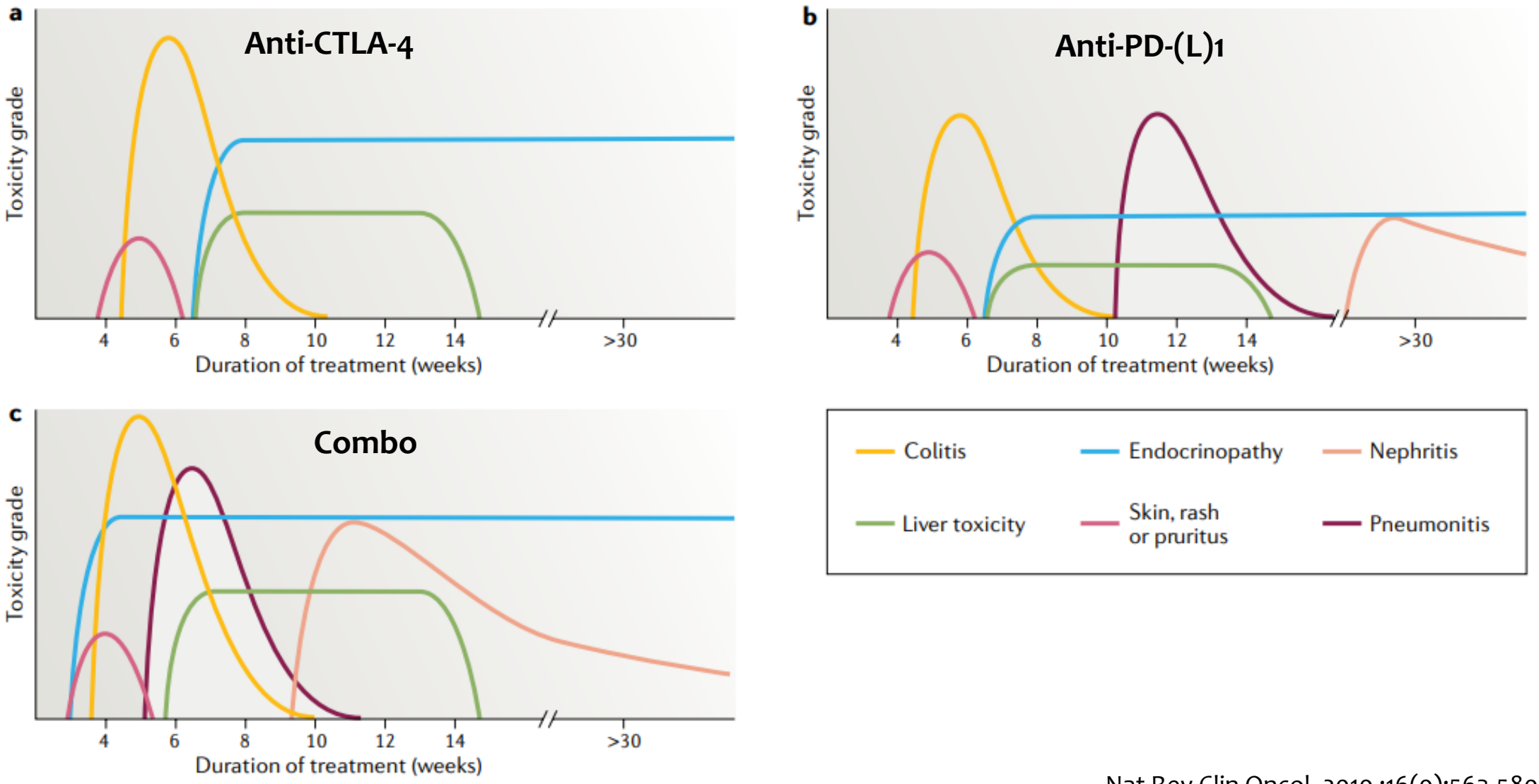


Increased preexisting AutoAb

Enhanced complement-mediated inflammation in CTLA-4 expressing tissue

N Engl J Med 2018;378:158-68

Kinetics of common irAEs



Nat Rev Clin Oncol. 2019 ;16(9):563-580

Different safety profiles among IO trials for lung cancer

Severe or life-threatening irAEs (grade ≥ 3)

- 20-30% for anti-CTLA-4
- 10–15% for anti-PD-(L)1
- ~55% for anti-CTLA-4/PD-(L)1

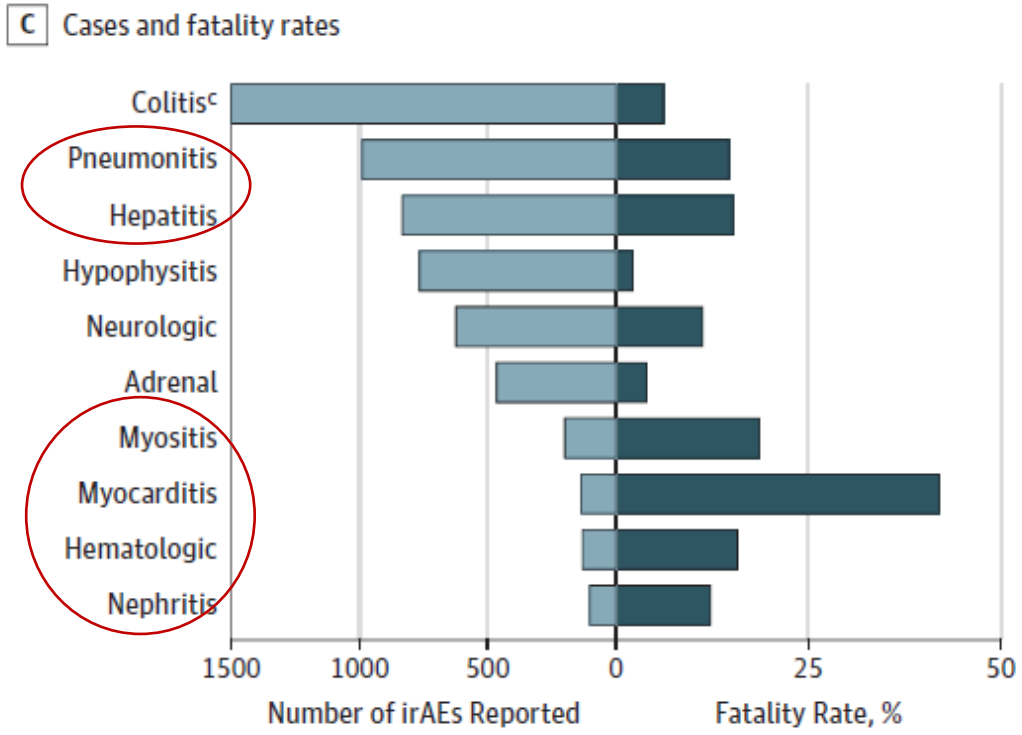
	Immune-related adverse events		
	Any (%)	≥G3 (%)	Top 3 most frequent (% of patients)
Keynote-024	29	10	Hypothyroidism (9), Hyperthyroidism (8), Pneumonitis (6)
Keynote-001	20	5	Hypothyroidism (8), Hyperthyroidism (5), Pneumonitis (5)
IMpower-110	40	7	Hepatitis (16), Rash (15), Hypothyroidism (9)
IMpower-010	52	8	Rash (18), Hepatitis (17), Hypothyroidism (17)
PACIFIC	24	3	Pneumonitis (11), Hypothyroidism (9), Hyperthyroidism (3)
Checkmate-227	NR	NR	Skin (34), Endocrine (24), gastrointestinal (18)

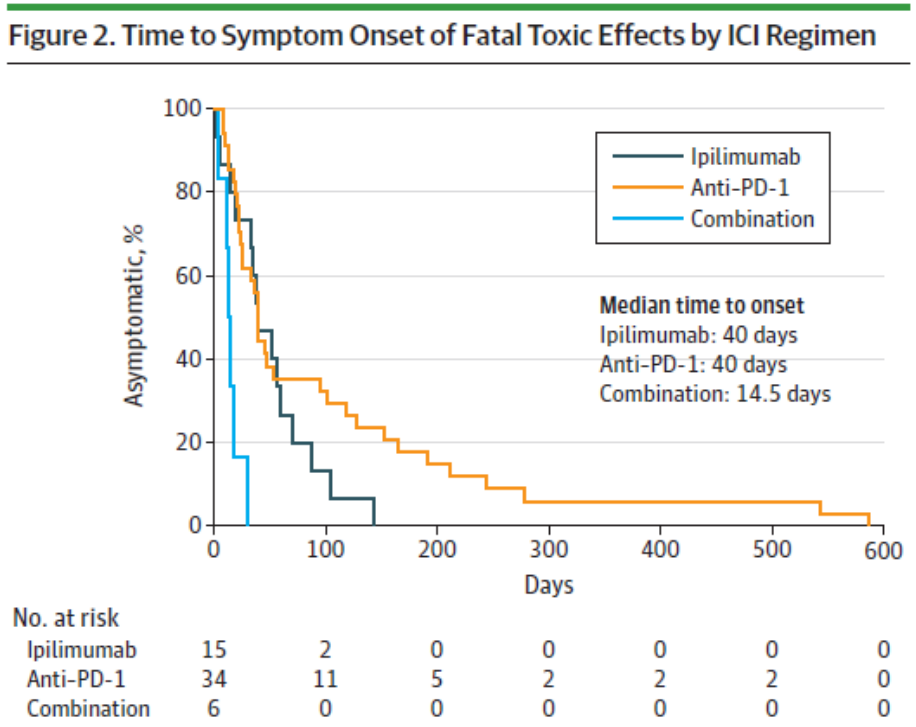
N Engl J Med 2015; 372:2018-2028; N Engl J Med 2016; 375:1823-1833; N Engl J Med 2019; 380:989-990; N Engl J Med 2020; 382:874-875; N Engl J Med 2020; 383:1328-1339; Curr. Oncol. Rep. 2020: 22, 39

Different fatality rates among different irAEs

Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors
A Systematic Review and Meta-analysis

- 613 fatal cases from 112 trials on IO





JAMA Oncol. 2018;4(12):1721-1728

Knowledge gap; Autoimmune dz (AID) and cancer

AID ➔ increased risk of several malignancies (lung cancer etc.)

14% to 25% of lung cancer pts have AID.

Patients with a history of AID have generally been excluded in most of I/O trials. (concern of SAE)

