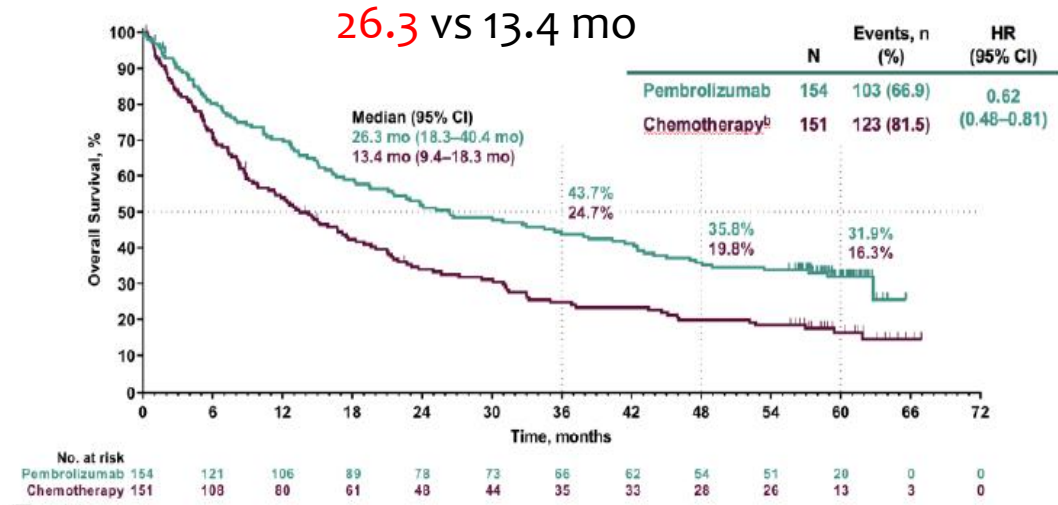


Not common but essential adverse events in patients being treated with ICIs

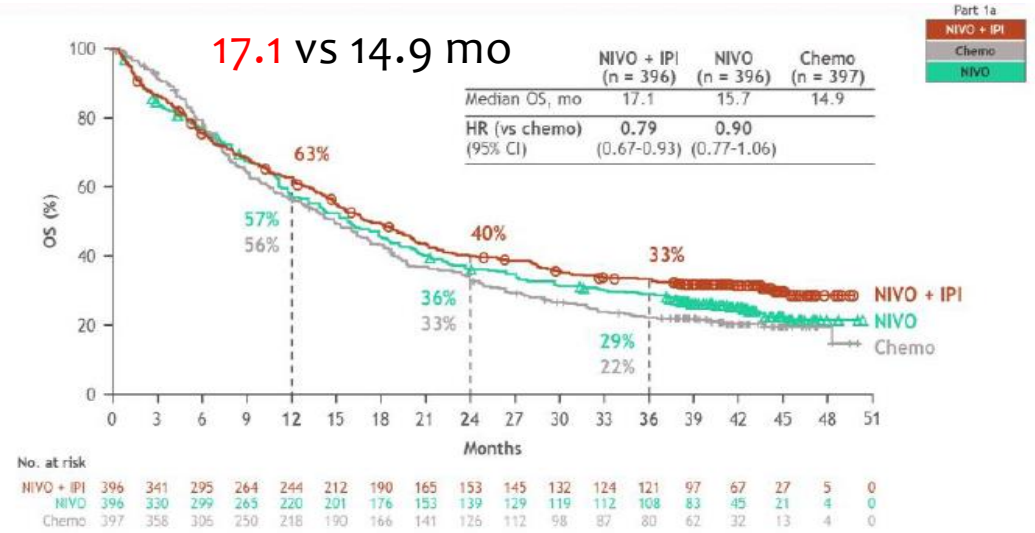
Seung Hyeun Lee
Department of Internal Medicine
Kyung Hee University Hospital

OS benefit of 1st-line IO in NSCLC

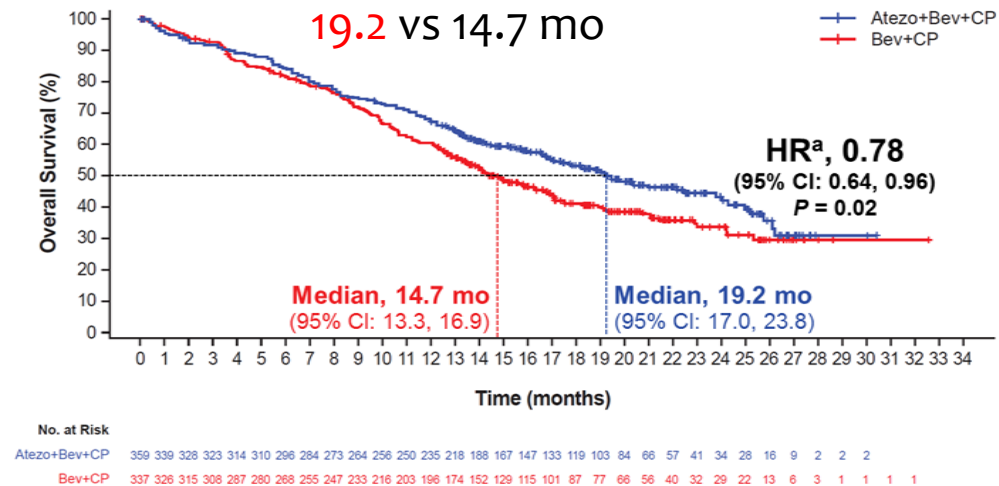
KEYNOTE-024 (PD-L1 $\geq$ 50%)



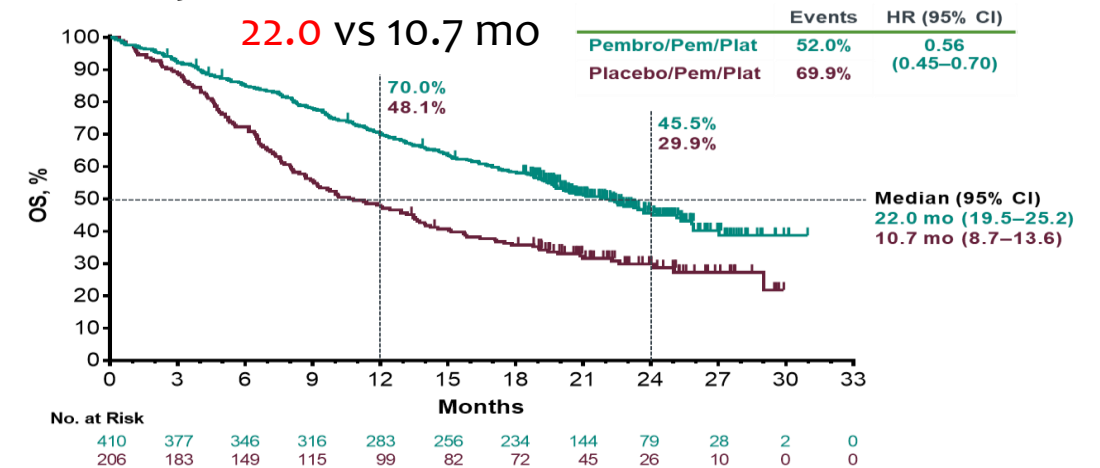
CHECKMATE-227



IMpower-150



KEYNOTE-189



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

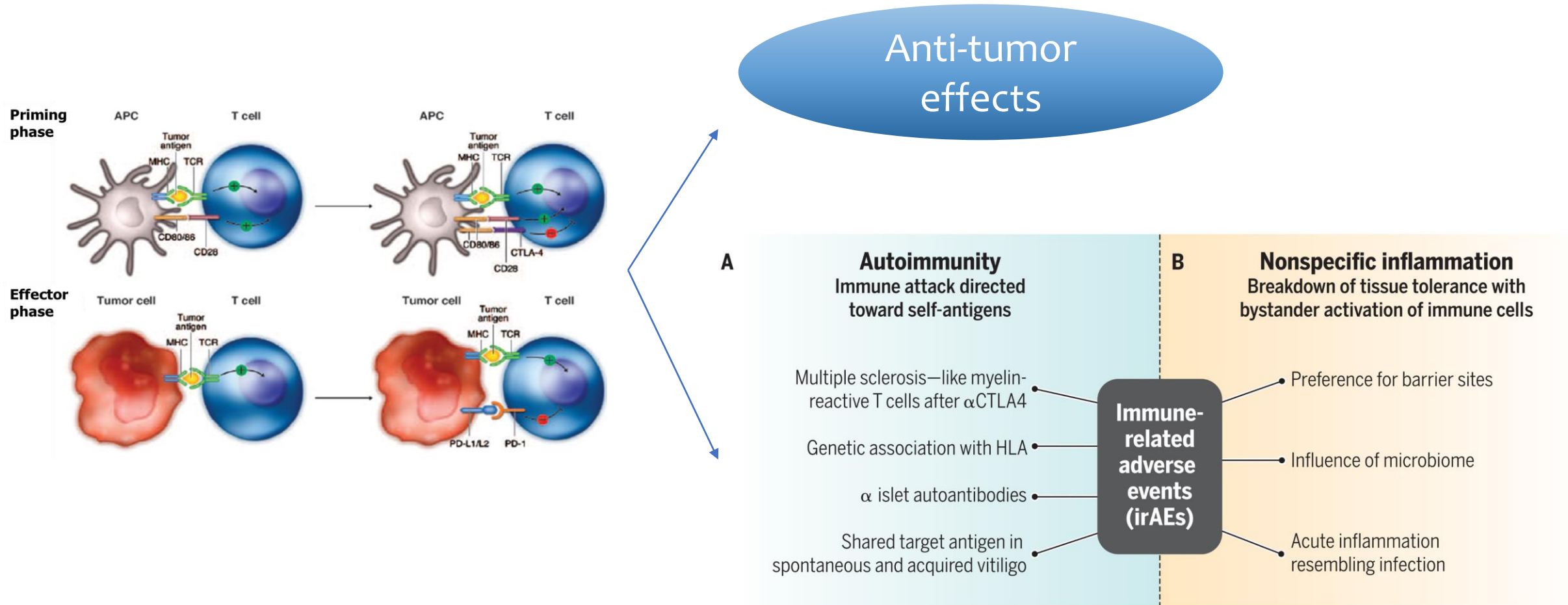
PD-(L)1 inhibitors



CTLA-4 inhibitor



Immune checkpoint inhibition: “Double-edged sword”



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?