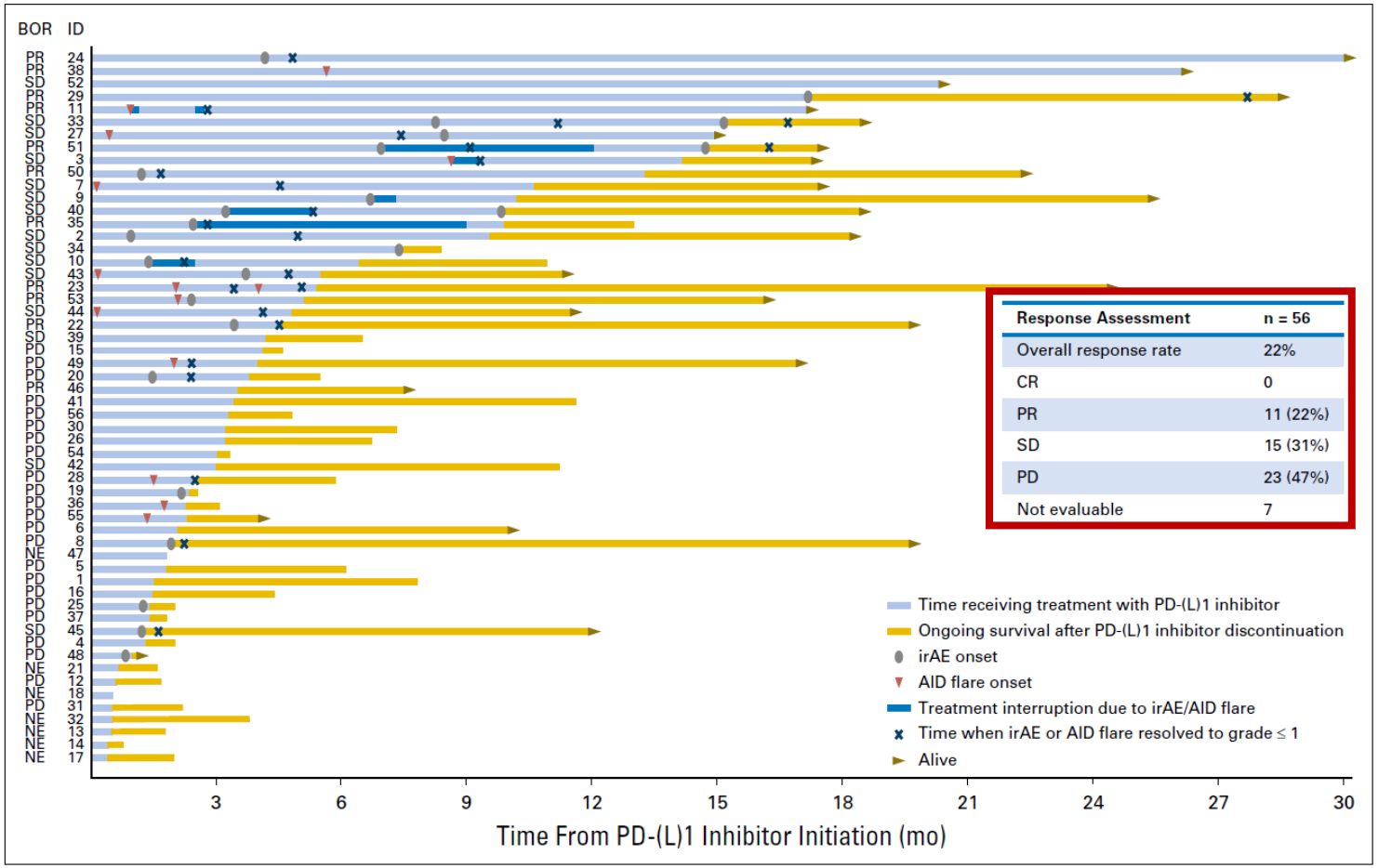
J Natl Cancer Inst 2022 Feb 21; JAMA Oncol 2:1507-1508, 2016; Anticancer Res 32:1119-1136, 2012

VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Safety of Programmed Death–1 Pathway Inhibitors Among Patients With Non–Small-Cell Lung Cancer and Preexisting Autoimmune Disorders

Giulia C. Leonardi, Justin F. Gainor, Mehmet Altan, Sasha Kravets, Suzanne E. Dahlberg, Lydia Gedmintas, Roxana Azimi, Hira Rizvi, Jonathan W. Riess, Matthew D. Hellmann, and Mark M. Awad



Response Assessment	n = 56
Overall response rate	22%
CR	0
PR	11 (22%)
SD	15 (31%)
PD	23 (47%)
Not evaluable	7

Table 3. Exacerbation of AID in Patients Treated With PD-(L)1 Inhibitors

Characteristic	Patients
Flare of underlying AID	
Patients who did not develop AID flare	43 (77)
Patients who developed AID flare	13 (23)
Exacerbations among 13 patients with AID flare	17
Grade 1-2*	13 (87)
Grade 3-4	2 (13)
Grade unknown†	2
Treatment required for AID flare‡	
No treatment required	4
Supportive care§	7
Hydroxychloroquine‖	1
Topical or intra-articular corticosteroids	6
Systemic corticosteroids	4
PD-(L)1 inhibitor dosing during AID flare	
Continued	11
Temporarily discontinued	2
Permanently discontinued	0

Table 5. Immune-Related Adverse Events

Characteristic	Patients
irAE unrelated to the underlying AID	
Patients who did not develop irAEs	35 (62)
Patients who developed irAEs*	21 (38)
irAEs experienced among 21 patients	23
Grade 1-2	17 (74)
Grade 3-4	6 (26)
Treatment required for irAEs†	
No treatment required	7
Supportive care‡	10
Systemic corticosteroids	7
PD-(L)1 inhibitor dosing during irAEs	
Continued	10
Temporarily discontinued	3
Permanently discontinued	8

J Clin Oncol 2018;36:1905-1912.

Pre-Existing Autoimmune Disease and Mortality in Patients Treated With Anti-PD-1 and Anti-PD-L1 Therapy

Kimberly Tang[1], BA, Bruce C. Tiu[1,2], BS, Guihong Wan[1,3], PhD, Shijia Zhang[1,3], BA, Nga Nguyen[1], BA, Bonnie Leung[1], BSc, Alexander Gusev[4], PhD, Kerry L. Reynolds[5], MD, Shawn G. Kwatra[6*], MD, Yevgeniy R. Semenov[1,2*], MD, MA

- **17,497** pts with AID treated with anti-PD-(L)1 vs matched controls (TriNetX Diamond network of US & Europe)
- No increased mortality in overall (HR, 1.03; 95% CI, 1-1.07; p=0.05)

Table 2: Association between baseline autoimmunity and survival among patients treated with anti-PD-1 or anti-PD-L1 therapy

Autoimmune Diagnosis	No.	Hazard Ratio (95% CI)[a]	P^b
Myasthenia gravis	108	1.31 (0.85-2.02)	0.21
Morphea	205	1.29 (0.93-1.79)	0.13
Vasculitis	494	1.18 (0.97-1.44)	0.09
Scleroderma	128	1.12 (0.77-1.63)	0.55
Type 1 diabetes	3960	1.11 (1.03-1.19)	0.002
Psoriasis	1827	1.07 (0.96-1.19)	0.24
Mucositis	3181	1.04 (0.97-1.12)	0.30
Inflammatory bowel disease	10415	1.03 (0.99-1.08)	0.17
Ankylosing spondylitis	164	1.02 (0.72-1.46)	0.90
Rheumatoid arthritis	3176	1.01 (0.93-1.09)	0.80
Autoimmune hepatitis	109	1.00 (0.64-1.57)	1.00
Graves disease	416	0.96 (0.76-1.20)	0.68
Multiple sclerosis	281	0.93 (0.70-1.23)	0.60
Dermatomyositis	79	0.93 (0.55-1.55)	0.77
Atopic dermatitis	1057	0.89 (0.77-1.03)	0.12
		0.89 (0.74-1.06)	0.19
		0.88 (0.76-1.01)	0.08
		0.86 (0.46-1.60)	0.64
		0.75 (0.62-0.90)	0.002
		0.74 (0.57-0.97)	0.03
		0.70 (0.53-0.93)	0.01
		0.61 (0.39-0.97)	0.04
		0.52 (0.34-0.81)	0.003
Any cutaneous diagnosis	17497	1.03 (1.00-1.07)	0.05

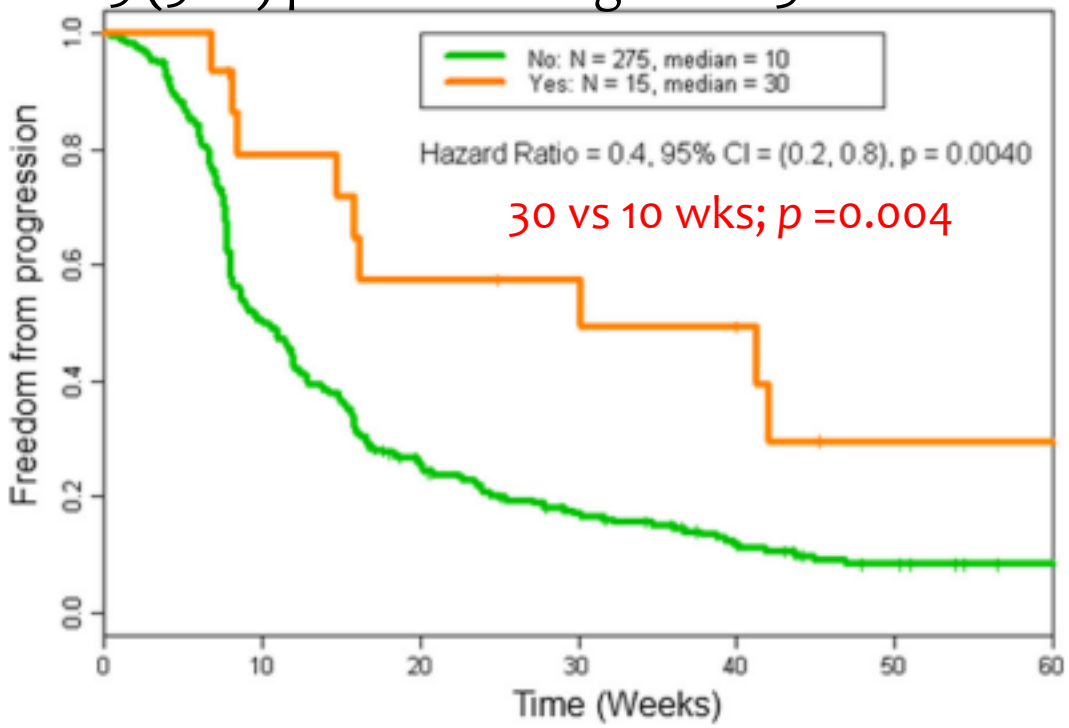
Patients with AID have
1) similar or slightly higher rates of classic irAEs
2) similar antitumor responses compared with those without
3) high incidences of autoimmune flares (20-25%)

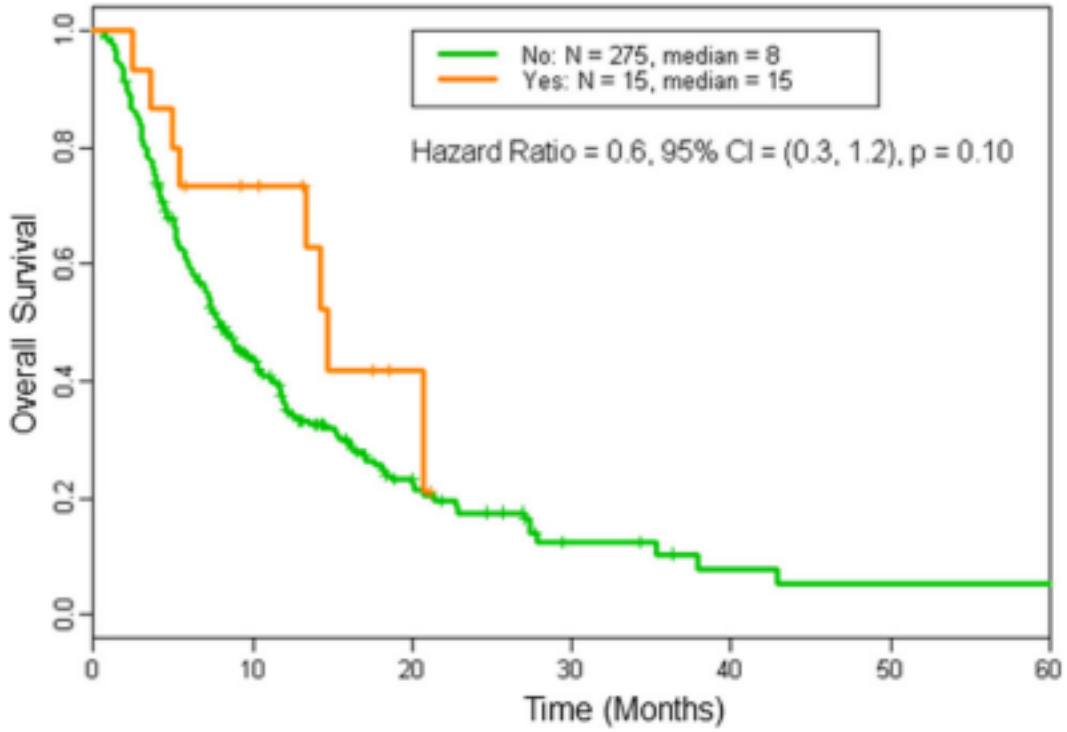
J Natl Cancer Inst. 2022 Feb 21;djac046 online ahead of print

irAEs and clinical outcome

Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience

- Single center, retrospective, 290 in IO trials, various cancers including NSCLC (12%)
- any-grade irAEs: 98/290 (34%) receiving anti–PD-1
- 15 (5.2%) patients with grade ≥ 3 irAEs





Invest New Drugs. 2018;36:638

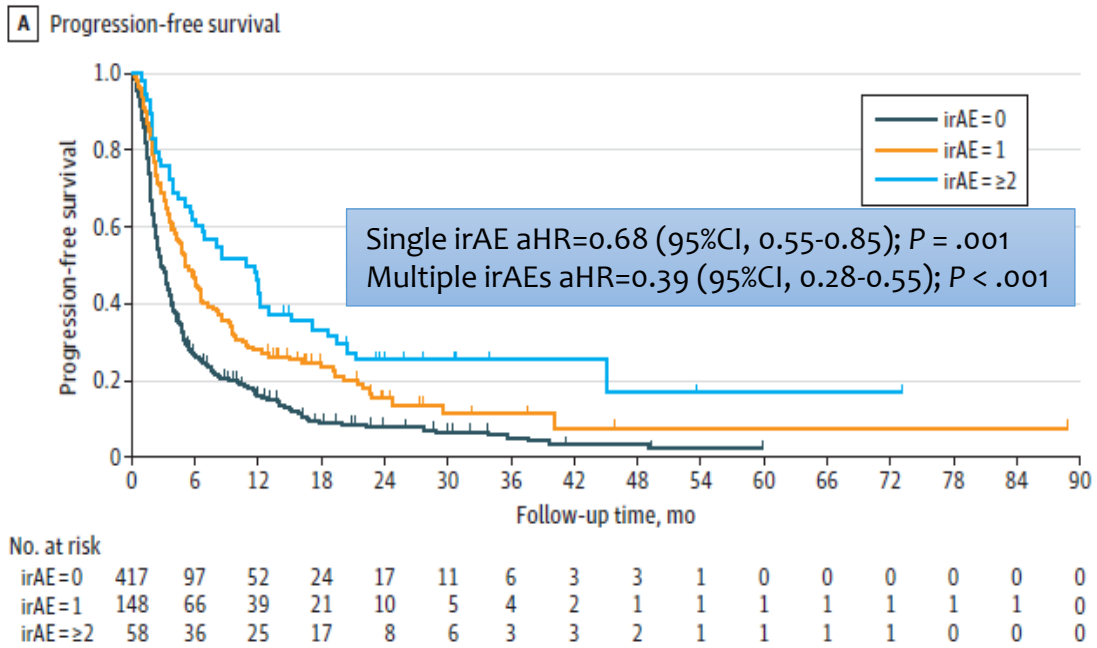
Research

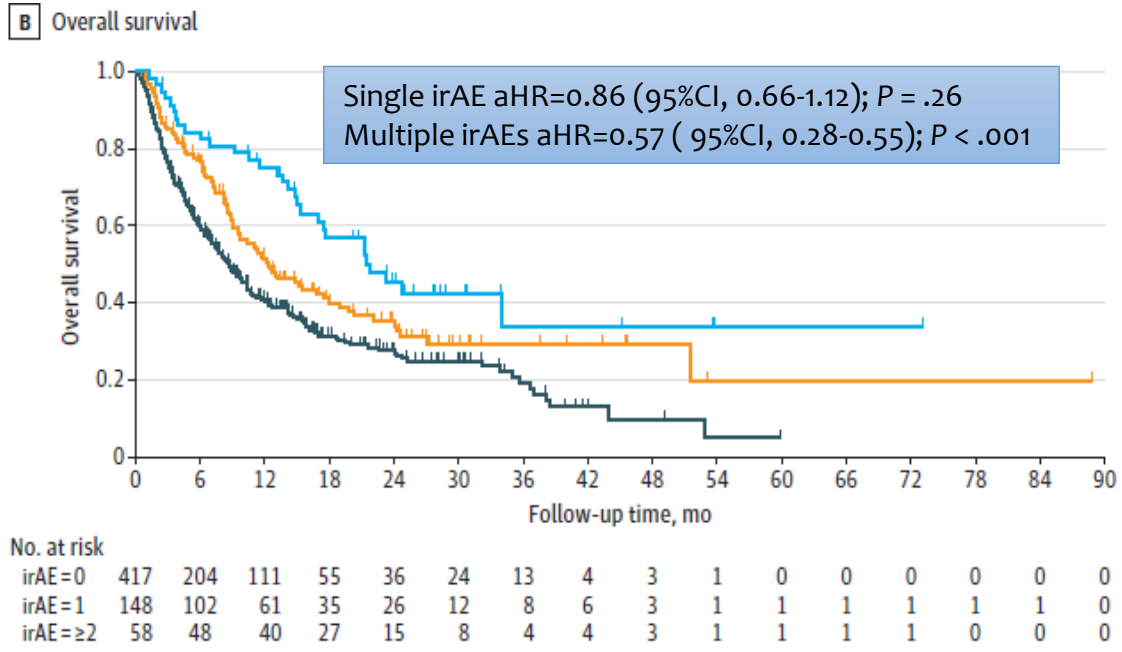
JAMA Oncology | Brief Report

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

- 5 centers including Johns Hopkins, 623 patients treated with anti-PD-(L)1 (mono in 95%)
- 148 (24%): single irAE, 58 (9.3%): multisystem irAEs
- m/c: pneumonitis (n=64, 12%), thyroiditis (n=53, 10%)
- Pneumonitis+thyroiditis (n=7, 14%), hepatitis + thyroiditis (n=5, 10%), dermatitis + pneumonitis (n=5, 10%), and dermatitis thyroiditis (n=4, 8%)

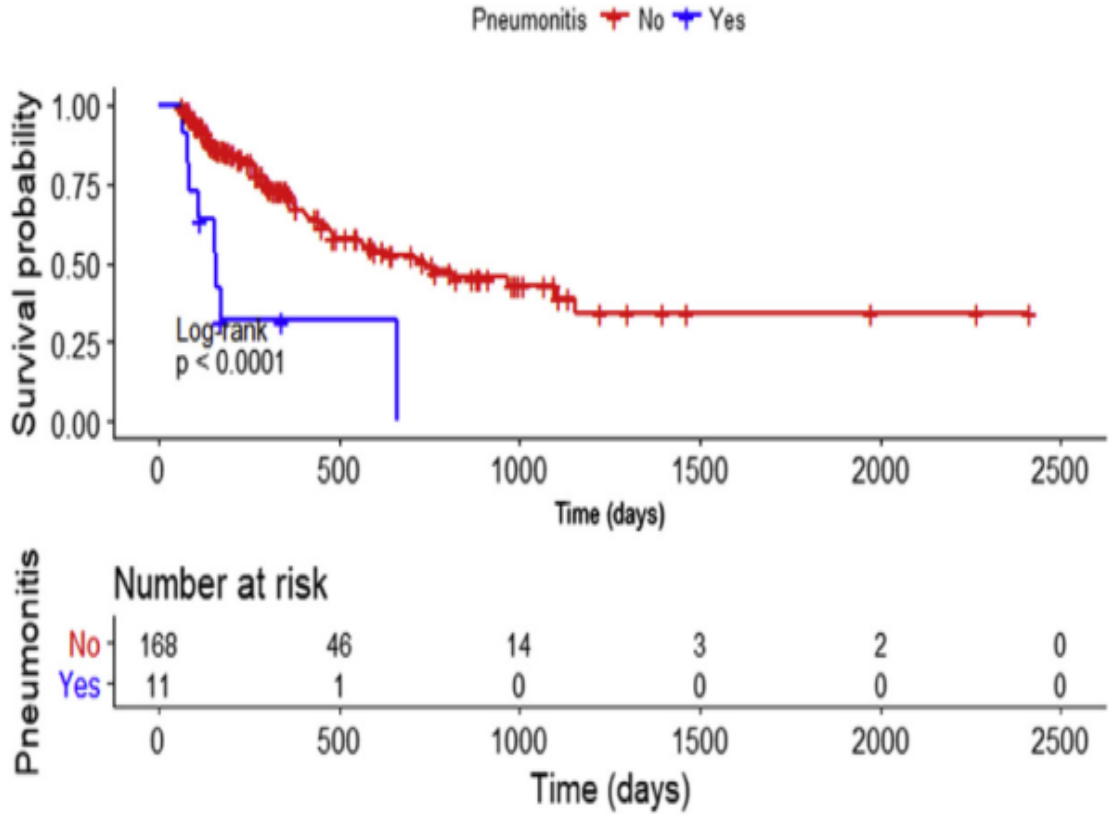




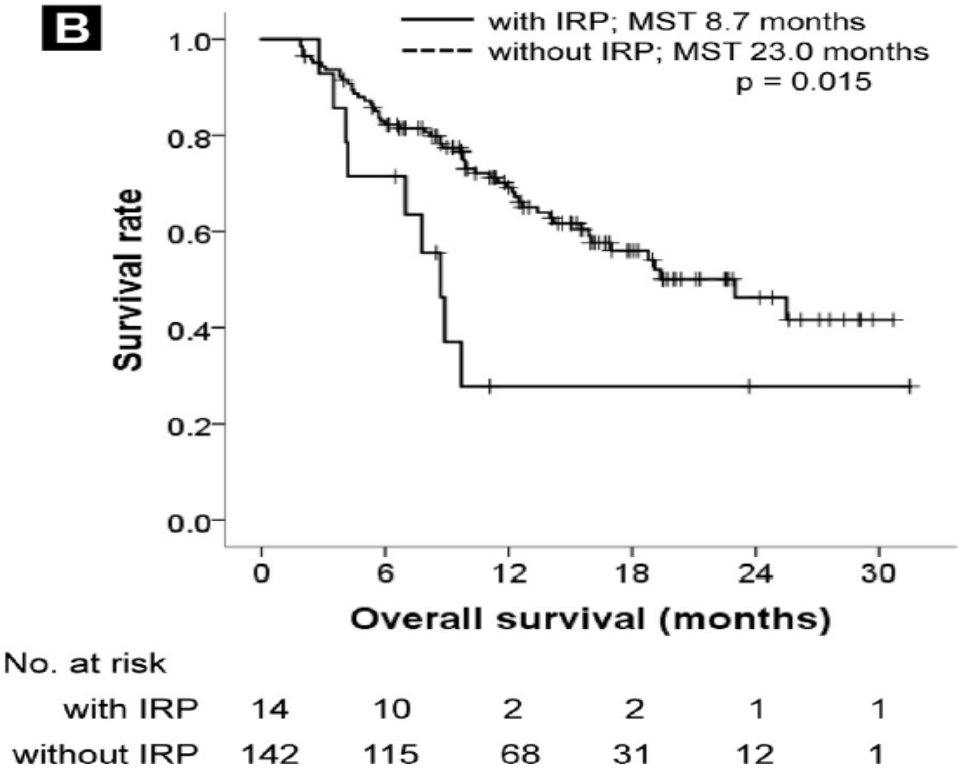
JAMA Oncol. 2020;6(12):1952-1956

Lower survival in NSCLC patients with immune-related pneumonitis(IRP)

- Single center (Johns Hopkins), using Markov multistate modeling, anti-PD-(L)1 mono or combo
- 179 (no IRP=168, **IRP=11**)



- Multicenter (Japan), anti-PD-(L)1 mono
- 165 (no IRP=142, **IRP=14**)



Clin Lung Cancer. 2020;21(3):e169-e170: J Thorac Oncol. 2019;14(3):494-502: Clin Lung Cancer. 2019;20(6):442-450

Severe irAEs in IO followed by TKIs

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

A. J. Schoenfeld[1], K. C. Arbour[1], H. Rizvi[1], A. N. Iqbal[1], S. M. Gadgeel[2], J. Girshman[3], M. G. Kris[1], G. J. Riely[1], H. A. Yu[1*†] & M. D. Hellmann[1*†]