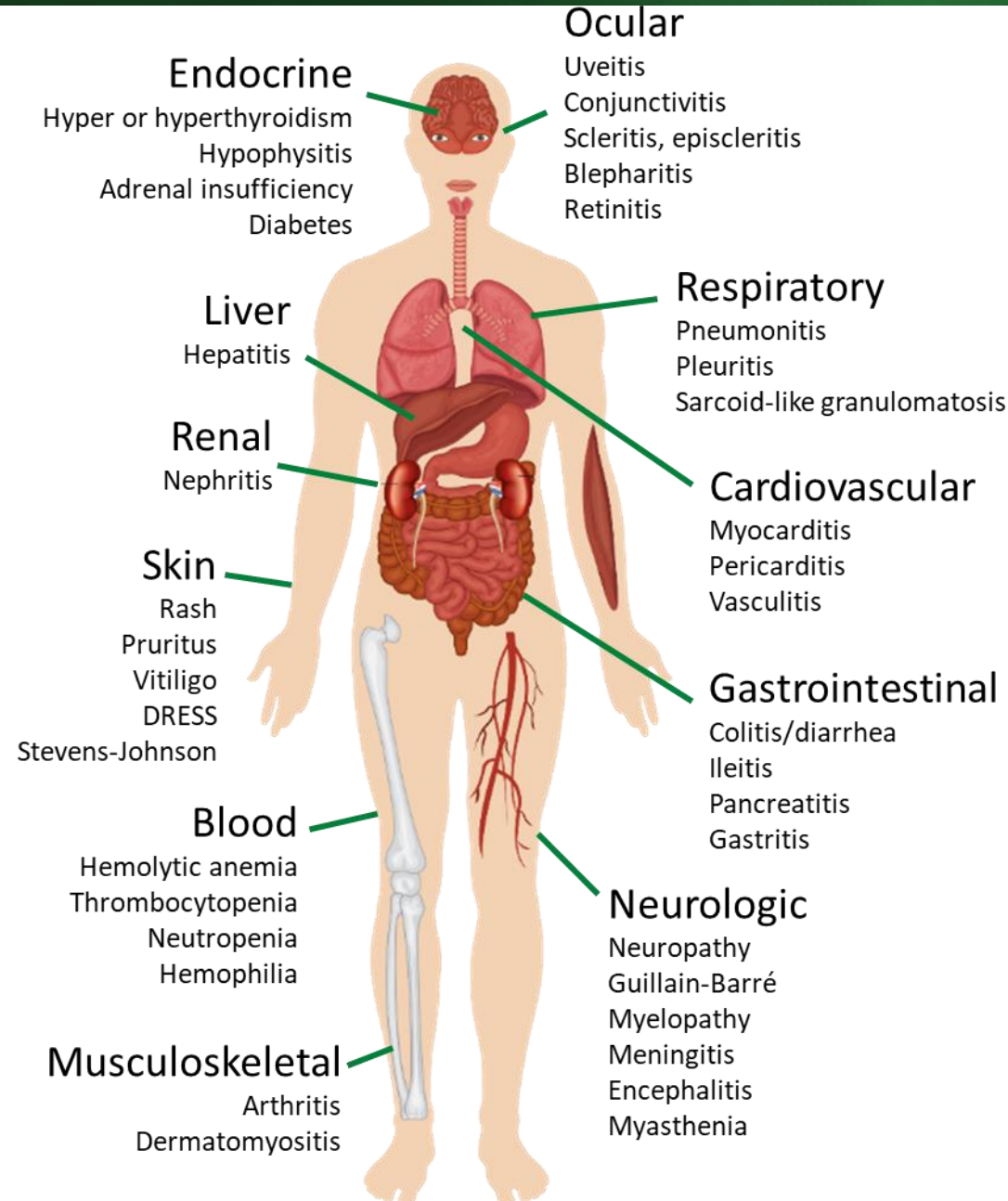
II. Organ-specific toxicities

- 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



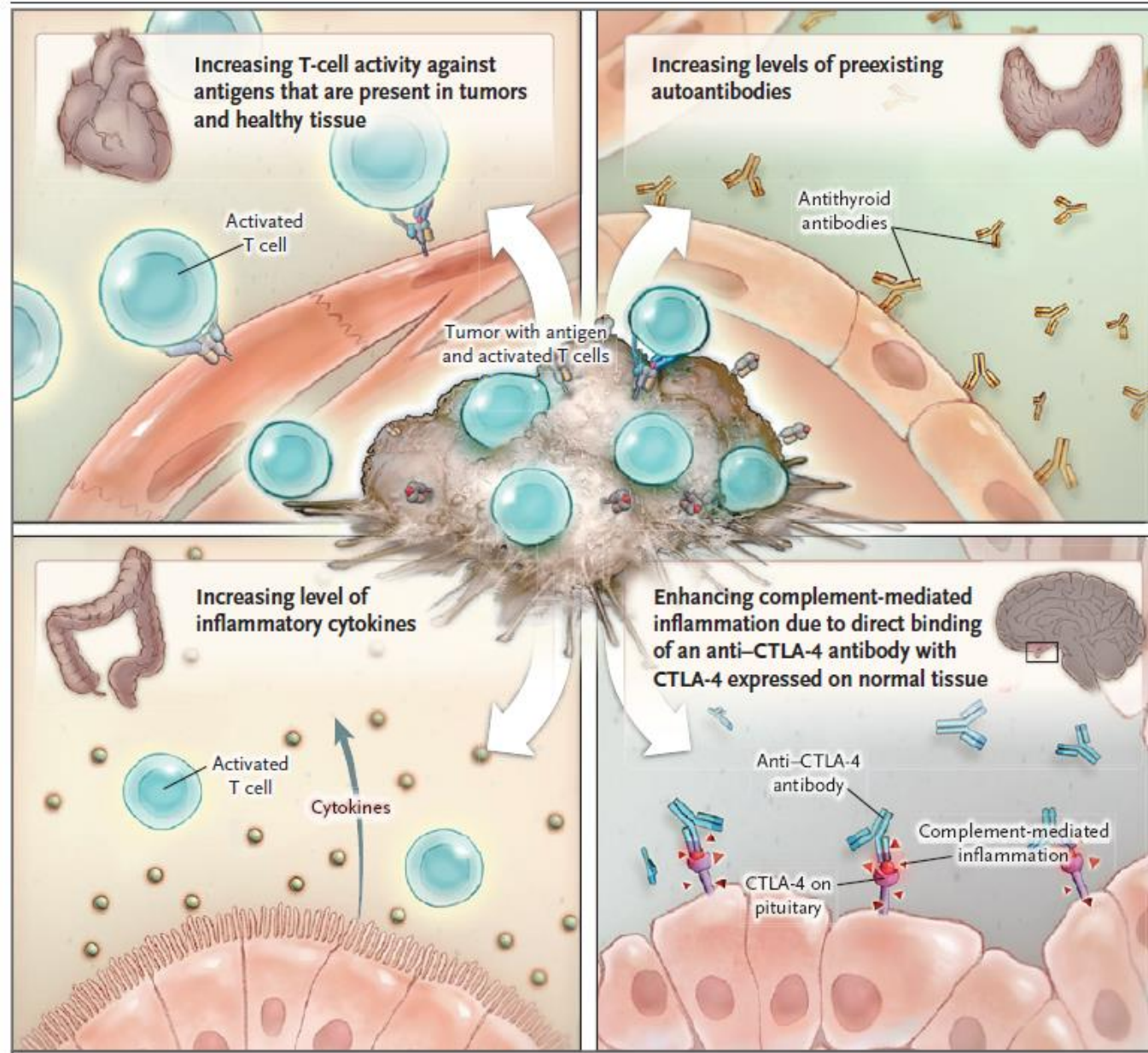
irAEs: basic concepts

- 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.

Possible mechanisms underlying irAEs

Increased T-cell activity

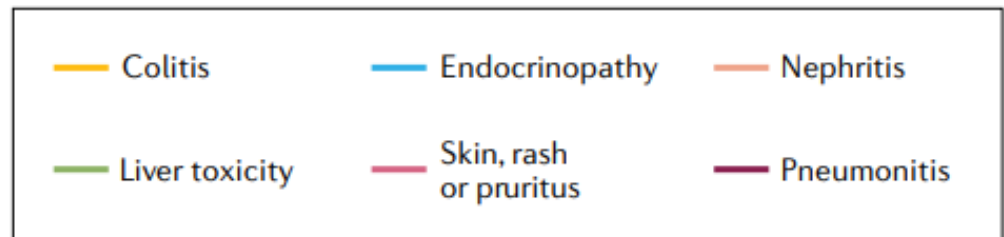
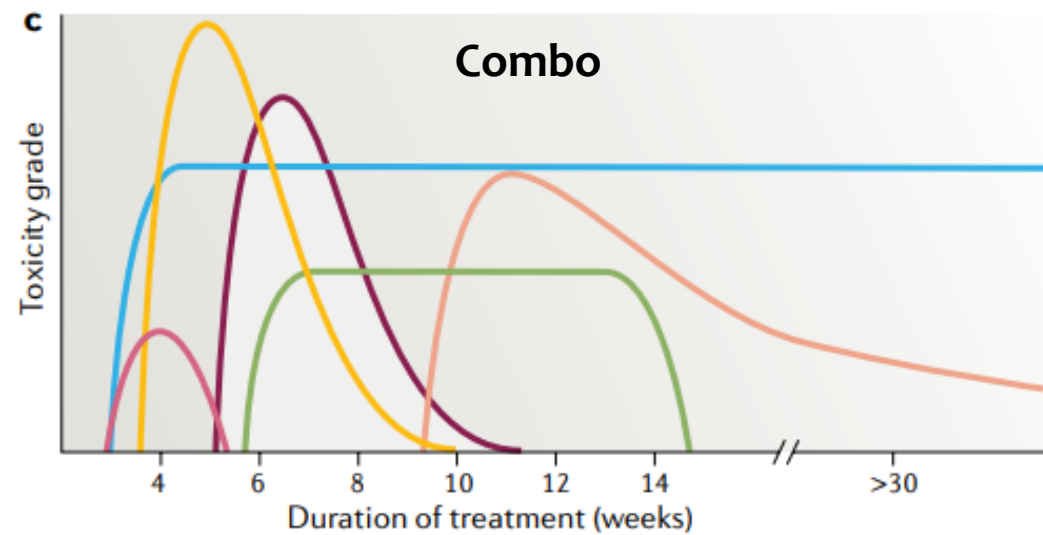
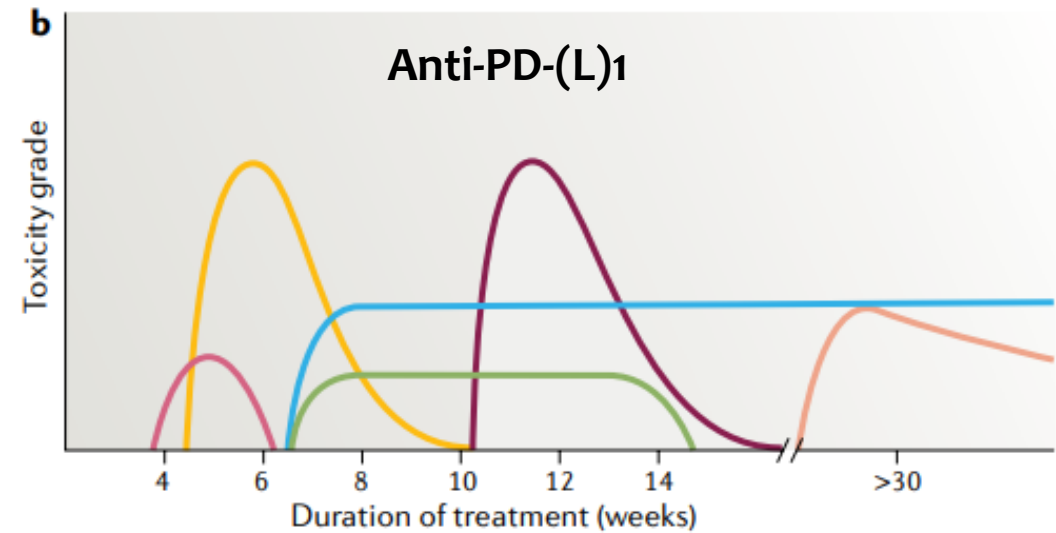
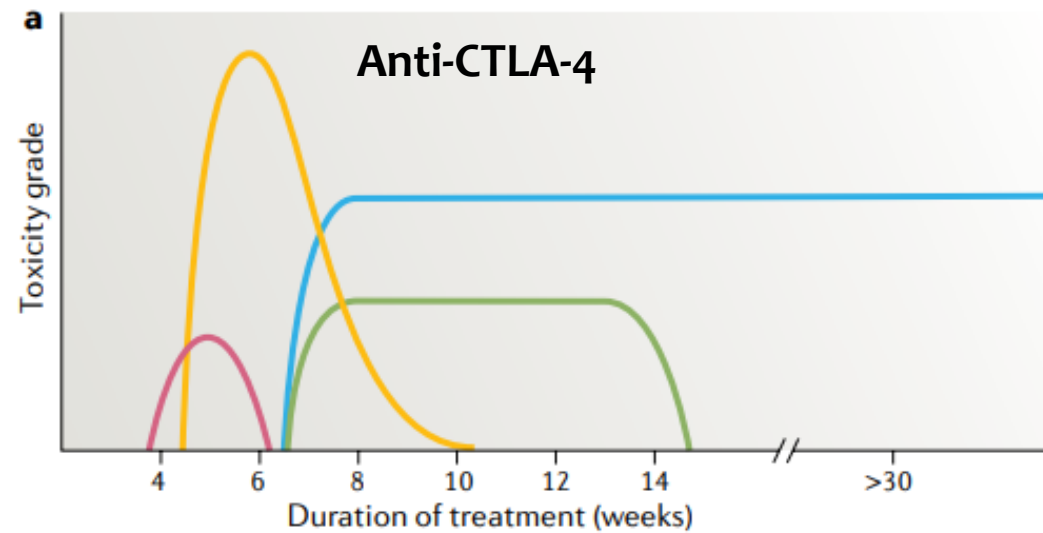
Inflammatory cytokines



Increased preexisting AutoAb

Enhanced complement-mediated inflammation in CTLA-4 expressing tissue

Kinetics of common irAEs



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 (%)	$\geq G3$ (%)	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)

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

C Cases and fatality rates

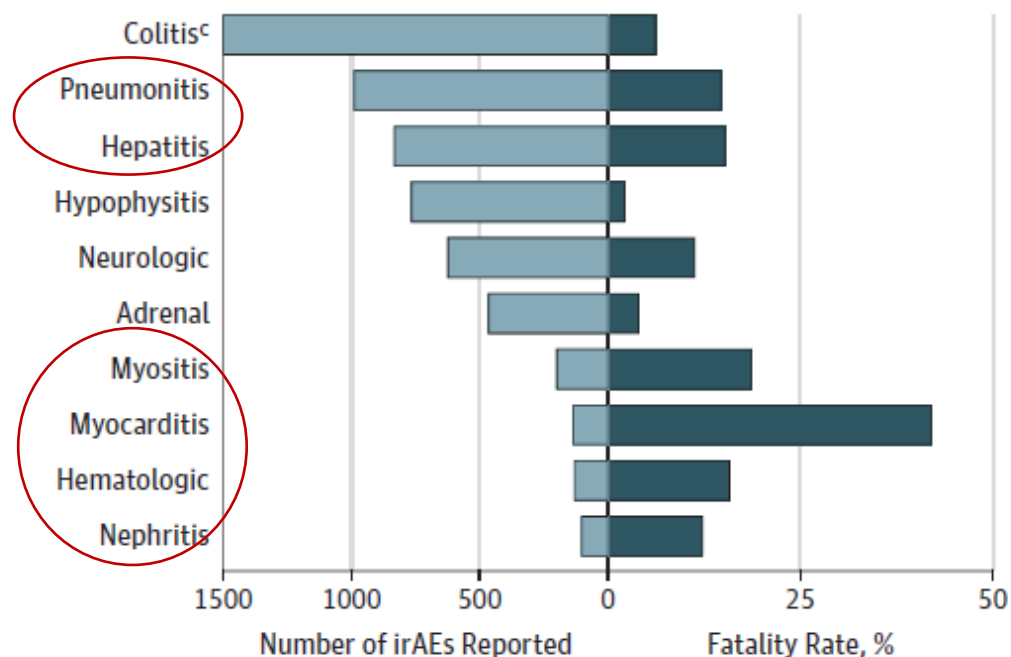
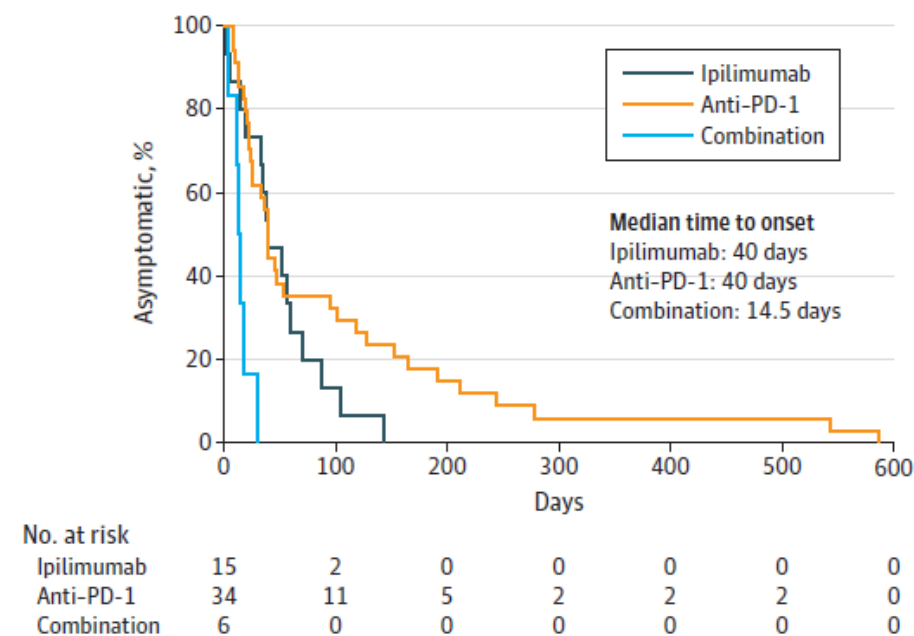


Figure 2. Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen



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)

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

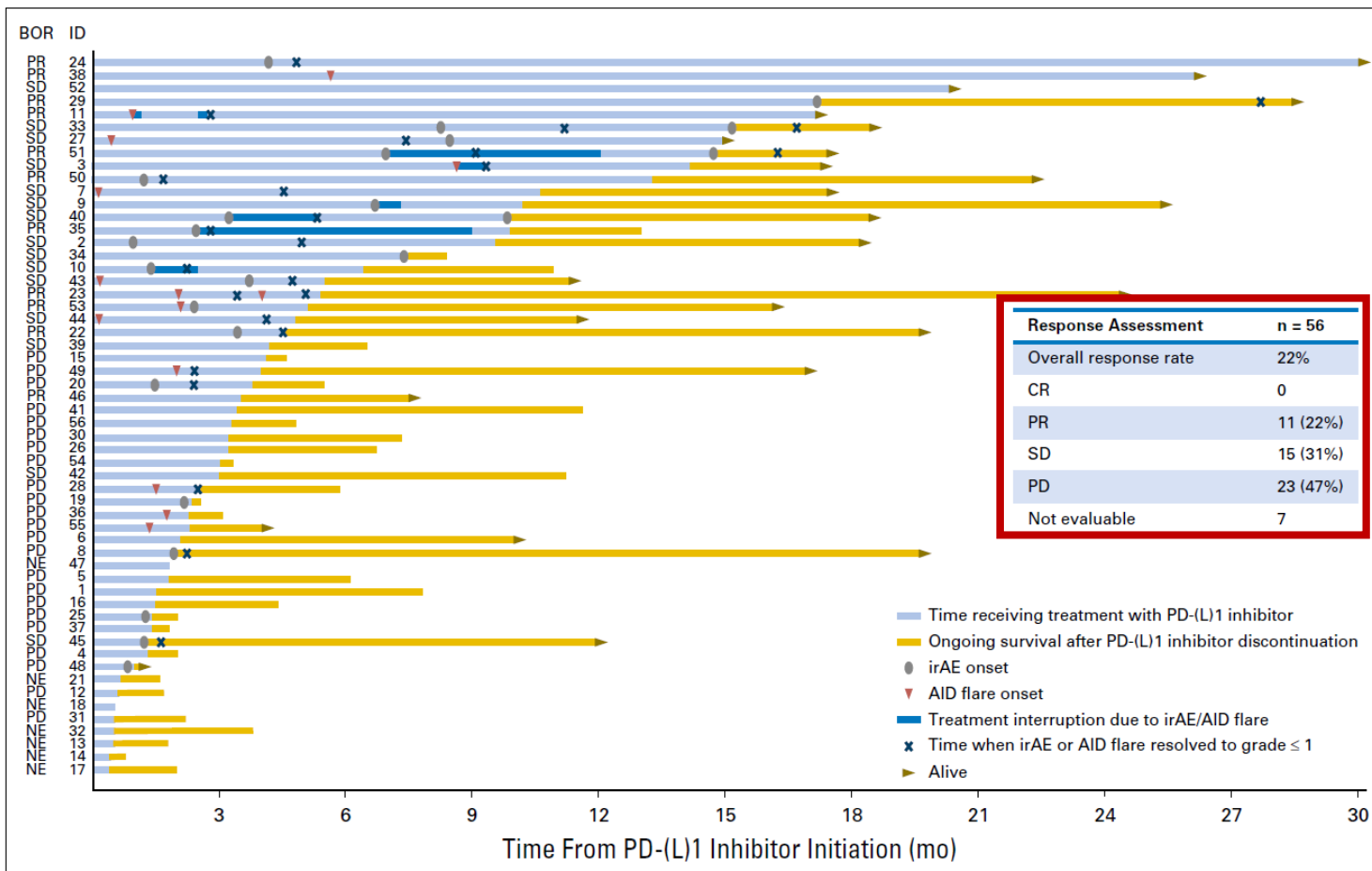


Table 3. Exacerbation of AID in Patients Treated With PD-(L)1 Inhibitors

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

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

Kimberly Tang¹, BA, Bruce C. Tiu^{1,2}, BS, Guihong Wan^{1,3}, PhD, Shijia Zhang^{1,3}, BA, Nga Nguyen¹, BA, Bonnie Leung¹, BSc, Alexander Gusev⁴, PhD, Kerry L. Reynolds⁵, 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)

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%)