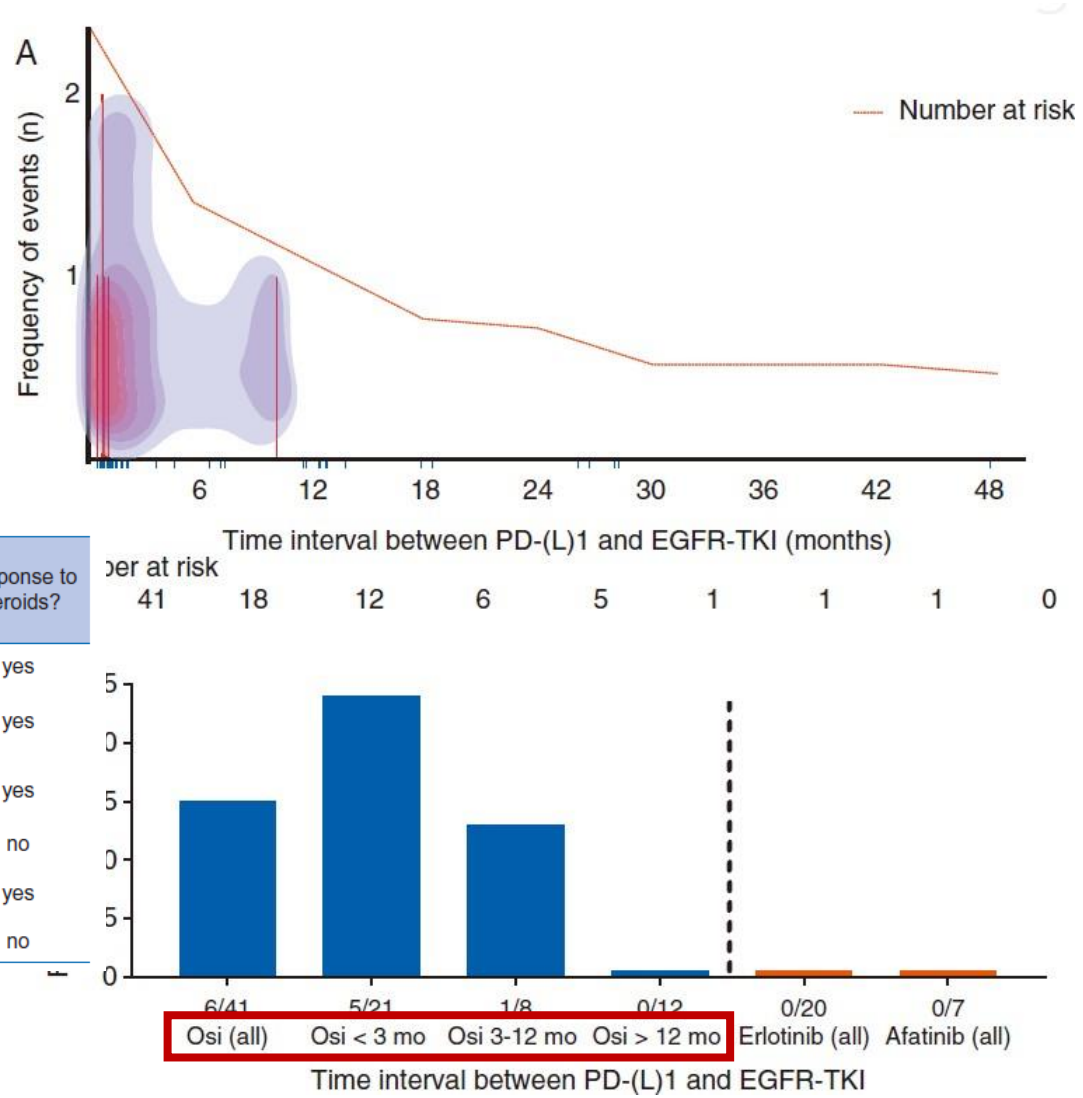
- N=70, restrospective, MSKCC (single center)
- Sequential Tx with IO & TKIs

Table 1. Clinical characteristics of patients who received sequential programmed death-ligand-1 (PD-(L)1) blockade followed by osimertinib and osimertinib followed by PD-(L)1 blockade

Characteristic	PD-(L)1 then osimertinb	Osimertinib then PD-(L)1

Patient No.	IO regimen	Time on IO	Time interval between IO and Osimertinib	Time to onset of toxicity after 1st dose of Osimertinib	Toxicity	Toxicity grade	Need for hospitalization?	Response to steroids?
1	nivolumab	14 days	29 days	24 days	Pneumonitis	3	yes	yes
2	carboplatin, pemetrexed, pembrolizumab	21 days	23 days	15 days	Pneumonitis	3	no	yes
3	ipilimumab, nivolumab	392 days	22 days	167 days	Pneumonitis	3	yes	yes
4	pembrolizumab	126 days	28 days	14 days	Colitis	3	yes	no
5	pembrolizumab	126 days	314 days	15 days	Pneumonitis	3	yes	yes
6	nivolumab	68 days	39 days	39 days	Hepatitis	4	yes	no

Time between PD-(L)1 and osimertinib, days	61 (12–1446)	5 (1–256)
Time on osimertinib, days	167 (15–927)	119 (30–707)
Severe immune-related adverse event	6 (15)	0 (0)



Ann Oncol. 2019;30(5):839-844

Sequential TKI can be a risk factor of IO-related pneumonitis

Original Article

Sequential Treatment with an Immune Checkpoint Inhibitor Followed by a Small-Molecule Targeted Agent Increases Drug-Induced Pneumonitis

Jongheon Jung[1], Hyae Young Kim[2], Dong-Gil Kim[1], Seog Yun Park[3], A Ra Ko[1], Ji-Youn Han[1], Heung Tae Kim[1], Jin Soo Lee[1], Youngjoo Lee[1]

Departments of [1]Internal Medicine, [2]Radiology, and [3]Pathology, National Cancer Center, Goyang, Korea

- N=242, retrospective, NCC of Korea
- Pneumonitis: 23/242 (9.5%), ≥G3: 13/23(56%)
- 149 received sequential Tx within 8wks

Table 4. Comparison of clinical courses of drug-induced pneumonitis according to sequential treatment after ICI (n=149)

Sequential treatment within 8 weeks	No. of patients	No. of prior CTx before ICI, lines	Time on ICI (day)	Interval between the last ICI and sequential CTx (day)	No. of pneumonitis, any grade (%)	Interval between the last ICI and the onset of pneumonitis (day)	Interval between sequential CTx to the onset of pneumonitis (day)	Proportion of grade ≥ 3 pneumonitis, n (%)	Hospitalization required, n (%)	Duration of admission (day)
No further CTx	79	1 (0-7)	78.0 (1-697)		4 (5.1)	81.5 (43-263)		2 (50)	2 (50)	12.5 (11-14)
Cytotoxic agent	54	2 (0-5)	44.5 (1-452)	23.0 (7-55)	4 (7.4)	62.0 (61-67)	41.0 (29-44)	0	1 (25)	20
Targeted agent	16[a)]	2 (1-6)	29.0 (1-176)	32.5 (16-56)	3[b)] (18.8)	35.0 (32-94)	12 (7-54)	3 (100)	3 (100)	17 (2-33)

CTx, chemotherapy; ICI, immune-checkpoint inhibitor. [a)]Received gefitinib (6), erlotinib (2), osimertinib (6), crizotinib (1), glesatinib (1), [b)]Received gefitinib (2), osimertinib (1).

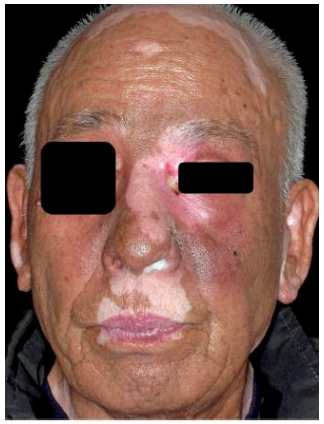
Two received gefitinib,
One received osimertinib

Cancer Res Treat. 2021;53(1):77-86

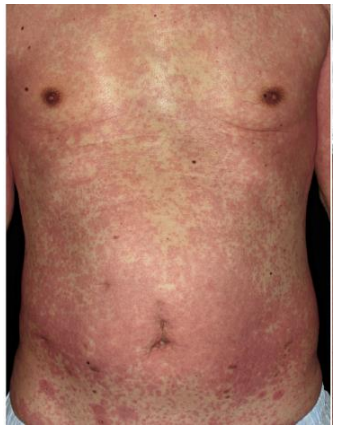
II. Organ-specific toxicities

Dermatologic toxicities

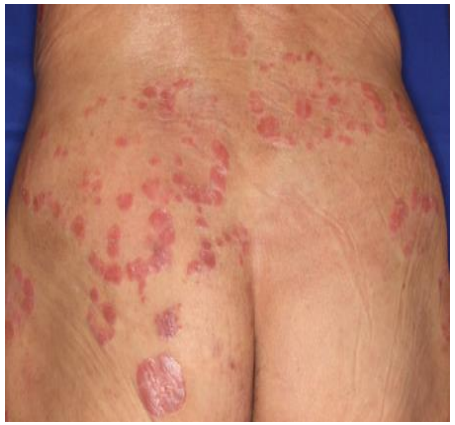
- Most common ICI-related toxicities
- Often appear the earliest after ICI therapy initiation (3~6 weeks)
- Most common: dry mouth, mucositis, rash, pruritus, and vitiligo
- SJS, DRESS, bullous pemphigoid: less common but serious
- G1-2: symptomatic Tx (anti-histamine, topical steroid etc)
- ≥G3: systemic steroid, consult to DM



Vitiligo



Maculopapular rash

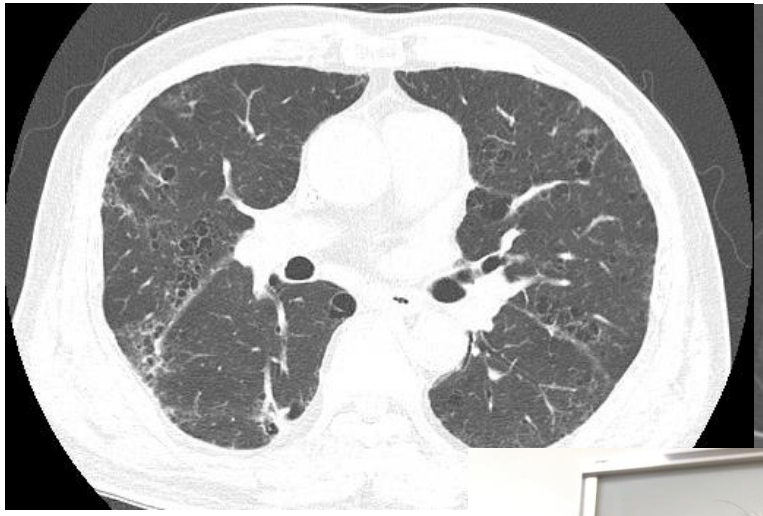


psoriasiform dermatitis

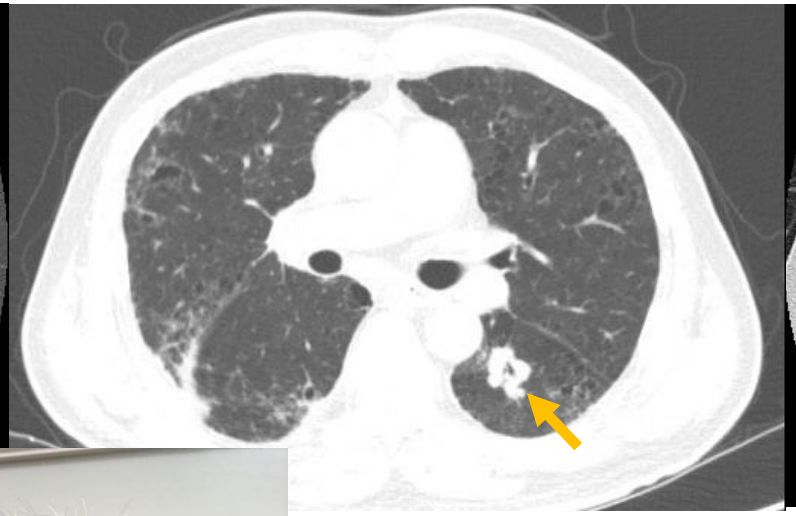
Allergol Int. 2022 Jan 28;S1323-8930(22)00002; Eur J Cancer. 2016;60:12–25: Curr Opin Oncol. 2016;28(4):254–63: J Clin Oncol.2019:JCO1802141