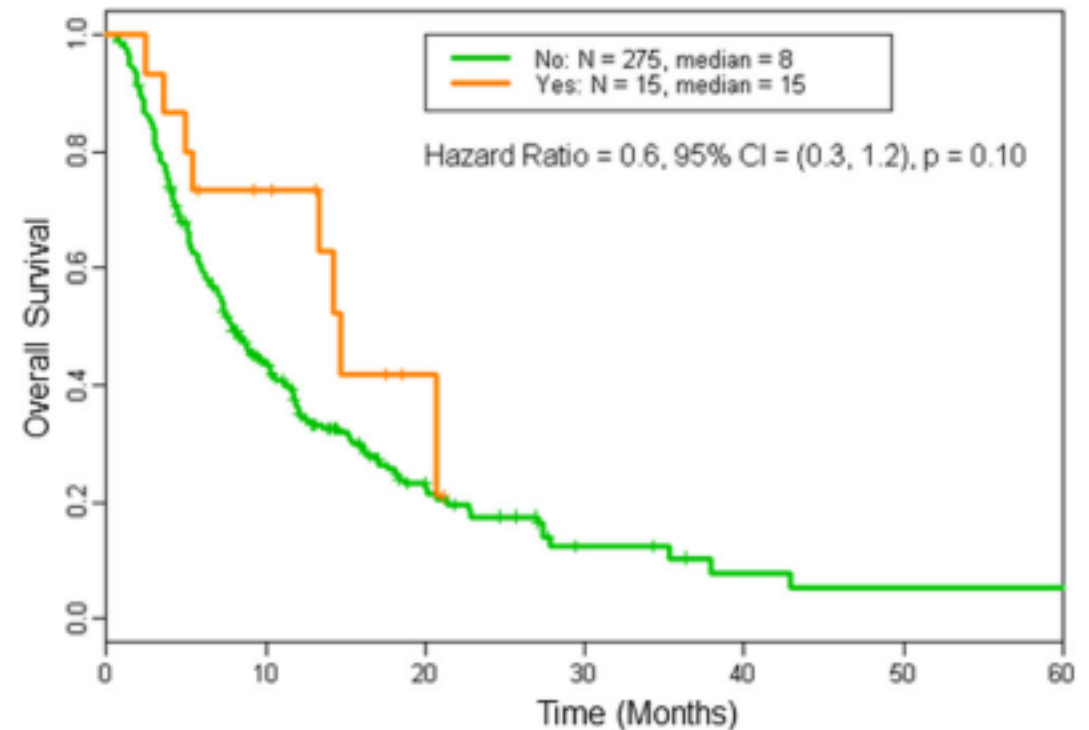
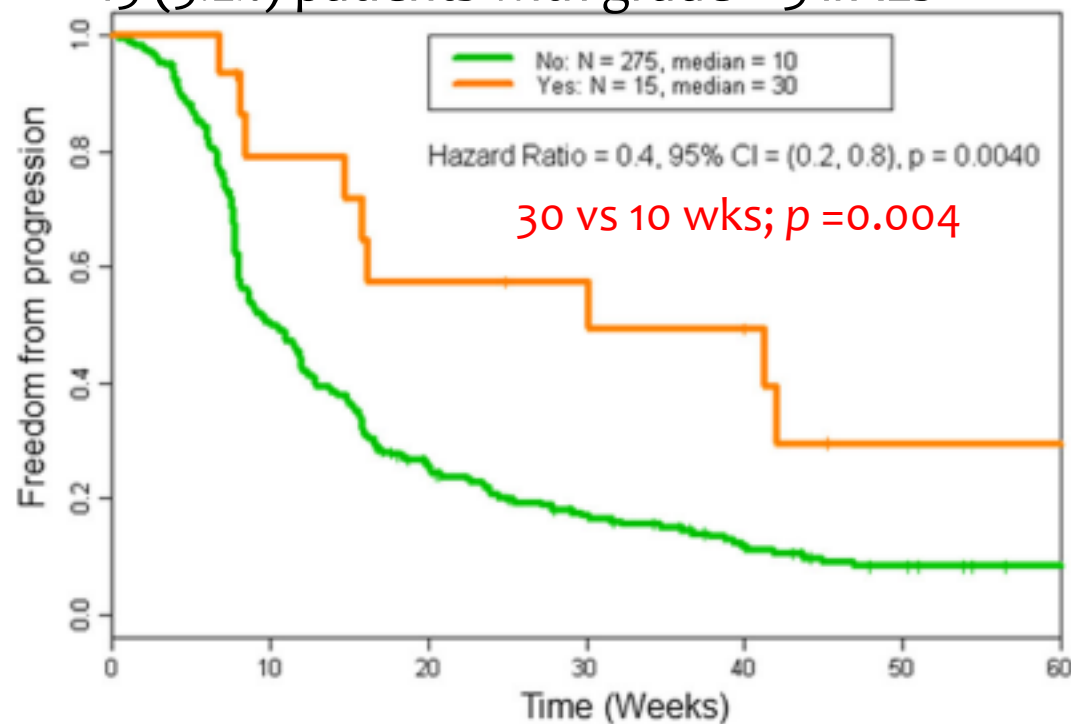
Table 2: Association between baseline autoimmunity and survival among patients treated with anti-PD-1 or anti-PD-L1 therapy

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

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

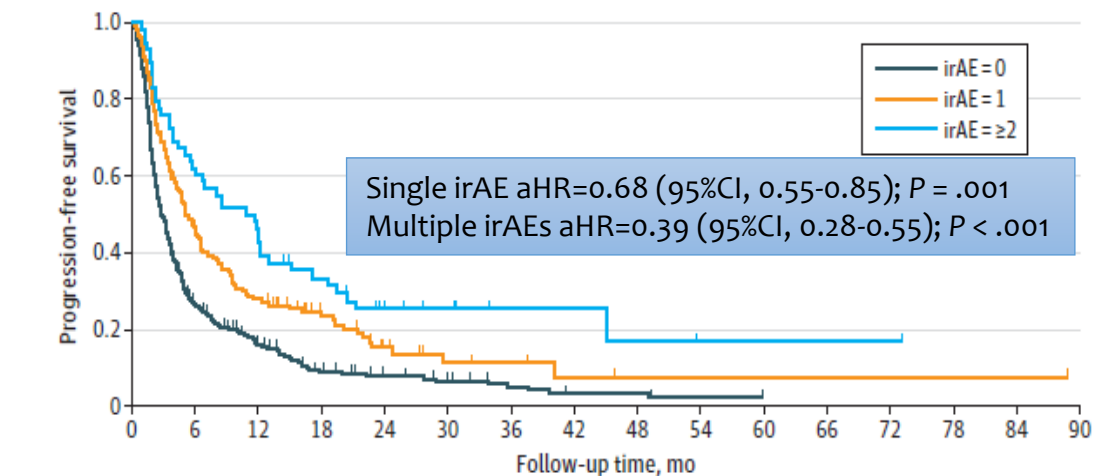


Multisystem Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors for Treatment of Non-Small Cell Lung Cancer

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; Yukihiko Toi, MD; Paul Walker, MD; Gregory A. Otterson, MD; Sandip H. Patel, MBBS; Shunichi Sugawara, MD; Jarushka Naidoo, MBBCh, MHS

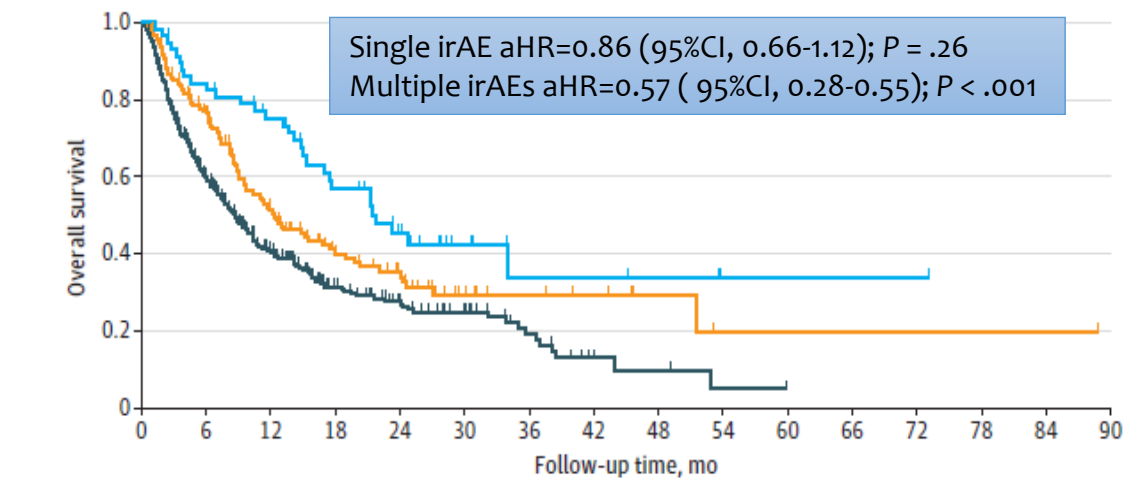
- 5 centers including Johns Hopkins, 623 patients treated with anti-PD-(L)1 (mono in 95%)
- 148 (24%): single irAE, **58 (9.3%): multisystem irAEs**
- m/c: pneumonitis (n=64, 12%), thyroiditis (n=53, 10%)
- Pneumonitis+thyroiditis (n=7, 14%), hepatitis + thyroiditis (n=5, 10%), dermatitis + pneumonitis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

A Progression-free survival



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
irAE=0	417	97	52	24	17	11	6	3	3	1	0	0	0	0	0	0
irAE=1	148	66	39	21	10	5	4	2	1	1	1	1	1	1	1	0
irAE≥2	58	36	25	17	8	6	3	3	2	1	1	1	1	0	0	0

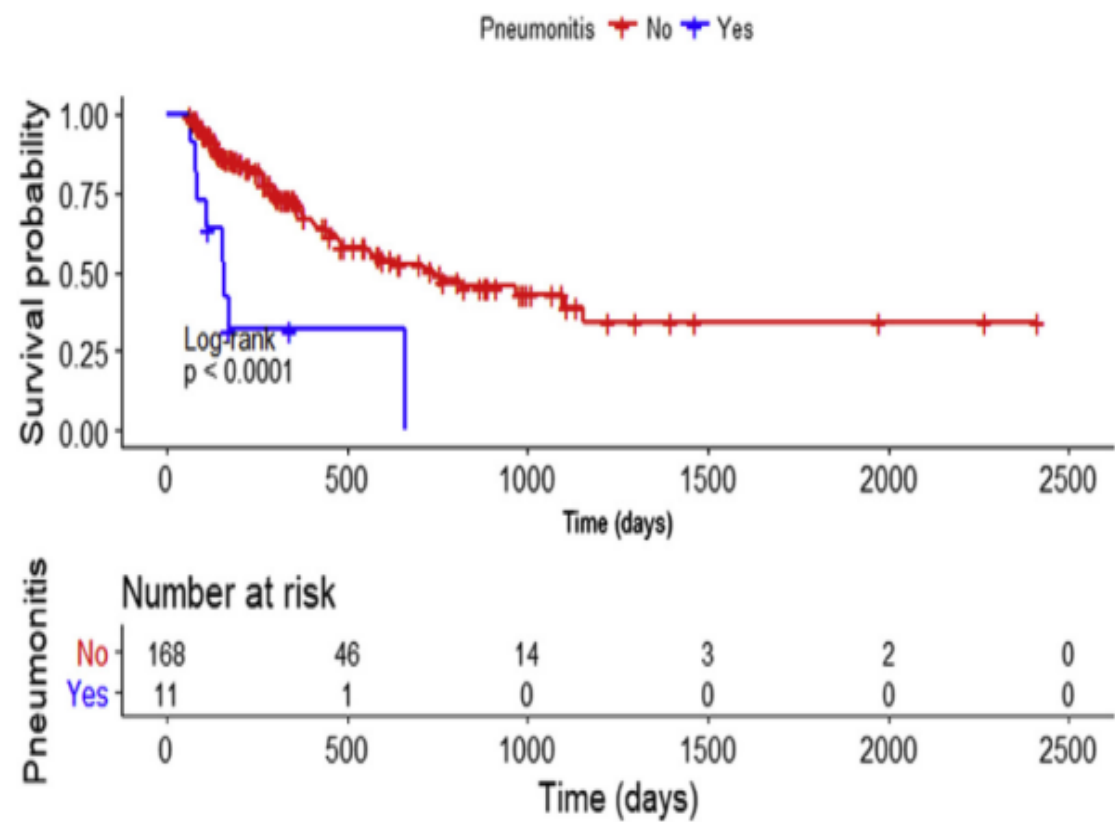
B Overall survival



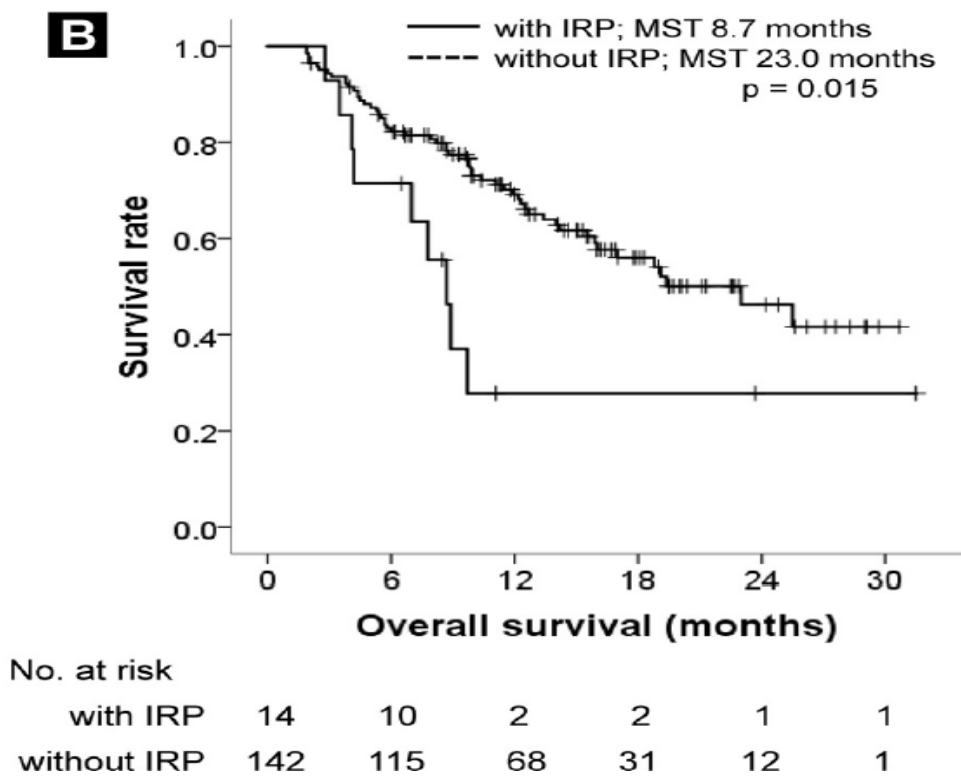
No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
irAE=0	417	204	111	55	36	24	13	4	3	1	0	0	0	0	0	0
irAE=1	148	102	61	35	26	12	8	6	3	1	1	1	1	1	1	0
irAE≥2	58	48	40	27	15	8	4	4	3	1	1	1	1	0	0	0

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**)



Severe irAEs in IO followed by TKIs

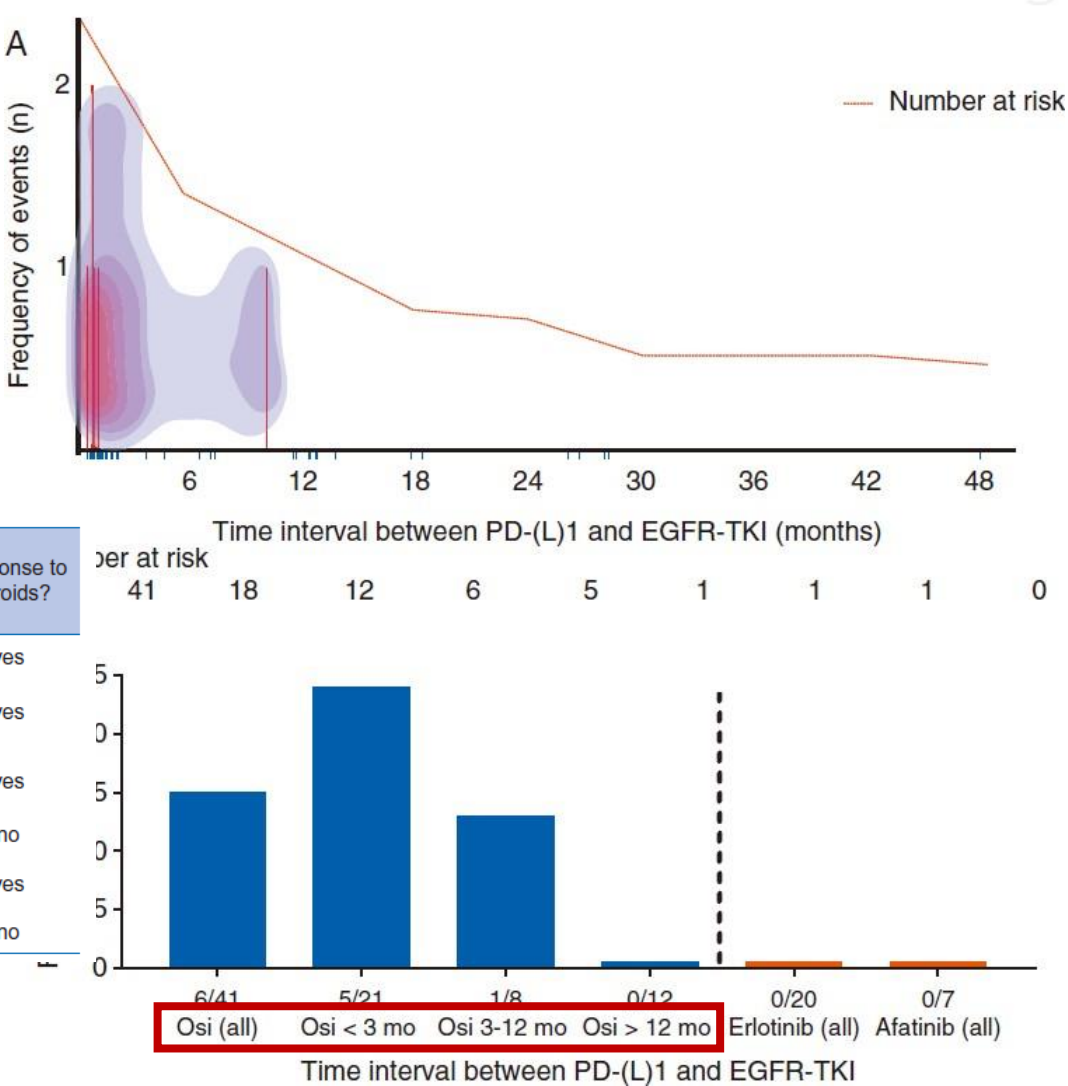
Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

A. J. Schoenfeld¹, K. C. Arbour¹, H. Rizvi¹, A. N. Iqbal¹, S. M. Gadgeel², J. Girshman³, M. G. Kris¹, G. J. Riely¹, H. A. Yu^{1*†} & M. D. Hellmann^{1*†}

- N=70, retrospective, 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 osimertinib			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 (12–144)			5 (1–25)			
Time on osimertinib, days		167 (15–927)			119 (30–707)			
Severe immune-related adverse event		6 (15)			0 (0)			



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 Jung¹, Hyae Young Kim², Dong-Gil Kim¹, Seog Yun Park³, A Ra Ko¹, Ji-Youn Han¹, Heung Tae Kim¹, Jin Soo Lee¹, Youngjoo Lee¹

Departments of ¹Internal Medicine, ²Radiology, and ³Pathology, 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

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)
- $\geq$ G3: systemic steroid, consult to DM



Vitiligo



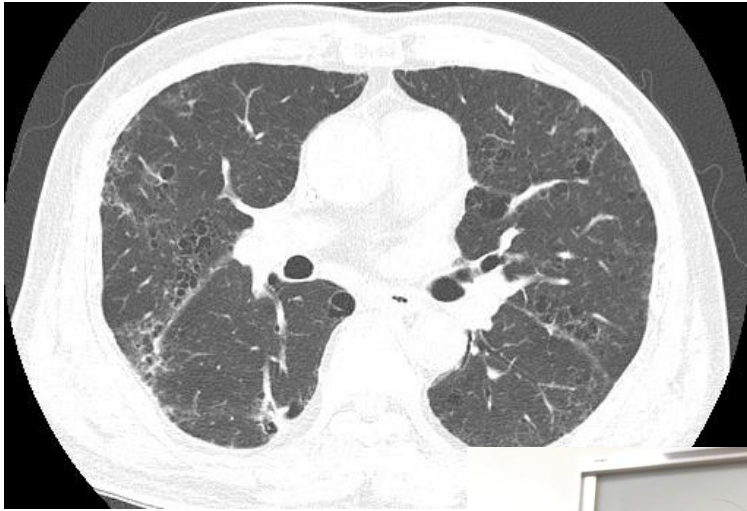
Maculopapular rash



psoriasiform dermatitis

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

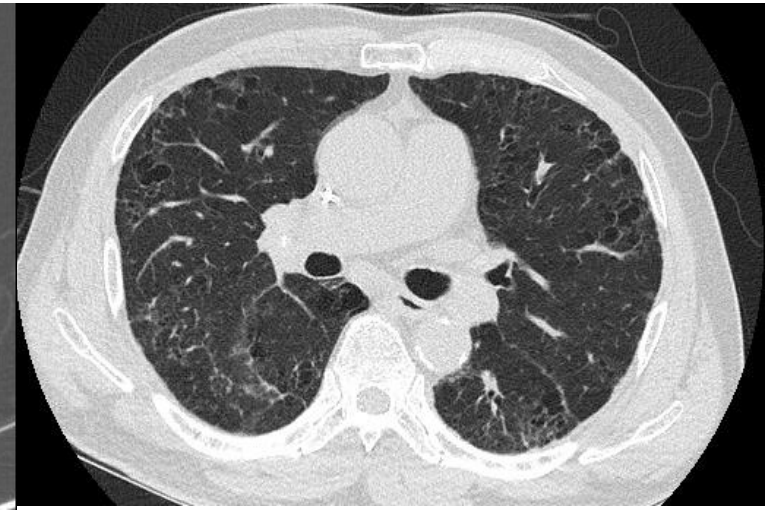
NSCLC(ADC, LLL, PD-L1 50%, pT4NoM1a, stageIVA) c lung to lung meta
s/p 1L 4C CTx(pemetrexed, cisplatin) with pemetrexed maintenance: 2019.6~ 2019.12.10
s/p 2L 1C ITx(pembro mono): 2019.12.31~



Aug-2019



Dec-2019



Aug-2021



2L Pembrolizumab

- 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!