M/78, abnormal CXR, ex smoker: 20PY

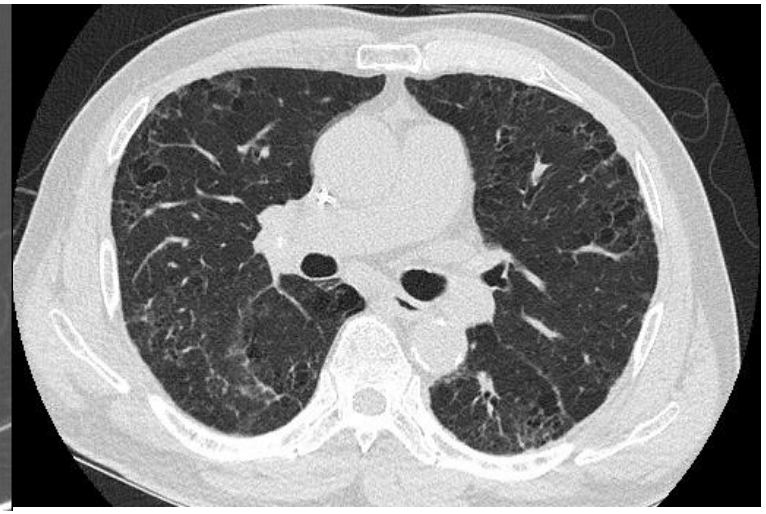
NSCLC(ADC, LLL, PD-L1 50%, pT4N0M1a, stageIVA) c lung to lung meta
s/p 1L 4C CTx(pemetrexed, cisplatin) with pemetrexed maintenance: 2019.6~ 2019.12.10
s/p 2L 1C ITx(pembro mono): 2019.12.31~



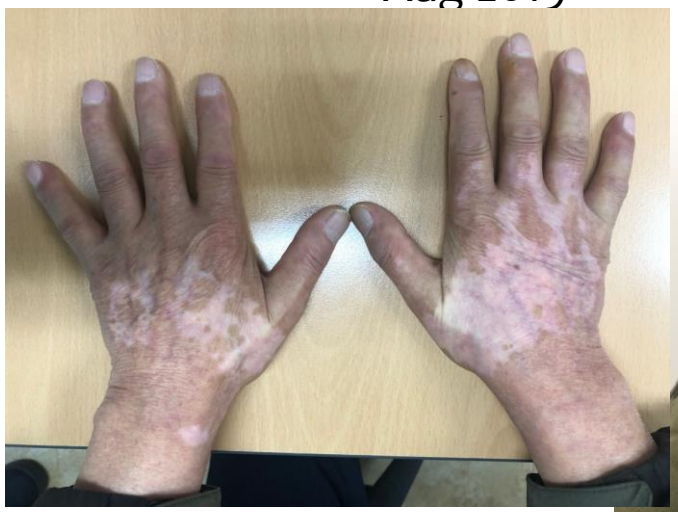
Aug-2019

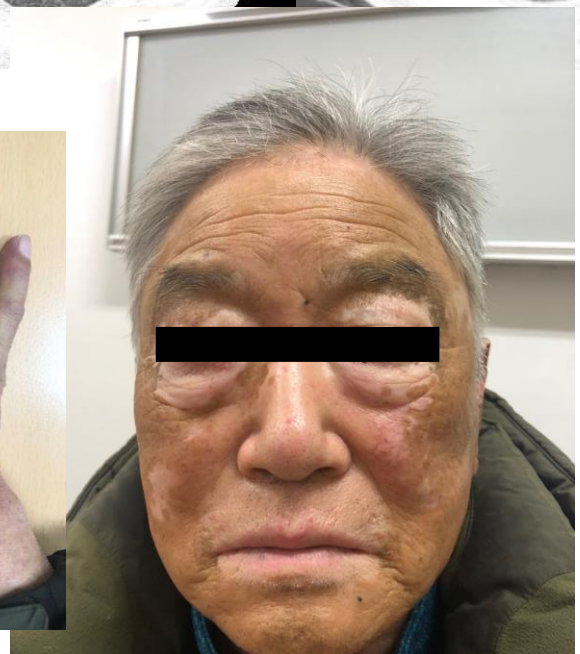


Dec-2019



Aug-2021





2L Pembrolizuamb

- After 6C pembro: itching and erythema on face, ant. neck, hands (area of sun exposure)

➔ Antihistamine
➔ No improvement
➔ DM consult

- Phototherapy & steroid lotion

Endocrinopathy (1): general

- One of the most common irAEs
- Thyroid dysfunction: most common
- **Readily treatable by hormone replacement**
- Type 1 diabetes: rare (<1%), can be rapid onset, anytime during Tx, exclusively seen in anti-PD-(L)1 Tx

- Increased risk and earlier onset in anti-PD-(L)1/anti-CTLA-4 (27% vs 9% and median 30 days vs 76days)
- Can be asymptomatic, thus screening is important!

Eur J Endocrinol. 2018;178:173

Endocrinopathy (2): thyroid dysfunction

- Most common, often found incidentally on routine lab
- Anti-PD-1 (5-10%), anti-CTLA-4 (1-5%), combo (~20%)
- Median time of onset: 3 months
- Some cases presenting years after discontinuation

- Tx: **oral levothyroxine** (often require lifelong replacement)
- IO cessation is generally unnecessary
- If symptomatic➔ admission, consultation, consider IV levothyroxine & beta-blocker

Endocrinol Investig. 2018;41(6):625–38: Cancer Treat Rev. 2017;58:70–6: Ann Oncol. 2015;26(12):2375–91.

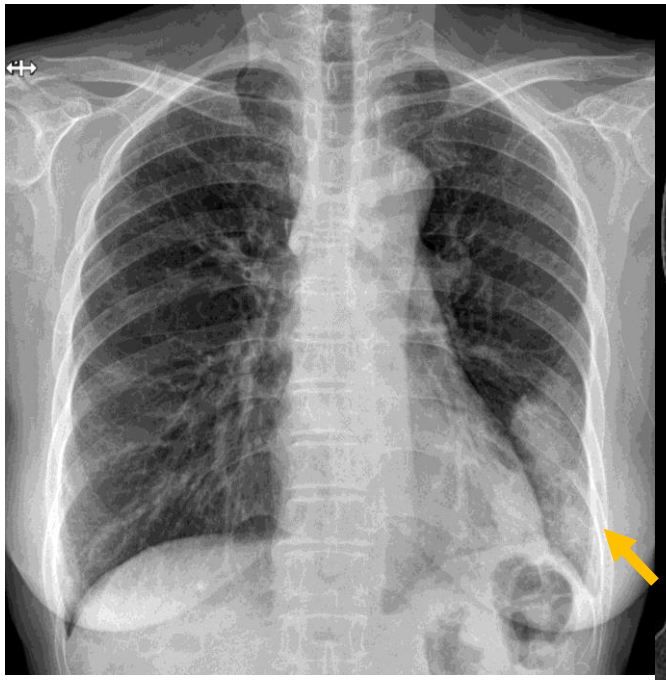
Endocrinopathy (3): diabetes

- Incidence: <1%
- New onset T1DM or exacerbation of T2DM
- Life-threatening DKA is possible
- Mostly occurs in anti-PD-1(71%); combo(15%), anti-CTLA-4(3%)
- Onset: few weeks~ a year after initial dose

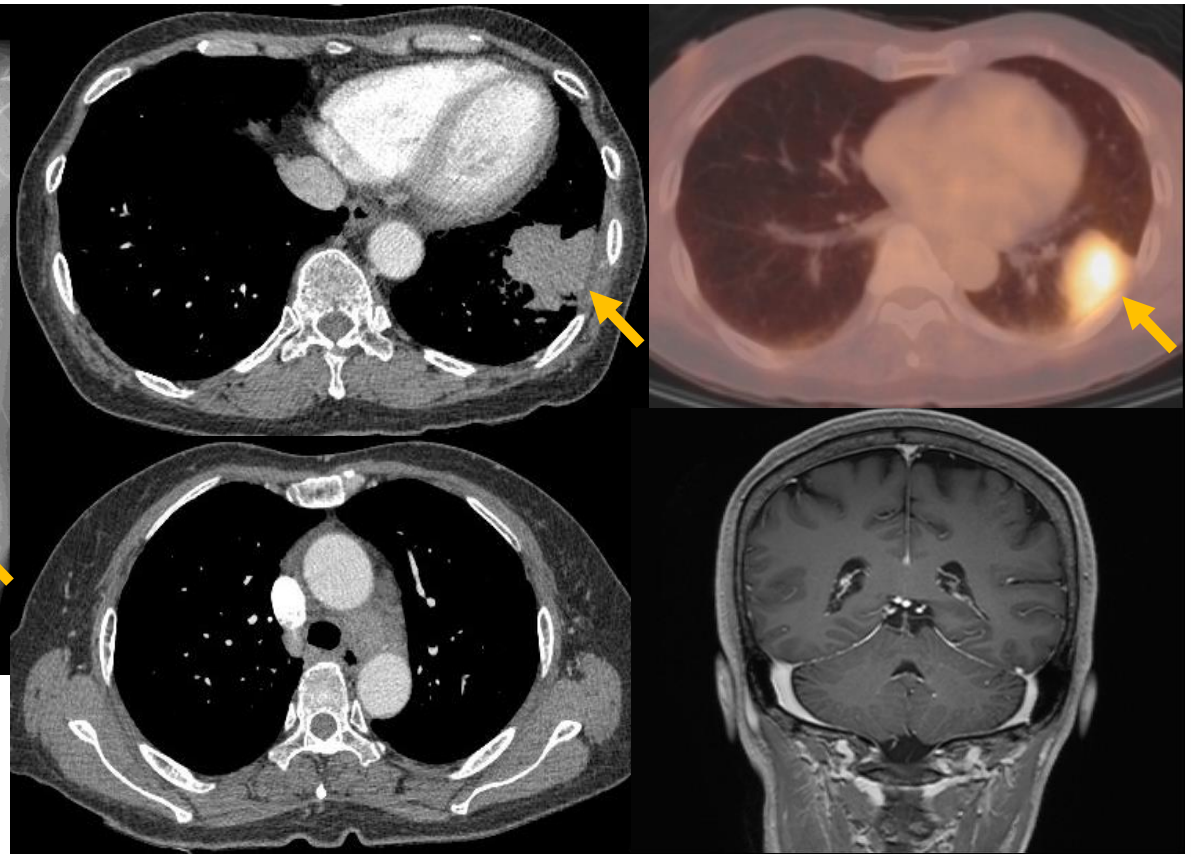
- **Blood glucose should be included routine lab panel.**
- New onset hyperglycemia→ C-peptide, anti-islet cell Ab
- Steroids is not advised (lack of data on its ability to ameliorate the immune response against beta cells)

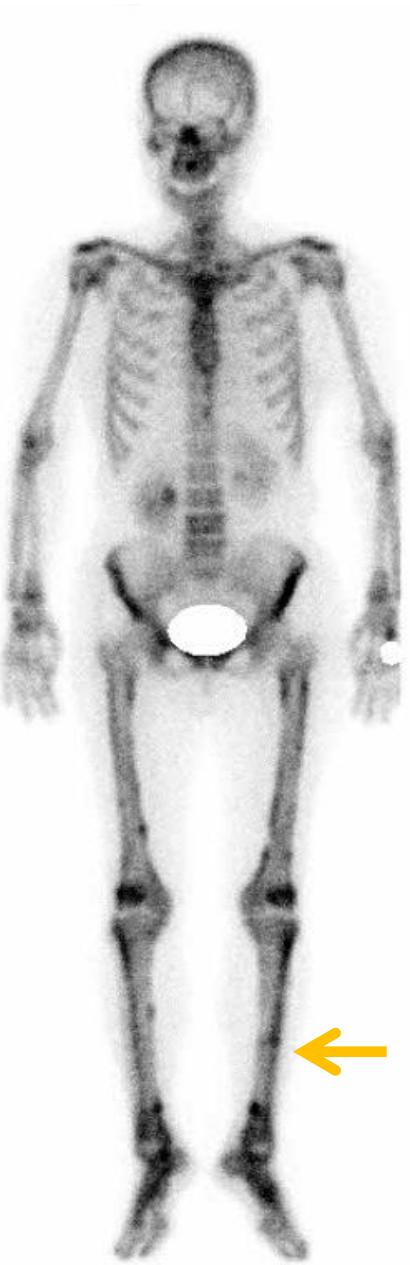
Diabetes Care. 2015;38(9):e137–8.: Eur J Endocrinol. 2019: Curr Opin Oncol. 2016;28(4):278–87

F/62, never smoker, both legs pain & abnormal CXR



Nov-2021





- NSCLC(ADC,LLL, cT4N2M1a, stage IVA, PD-L1 1%) with lung to lung meta
- Hypertrophic pulmonary osteoarthropathy
- EGFR (-), ALK (-), ROS1 (-)
- NSAIDs
- Started 1L 1C CITx(pemetrexed,pembro,carbo) at 2021.11 awaiting NGS result

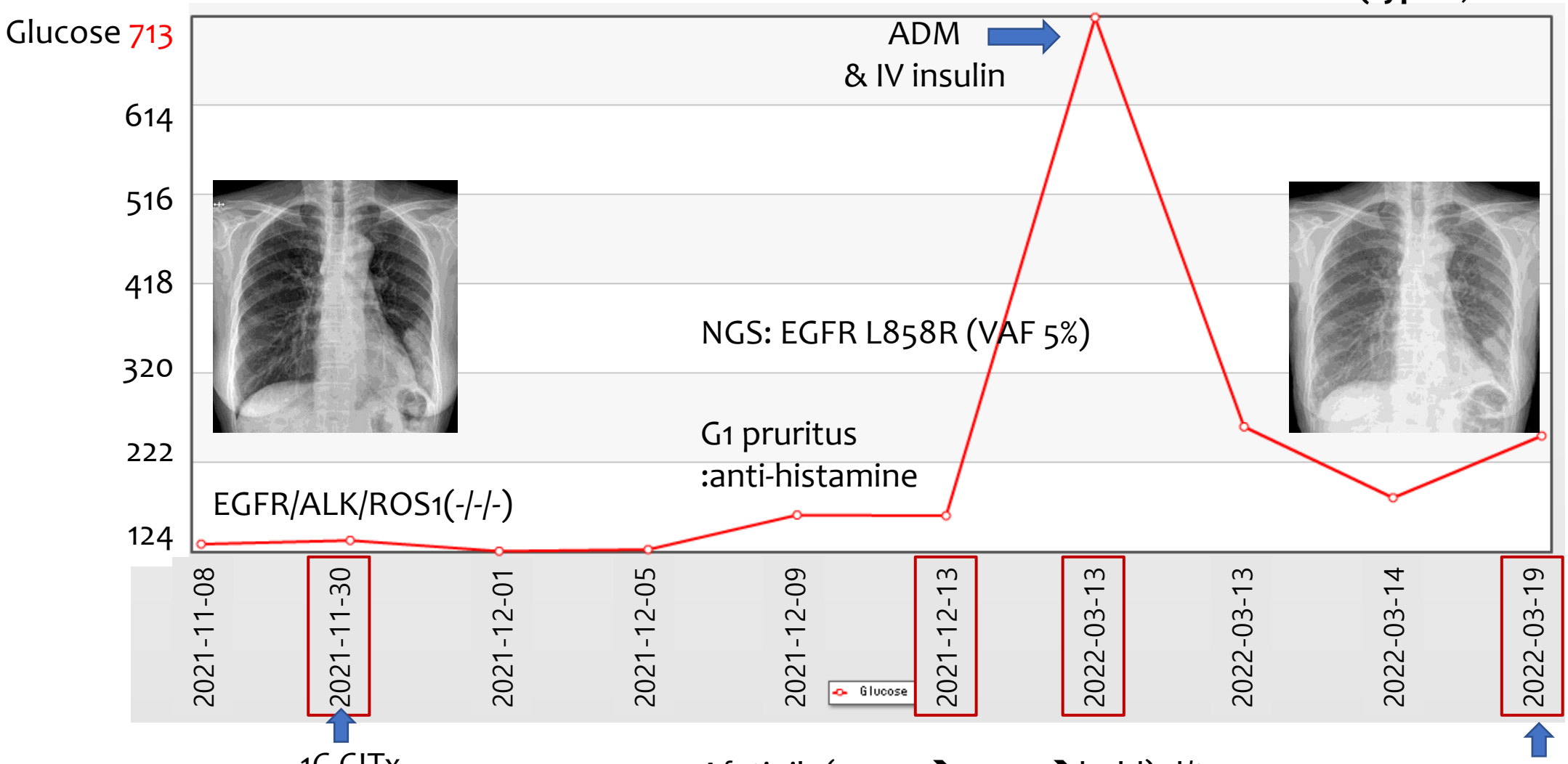
Clinical course (1)

- 1st OPD(day#12); G1 pruritus➔ antihistamine➔ improved
- NGS: EGFR L858R (VAF 5%)

- Afatinib 40mg: 2022.1.3~
- 2022.1.17: mucositis, diarrhea, acneform rash, paronychia: all G2 (+)
  oral intake<50%
- Afatinib 40mg→ 30mg→20mg for 1m
- Wt loss 5kg, mucositis, rash G2➔ afatinib hold
- 2022.3.13 (ER): **glucose 710 mg/dL**
  ABGA : pH 7.293, pCO2 10.3, pO2 88.0, HCO3 4.9 / Lactic acid 3.67
  HbA1 5.9% ➔ 10.0%
  c/w DKA

Clinical course (2)

Dx: Pembro-induced DM (type 2, anti-islet cell Ab (-))



Pulmonary toxicities (1)

- Pneumonitis (m/c), sarcoidosis, pleural effusion, and reactive airway dz have been described.
- Incidence of pneumonitis

- a meta-analysis involving 16 trials (N=6,208)

: 4% (≥G3 in 1.5%)

similar between PD-L1 and PD-1 inhibitors

- a real-world study

: 5% in anti-PD-(L)1 vs 10% in ipi/nivo

Fatal pneumonitis: 0.4% in anti-PD-(L)1 vs 1.2% in ipi/nivo

Most frequent cause of fatal irAE (35% of fatal toxicities)

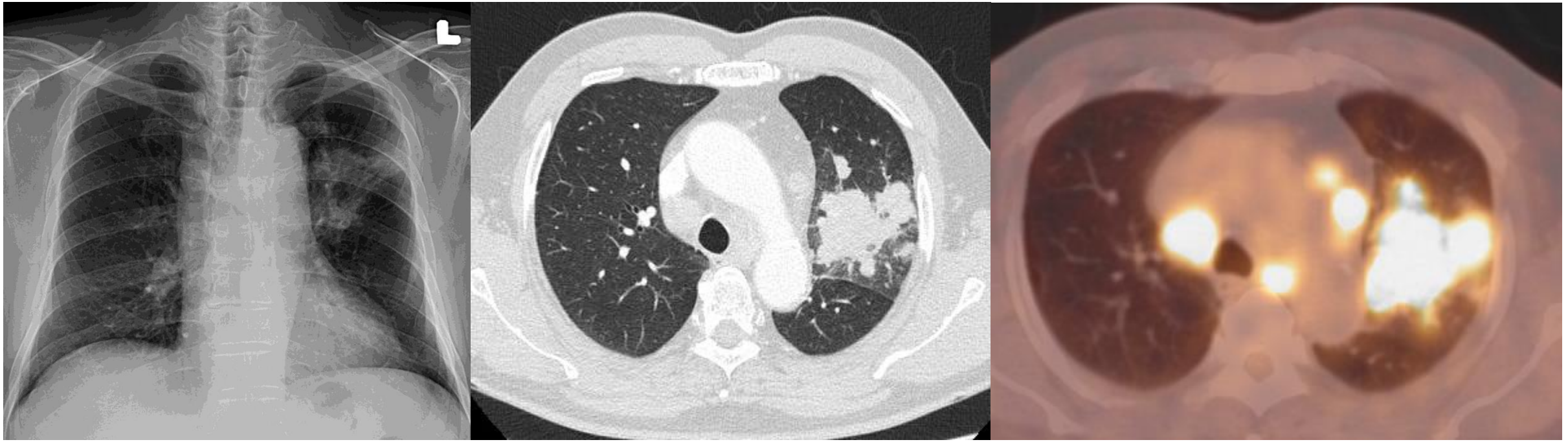
BMC Cancer 2019:19,558; Cancer Med. 2019:8, 2664–2674; J. Clin. Oncol. 2017:35,709–717; JAMA Oncol. 2018:4, 1721–1728

Pulmonary toxicities (2)

- Onset is variable, with new toxicity reported days up to 19 months after initiation of ICI therapy
- **GGO (bi- or unilateral), consolidation (organizing pneumonia)…**
- **Risk factors: ILD, thoracic RTx, combo (>mono), pembro (>nivo), low albumin…**
- No pathognomonic feature; rule out other etiologies (infection, cancer progression, cardiac problems)
- Usually steroids responsive
- Data on the second-line immunosuppressive agents for steroid-refractory pneumonitis are lacking.

Chest 2022, online ahead of print; J Thorac Oncol. 201;14(3):494–502: J Clin Oncol.2017;35(7):709–17; Clin Lung Cancer. 2019 Nov;20(6):442-450

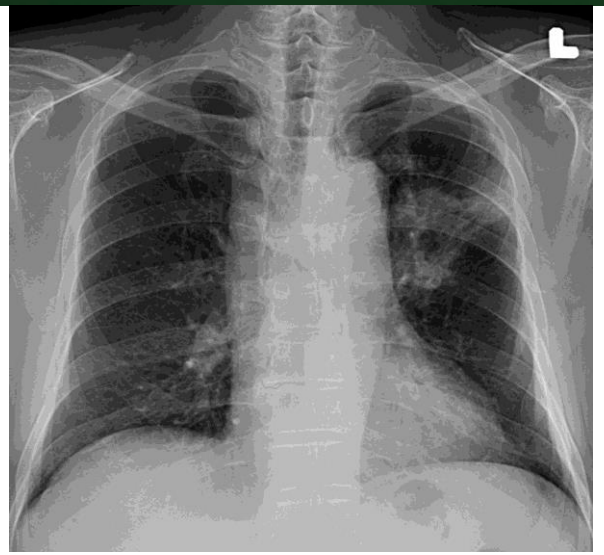
M/72, abnormal CXR, ex-smoker(30PY)



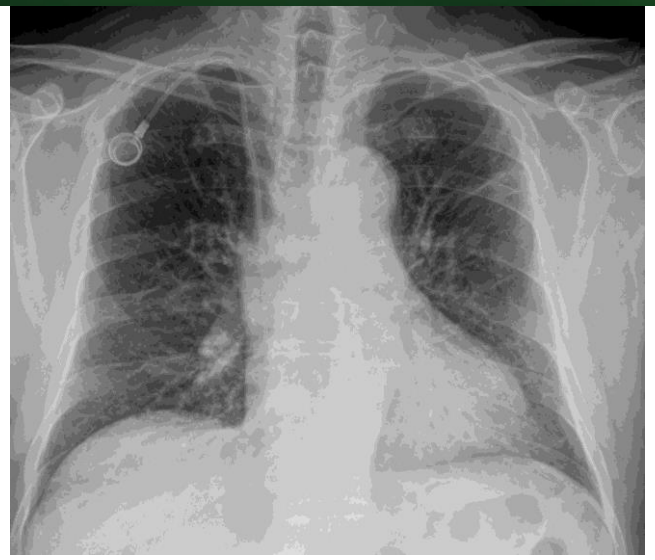
June-2020

- NSCLC(ADC,cT4N3M1c, stage IVB) with pleura, sacrum, iliac, left perirenal & multiple LNs meta
- EGFR/ALK/ROS1: (-/-/-)
- PD-L1 (SP263): 3%
- 1L 1C CITx (pemetrexed,pembrolizumab,cisplatin): 2020.6.~