Endocrinopathy (2): thyroid dysfunction

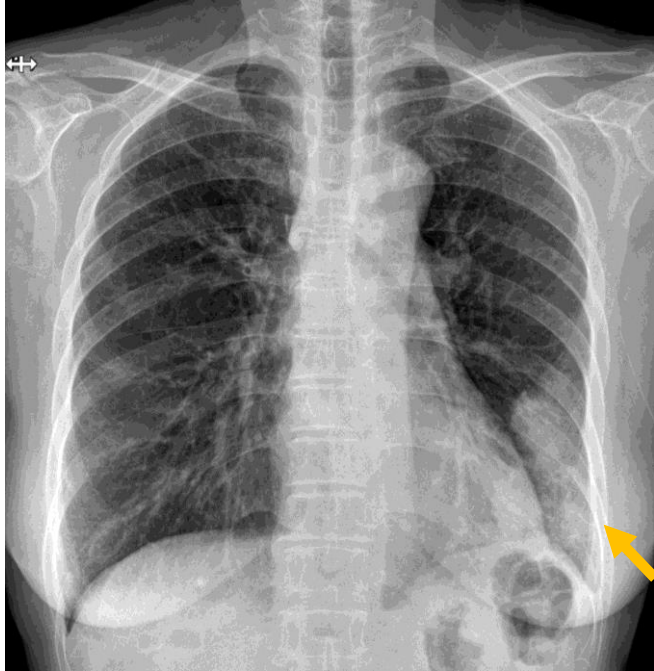
- Most common, often found incidentally on routine lab
- Anti-PD-1 (5-10%), anti-CTLA-4 (1-5%), combo (~20%)
- Median time of onset: 3 months
- Some cases presenting years after discontinuation

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

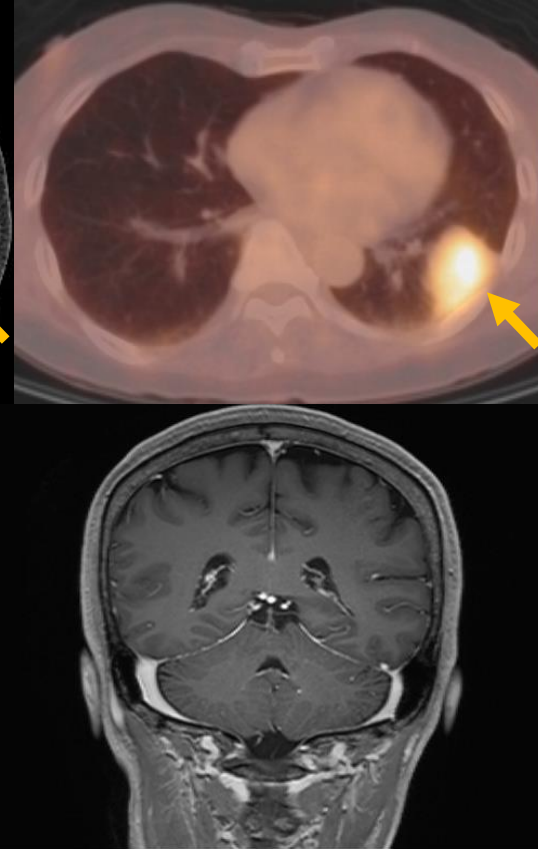
Endocrinopathy (3): diabetes

- 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)

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



Nov-2021

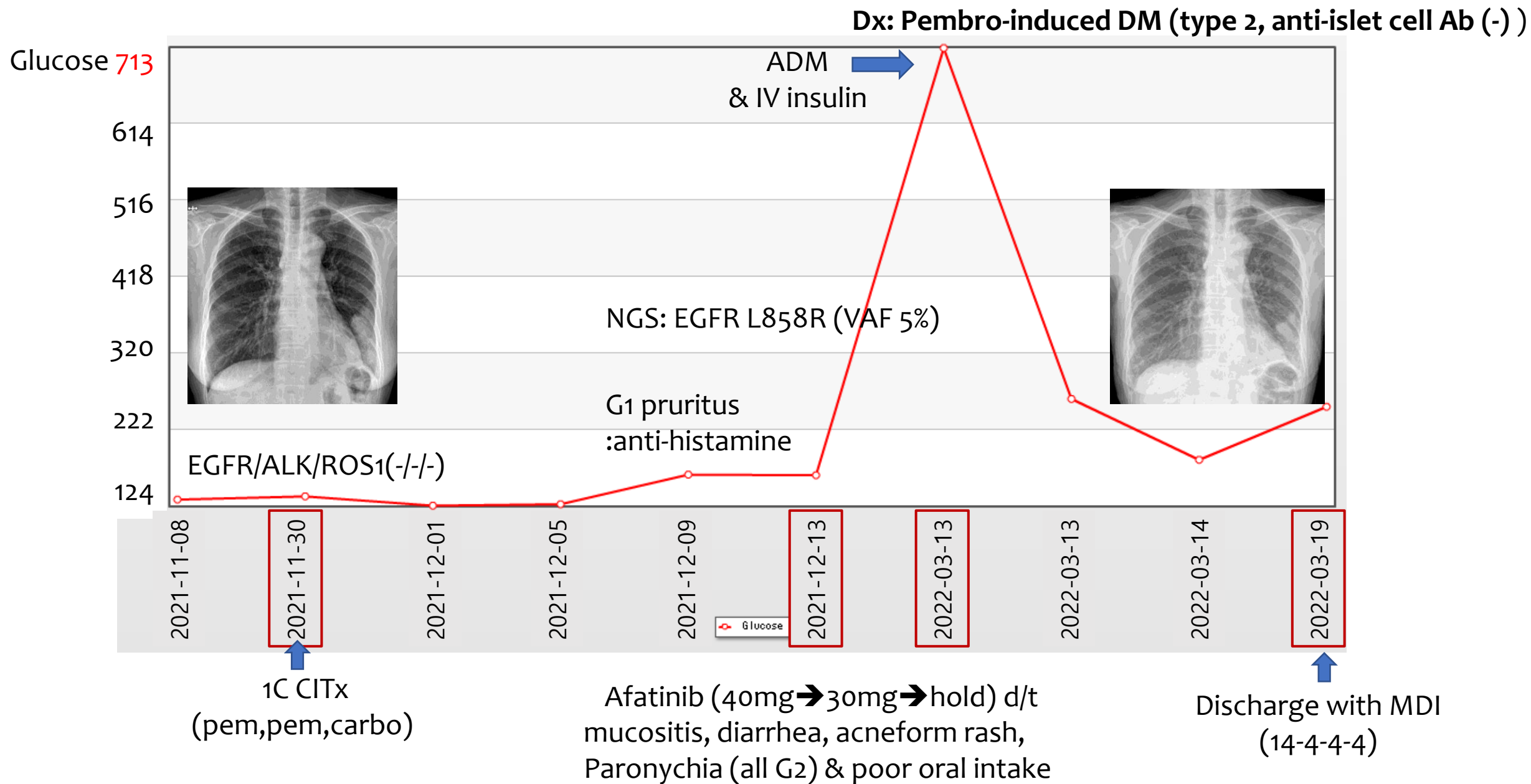


- NSCLC(ADC,LLL, cT4N2M1a, stage IVA, PD-L1 1%) with lung to lung meta
- Hypertrophic pulmonary osteoarthropathy
- EGFR (-), ALK (-), ROS1 (-)
- NSAIDs
- Started 1L 1C CITx(pemetrexed,pembro,carbo) at 2021.11 awaiting NGS result

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
HbA1c 5.9% → 10.0%
c/w DKA

Clinical course (2)



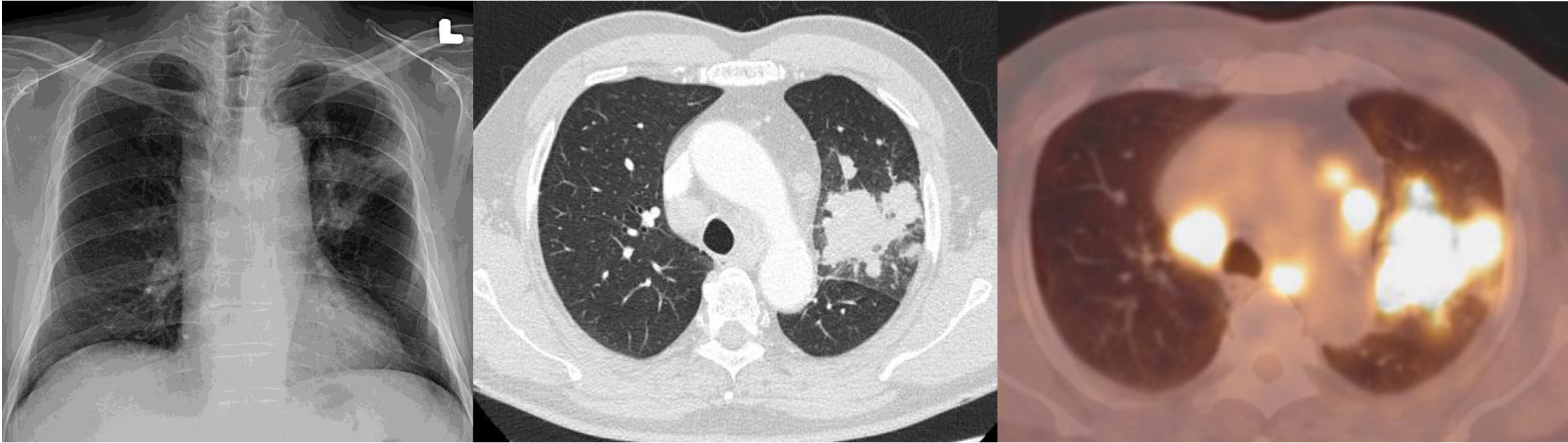
Pulmonary toxicities (1)

- 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% ($\geq$ 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)

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.