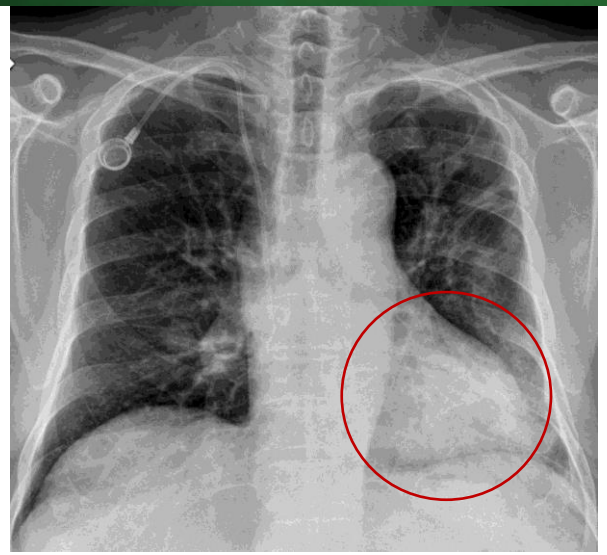
Clinical course



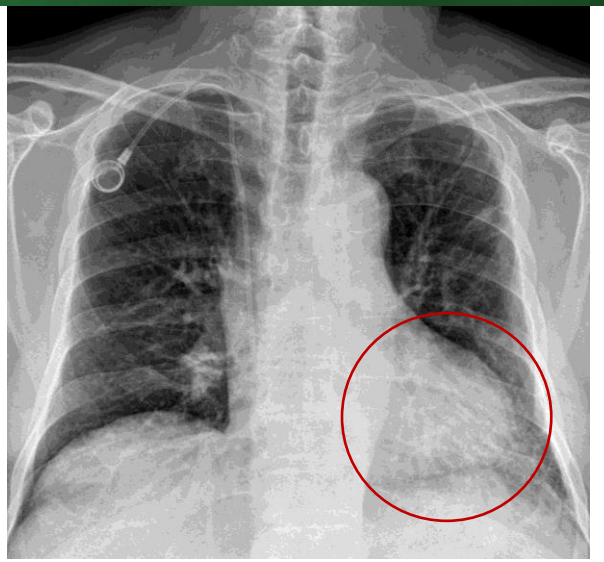
June-2020



May-2021



Sept-2021

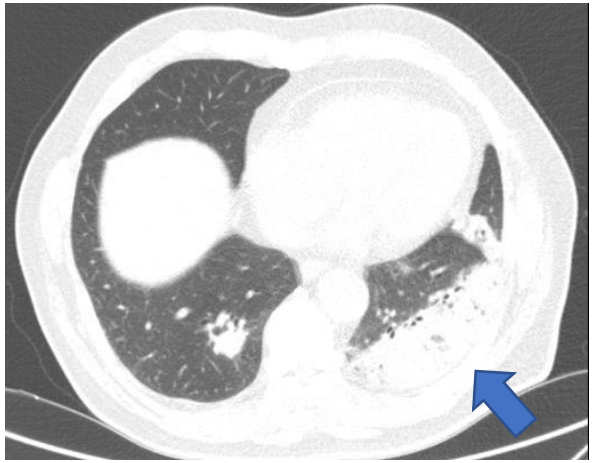


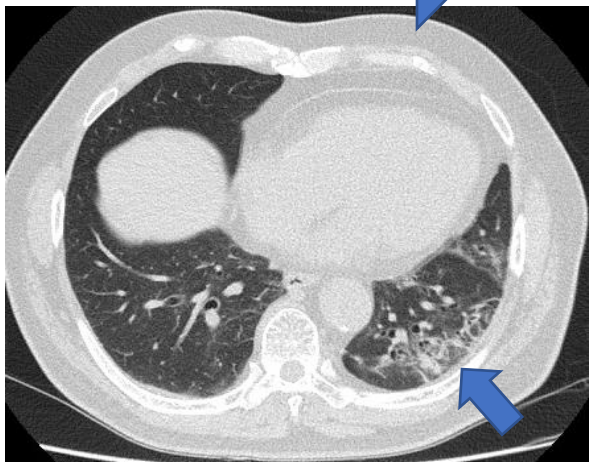
Nov-2021

Hold pembro and methylpred. 40mg with tapering for 6wks

- After 15 months (19C, Sept 2021): dyspnea (+)
- CRP 4.0

- Rechallenge (2021-11-23), no recurrence by Mar 2022 (24C)





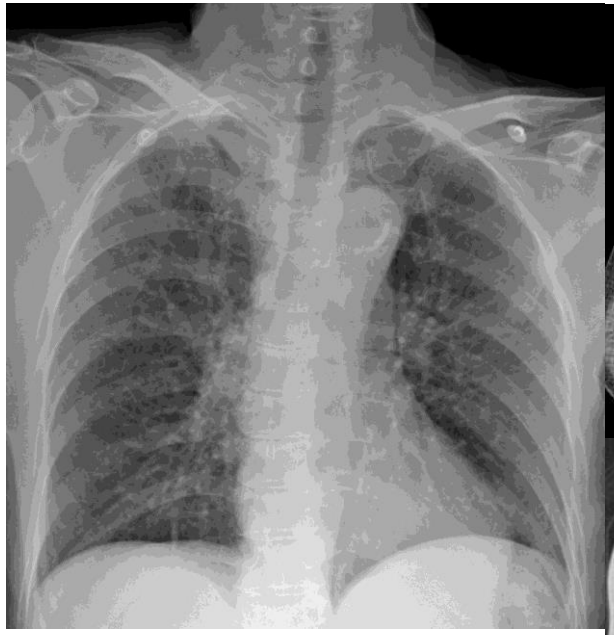
Feb-2022

Hepatitis

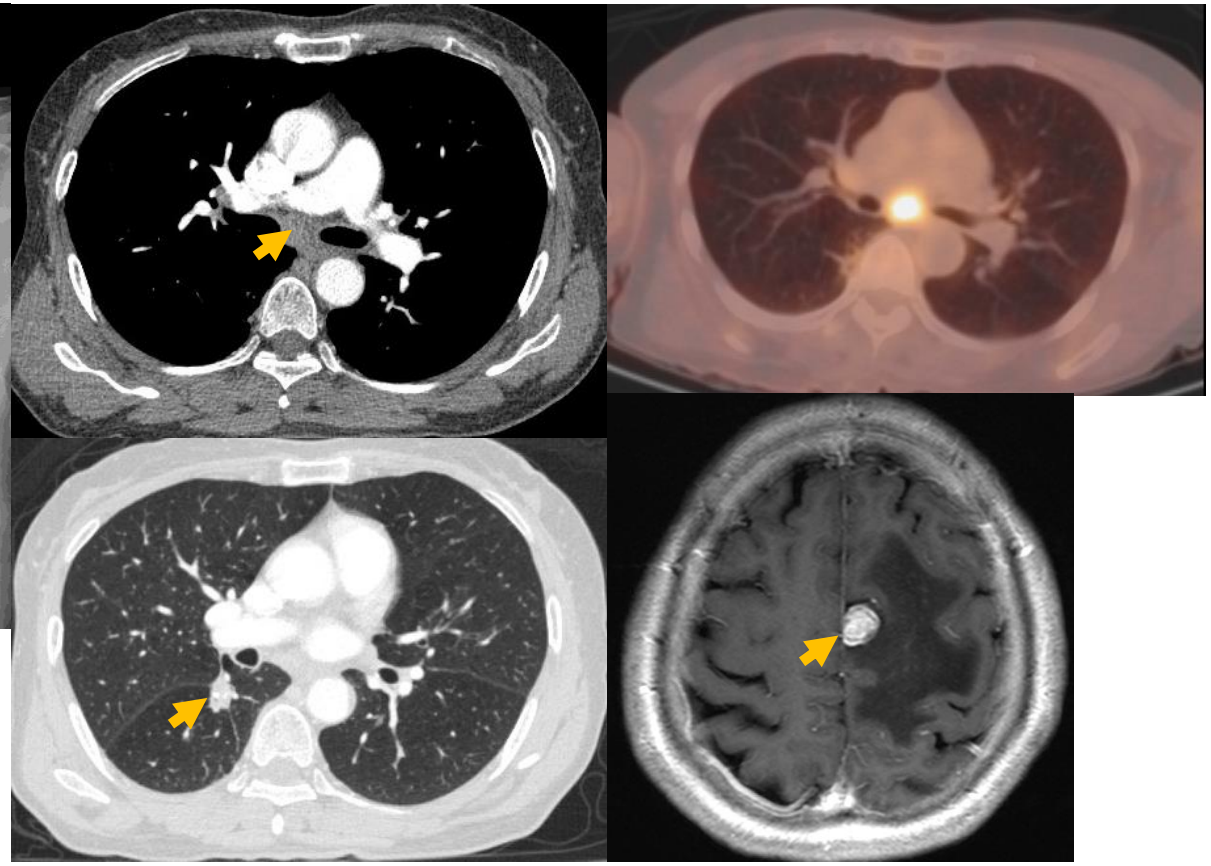
- Either symptomatic (jaundice, RUQ pain, vomiting) or asymptomatic
- May have nonspecific symptoms (fever, malaise)
- **First, rule-out other etiologies:** viral hepatitis, alcoholic hepatitis, **myositis** (**AST>ALT**)…
- G1-2: Hold IO and steroids for 4-6wks
- ≥G3: admission, consultation to hepatology, consider liver Bx and MMF in addition to steroids

Curr Oncol Rep (2020) 22: 39: Oncologist. 2018;23(9):991–7: J Clin Oncol. 2018;36(15_suppl):3087

Case, F/64, Rt side weakness, current smoker: 30PY



Dec-2020



- NSCLC(ADC,cT1bN3M1c, stage IVB, EGFR/ALK (-/-), PD-L1 90%) with multiple brain meta
- s/p GKS: 2020.12
- s/p 1L 4C CTx (pemetrexed,cisplatin): 2021.1.7~3.16
- s/p 6C pemetrexed maintenance: 2021.4.13~ 2021.7.27

Clinical course (2)

ALT 303

252

202

151

101

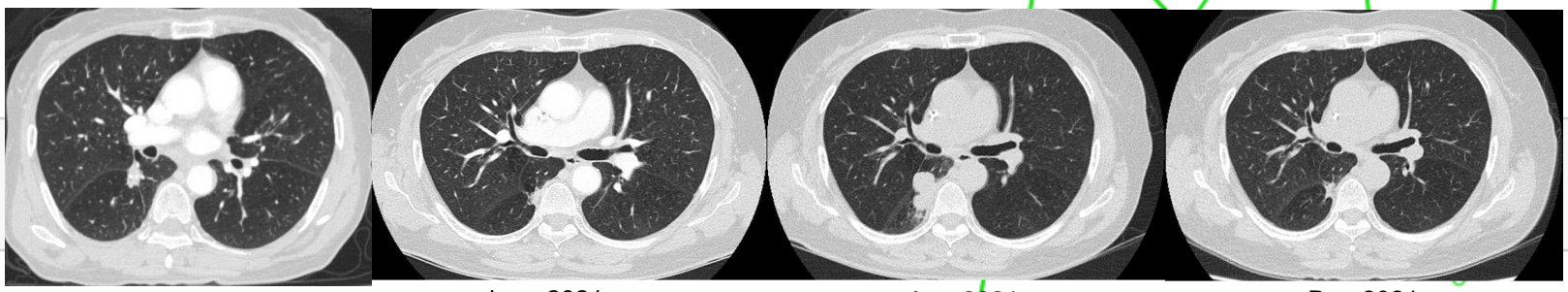
50

0

누적결과 수치

No	검사항목	검체명	참고치	2020-12-04 06:00	2020-12-17 00:07	2021-01-05 08:48	2021-06-03 09:44	2021-12-07 09:52	2021-12-07 12:12	2021-12-20 10:10	2022-02-08 08:07
1	T3	Serum(S)	81~197	164	109	182	186	65		154	188
2	F-T4	Serum(S)	0.89~1.79	1.25	1.20	1.42	1.03	0.14	0.18	0.69	1.15
3	TSH	Serum(S)	0.3~4.0	3.61	8.07	6.35	3.63	80.71	> 85	41.29	5.38

Chronic liver disease
with fatty infiltration



June-2021 Aug-2021 Dec-2021

2020-12-03 20:28
2020-12-11 02:14
2020-12-17 00:07
2020-12-24 06:00
2021-01-06 15:31
2021-01-26 07:58
2021-02-16 12:03
2021-03-04 15:30
2021-03-16 08:06
2021-04-08 13:39
2021-05-04 07:05
2021-05-13 10:07
2021-05-25 07:30
2021-06-08 15:51
2021-08-05 11:39
2021-08-09 07:54
2021-09-07 09:33
2021-10-13 14:53
2021-10-19 08:18
2021-10-28 08:30
2021-11-09 08:29
2021-11-23 08:16
2021-12-07 09:52
2021-12-19 21:09
2022-01-10 10:14
2022-01-12 10:23
2022-01-19 08:31
2022-01-20 09:13
2022-02-08 08:07
2022-02-22 09:45

Total Bilirubin ALT(GPT)

Final Dx: Pembro-induced hepatitis and hypothyroidism

2L 1C Pembro mono

5C Pembro mono

Hold & hepatotonics

Rechallenge (6C pembro) & levothyroxine

7C Pembro

8C Pembro

Neuro-muscular toxicities

- Relatively infrequent (~ 1%)

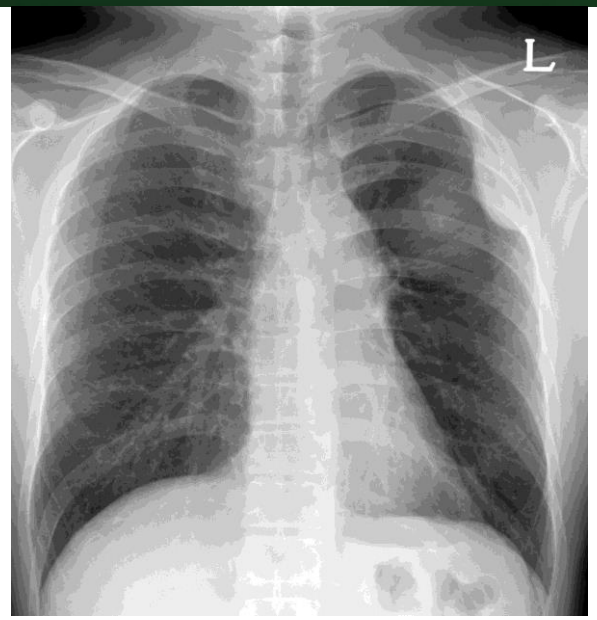
- Myalgia/**myositis**
- Peripheral neuropathy
- **Myasthenia Gravis**
- Guillain-Barre syndrome
- Transverse Myelitis

- Numbness, tingling, foot drop, and localized muscle weakness

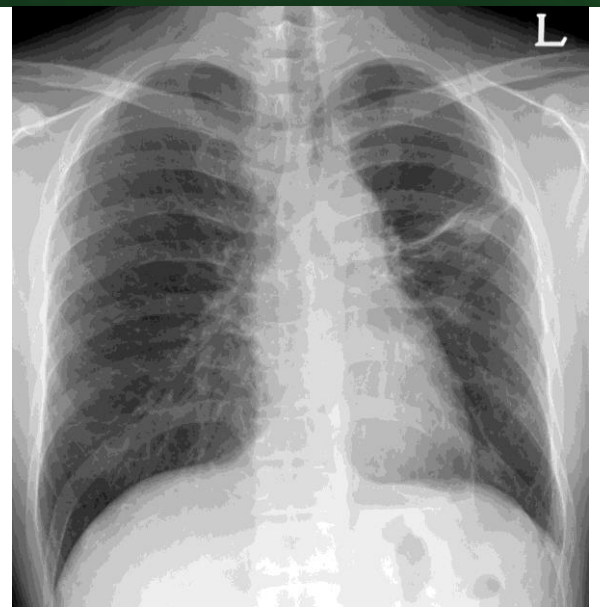
Management

- Get a neurologic consult!
- ≥ 2G: discontinue ICI, workup including labs and brain MRI, high-dose corticosteroid with a prolonged taper, neurology consultation, EMG if appropriate
- If MG or GBS: hospitalize
- G3/4 without resolution of symptoms within 24-48 hrs: consider rapidly moving to IV Ig and infliximab

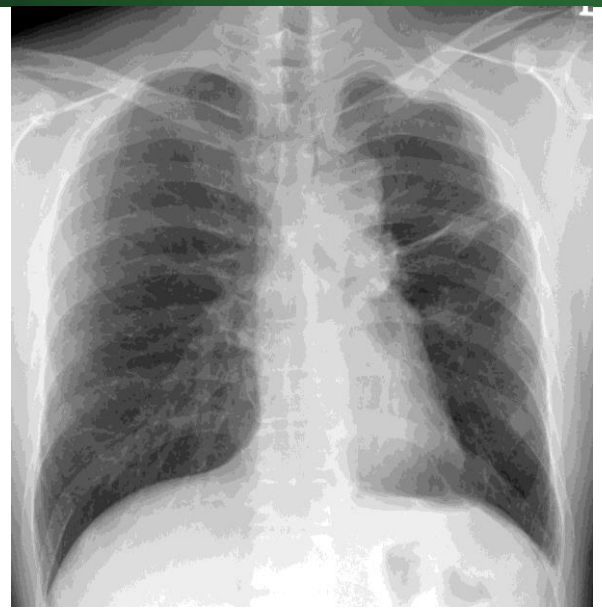
M/44, abnormal CXR



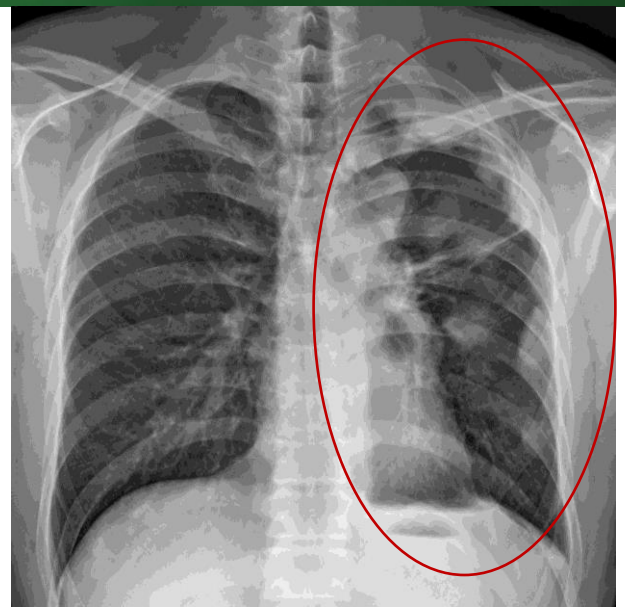
Oct-2020
(pre-2nd RTx)



Mar-2021
(post-2nd RTx)



Sep-2021



Nov-2021

- **Thymic carcinoma with pleural meta (Masaoka stage IVA): 2018.3.14**
- s/p CCRTx to central & mediastinal mass, Taxol,carbo (2018.7.30~8.23): 66Gy/33fx
- s/p RTx-pneumonitis
- s/p palliative RTx on pleural mass extension (36fx): ~2019.11.12
- s/p palliative RTx on Lt. upper pleural/post-lateral lesion (2000cGy/10fx): ~2020.12.4

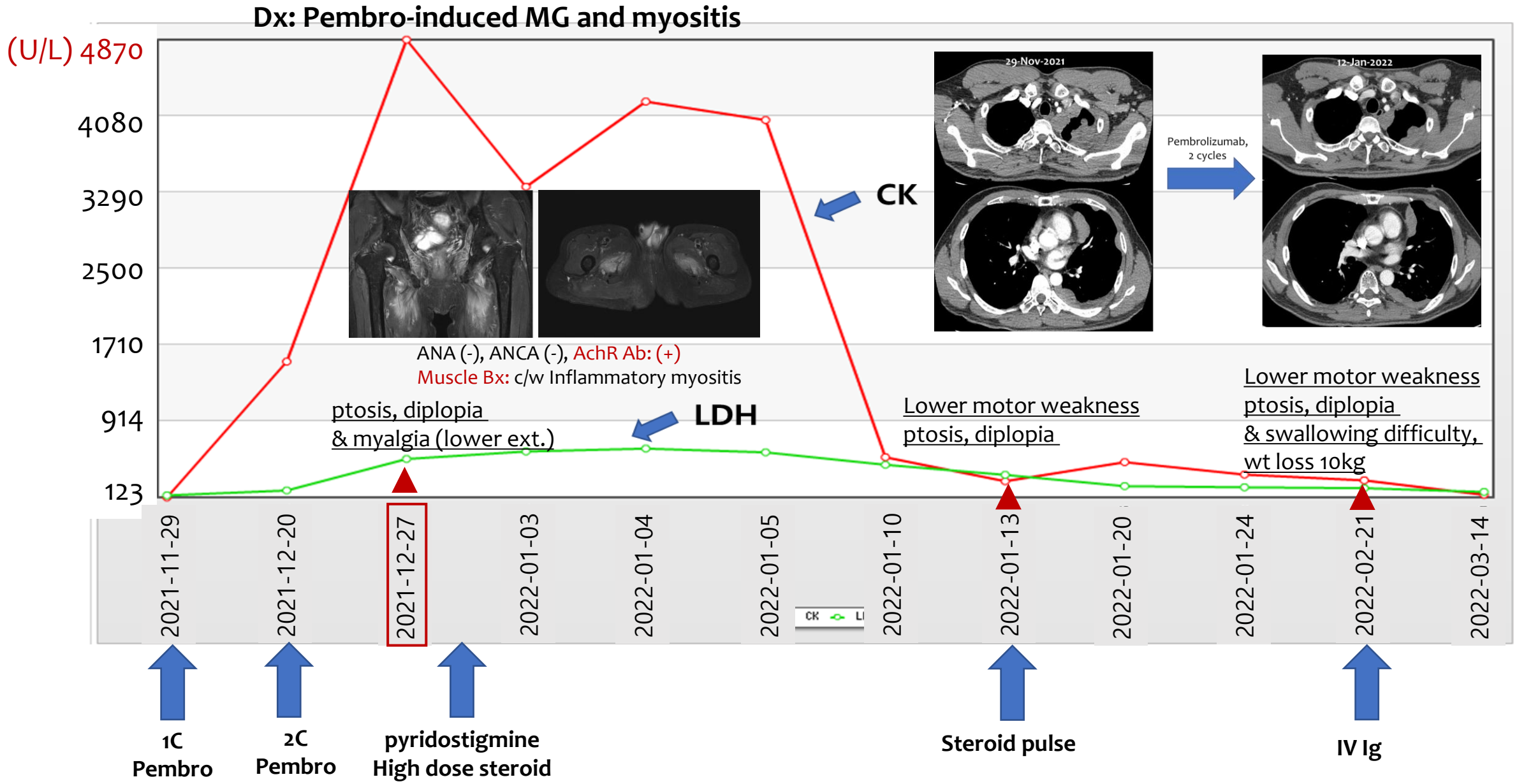
Clinical course (1)

- 2L 1C ITx(pembrolizumab): 2021.11.30~, tolerable
- 2C 2C ITx: 2022.12.21
- 2022.12.27: ptosis, diplopia & myalgia (lower ext.)
- Myoglobin 1,750 U/L

[진검] 일반화학[Serum] [체취일시:2021-12-27 08:39] [접수일시:2021-

검사명	결과	판정	단위
Total Bilirubin	0.92		mg/dL
AST(GOT)	297	▲	U/L
ALT(GPT)	202	▲	U/L
ALP	63		U/L
γ-GTP	65	▲	U/L
LD	520	▲	U/L
CK	4871	▲	U/L

Clinical course (2)



Take-home messages

- irAEs can involve **any organ** systems and occur **anytime during treatment**.
- **Multiple irAEs** can occur in any given patient and can be asymptomatic.
- **Sequential TKIs** after IO should be used with great caution due to severe irAEs.
- Keeping up with the **knowledge, close monitoring, and multidisciplinary approach** are crucial for the better management.
- Future work should focus on the understanding the **pathophysiology** and identification of relevant **biomarkers** to predict immune-related toxicities.

경청해주셔서 감사합니다.