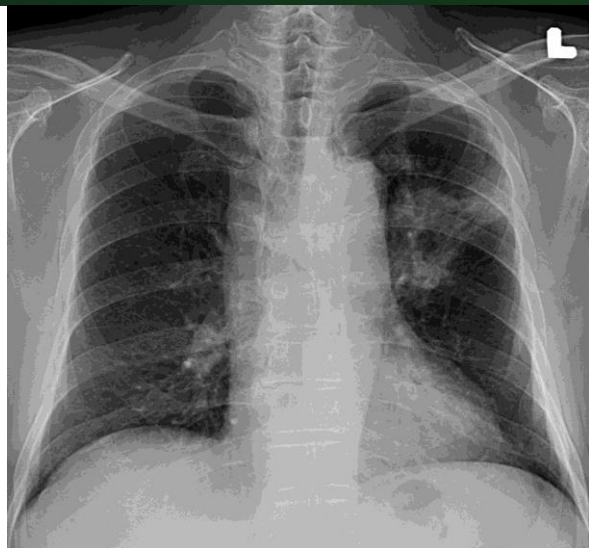
M/72, abnormal CXR, ex-smoker(30PY)



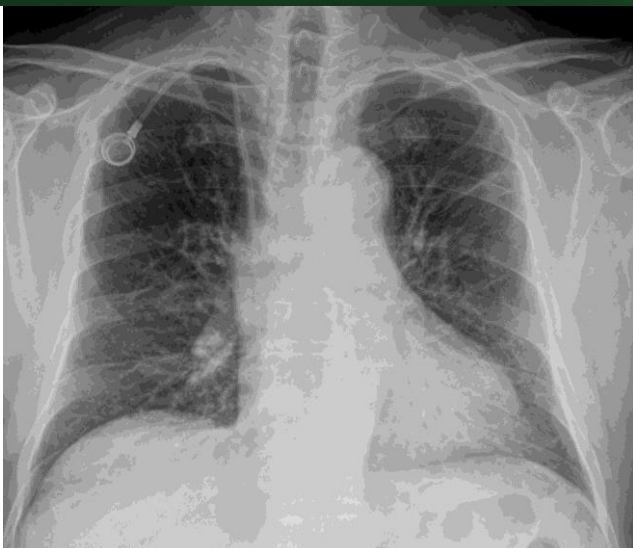
June-2020

- 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.~

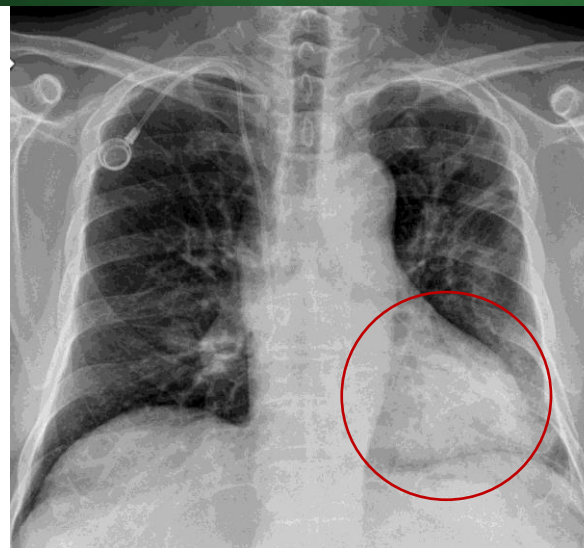
Clinical course



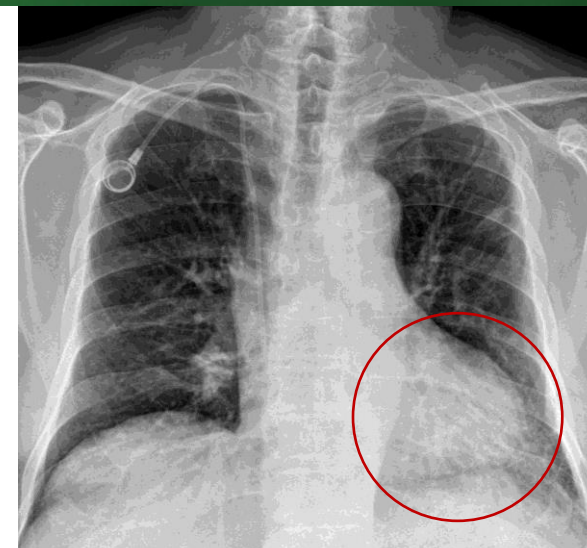
June-2020



May-2021



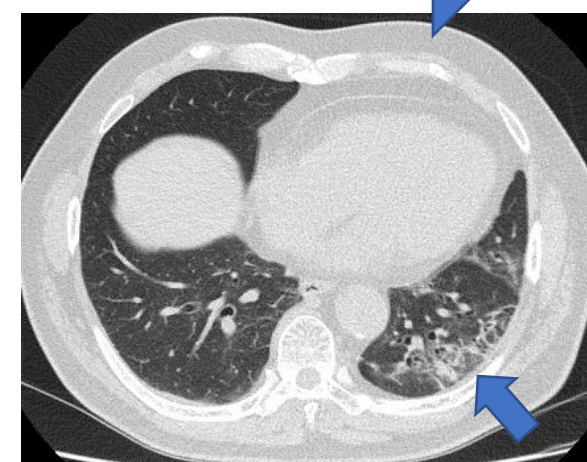
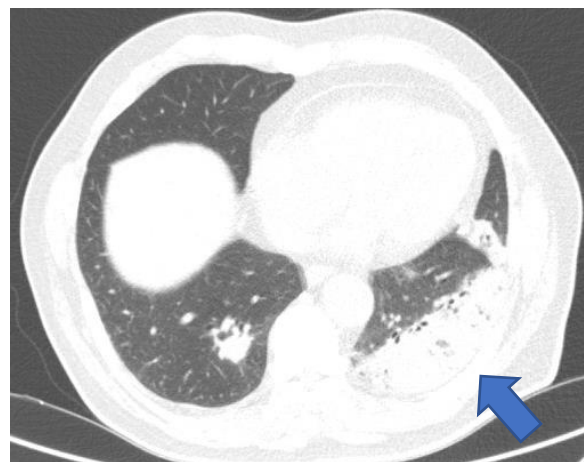
Sept-2021



Nov-2021

- After 15 months (19C, Sept 2021): dyspnea (+)
- CRP 4.0
- Rechallenge (2021-11-23), no recurrence by Mar 2022 (24C)

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

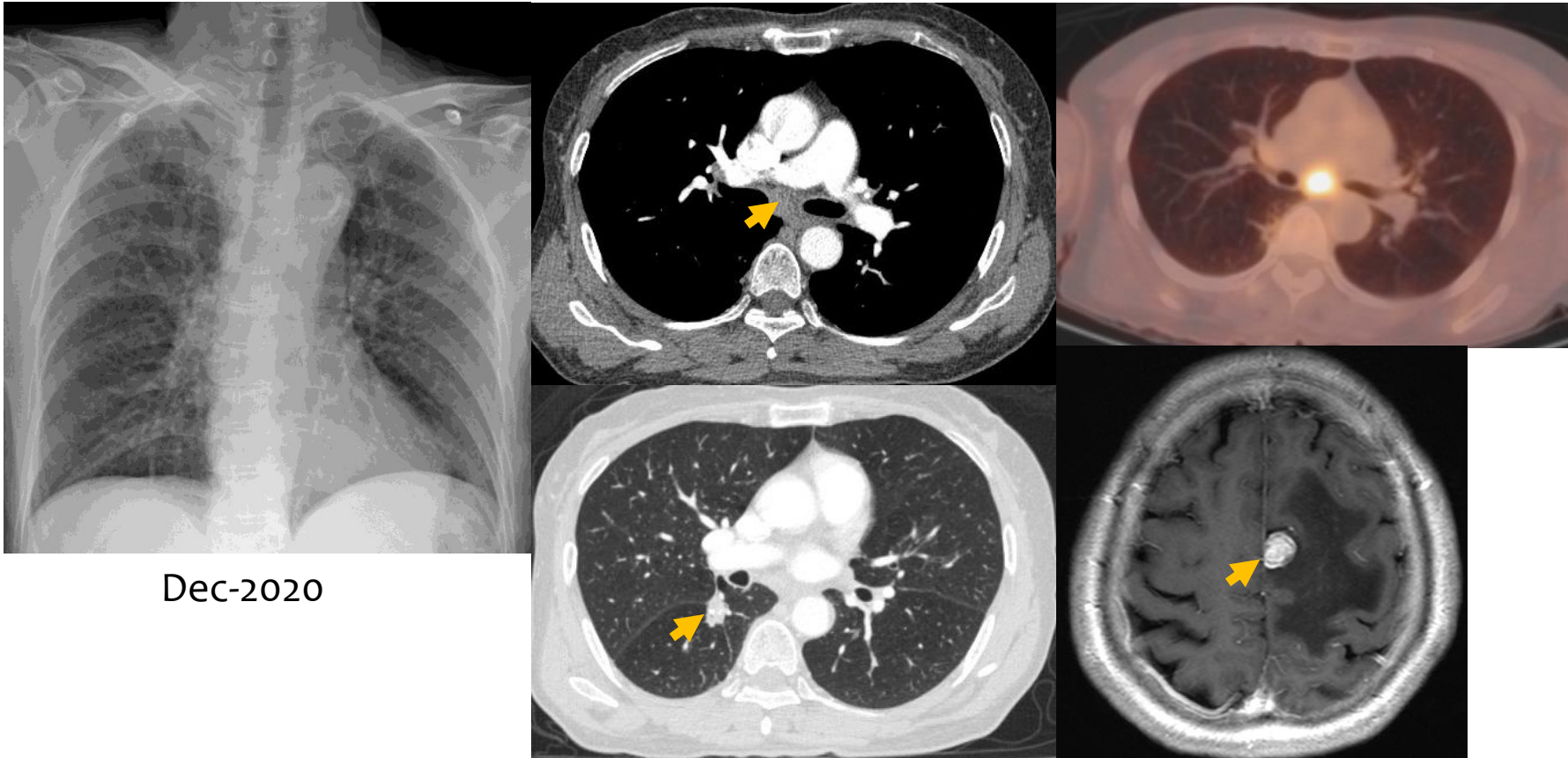


Feb-2022

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

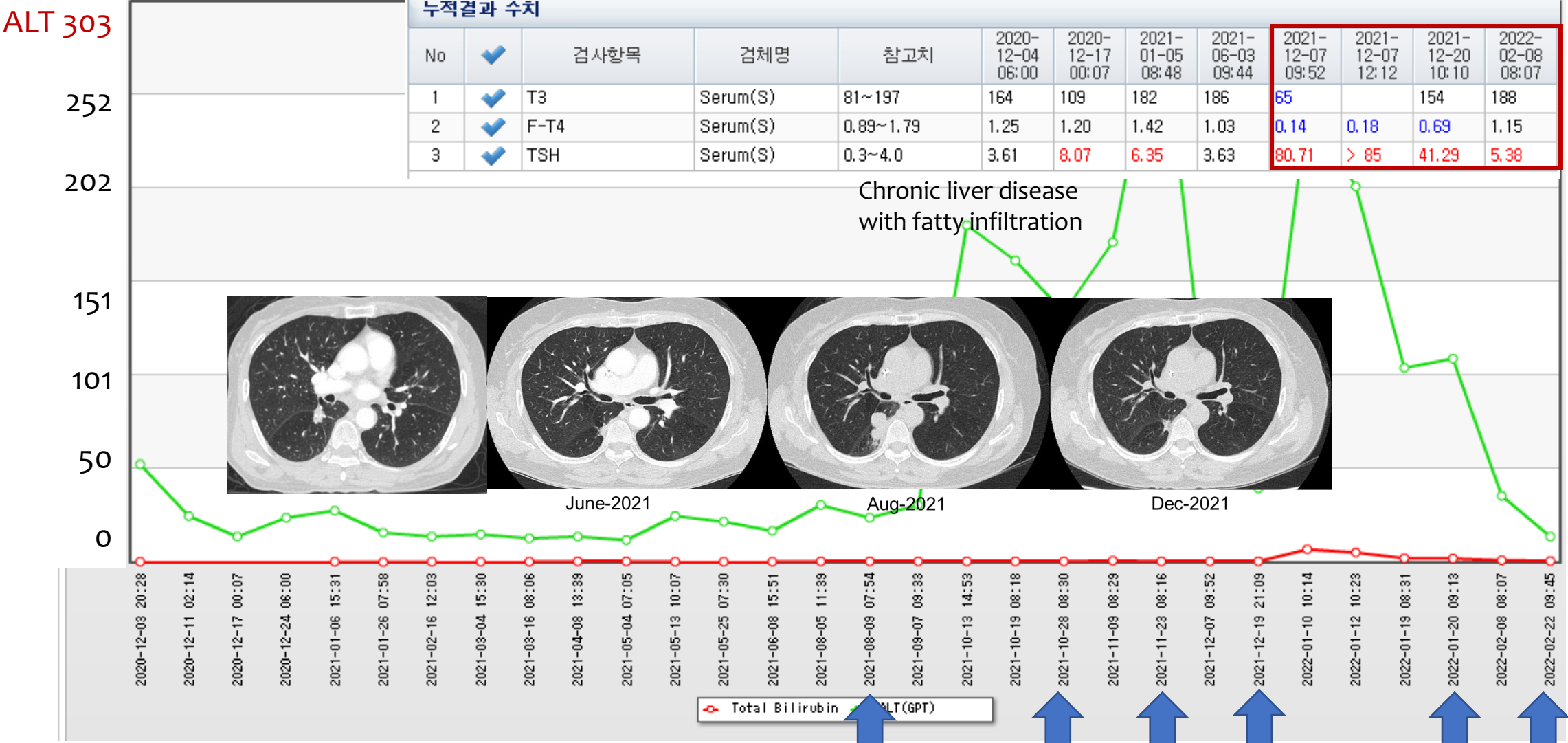
Case, F/64, Rt side weakness, current smoker: 30PY



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)



Final Dx: Pembro-induced hepatitis and hypothyroidism

- 2L 1C Pembro mono
- 5C Pembro mono
- Hold & hepatotonics (6C pembro) & levothyroxine
- 7C Pembro
- 8C Pembro

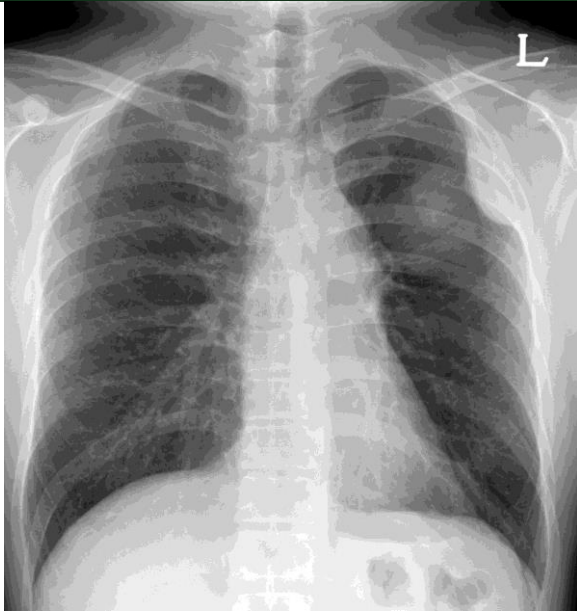
Neuro-muscular toxicities

- Relatively infrequent (~ 1%)
- Myalgia/**myositis**
- Peripheral neuropathy
- **Myasthenia Gravis**
- Guillain-Barre syndrome
- Transverse Myelitis
- Numbness, tingling, foot drop, and localized muscle weakness

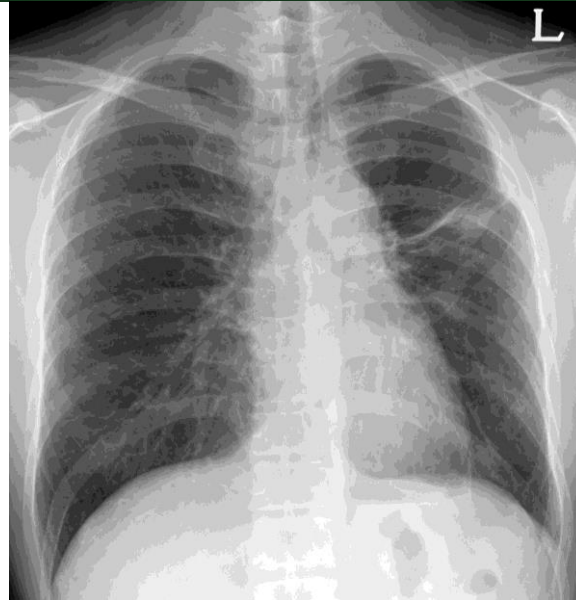
Management

- Get a neurologic consult!
- $\geq 2G$: 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

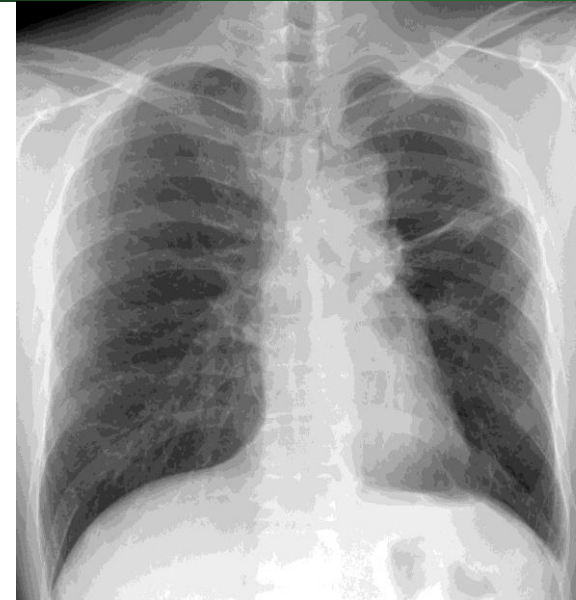
M/44, abnormal CXR



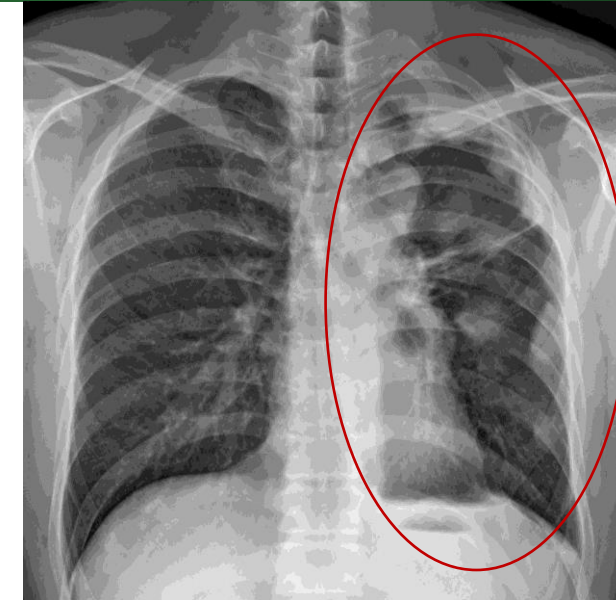
Oct-2020
(pre-2nd RTx)



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)

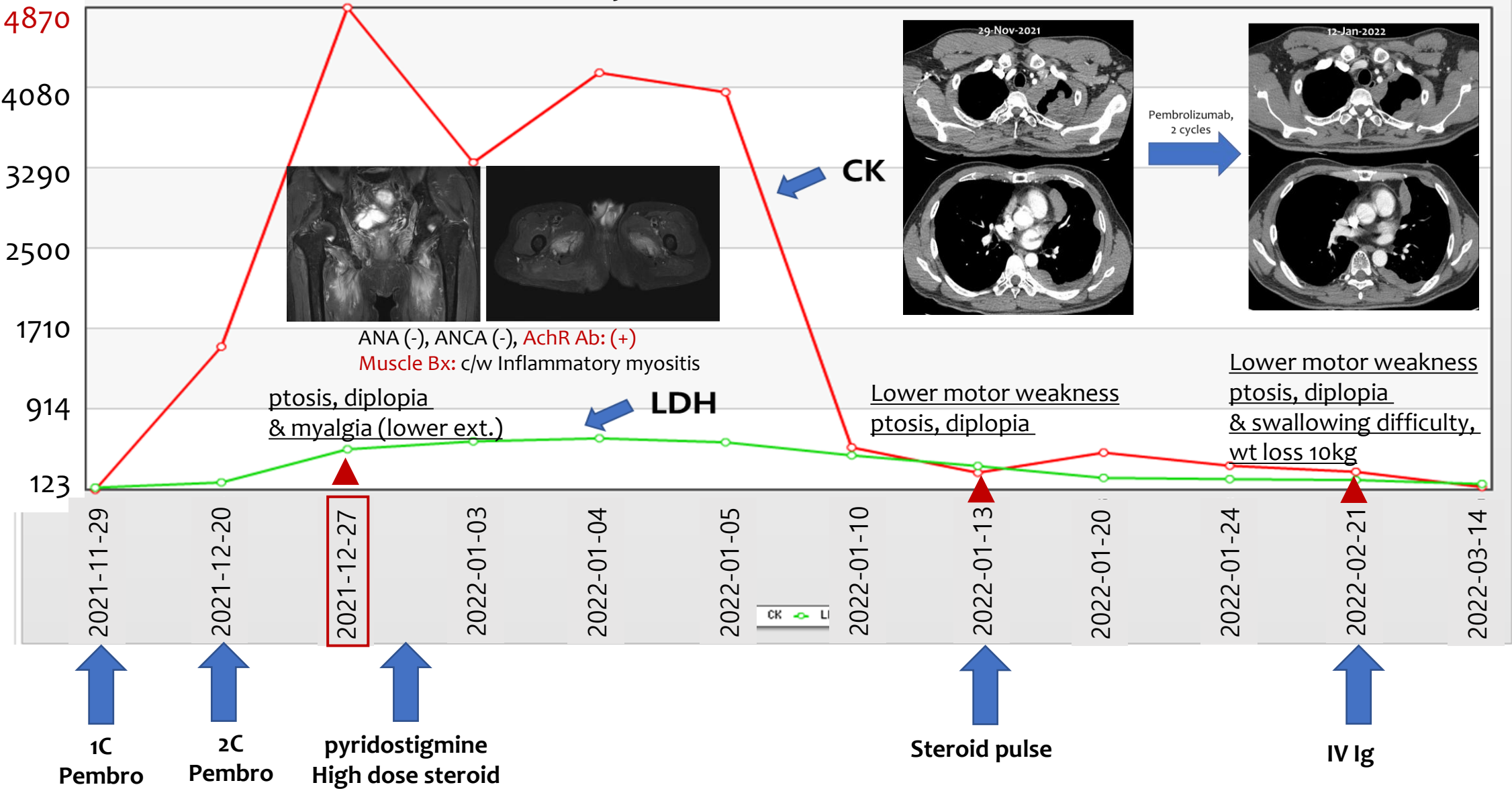
- 2L 1C ITx(pembrolizumab): 2021.11.30~, tolerable
- 2C 2C ITx: 2022.12.21
- 2022.12.27: ptosis, diplopia & myalgia (lower ext.)
- Myoglobin 1,750 U/L

● [진검] 일반화학[Serum] [채취일시:2021-12-27 08:39] [접수일시:2021-12-27 08:39]				
✓	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)

Dx: Pembro-induced MG and myositis

(U/L) 4870



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.

