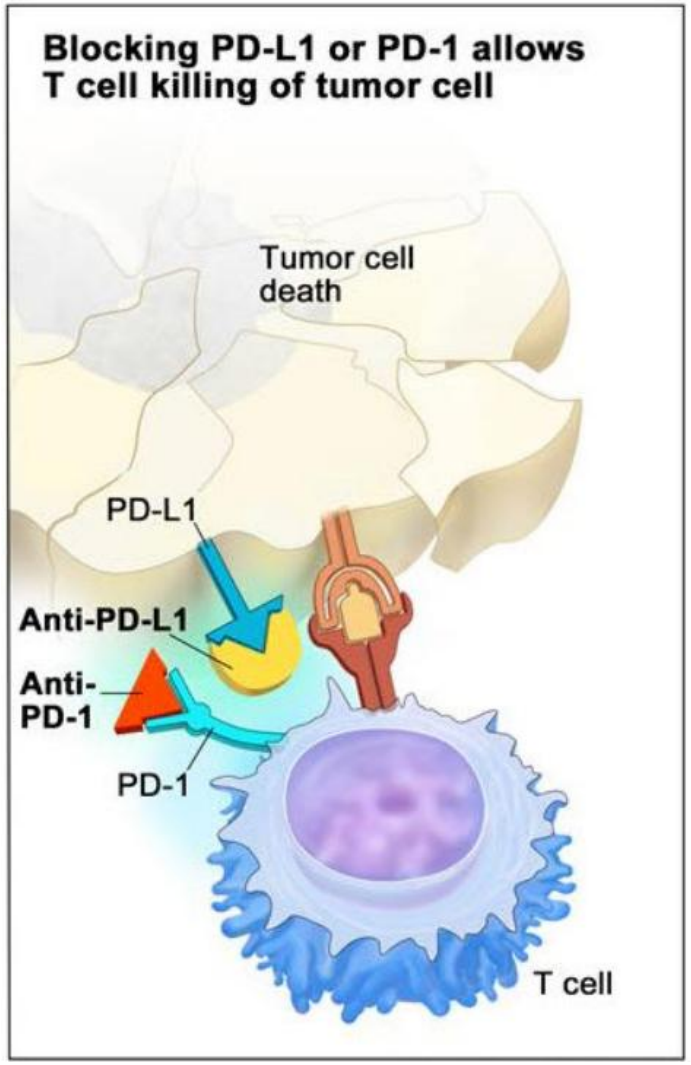
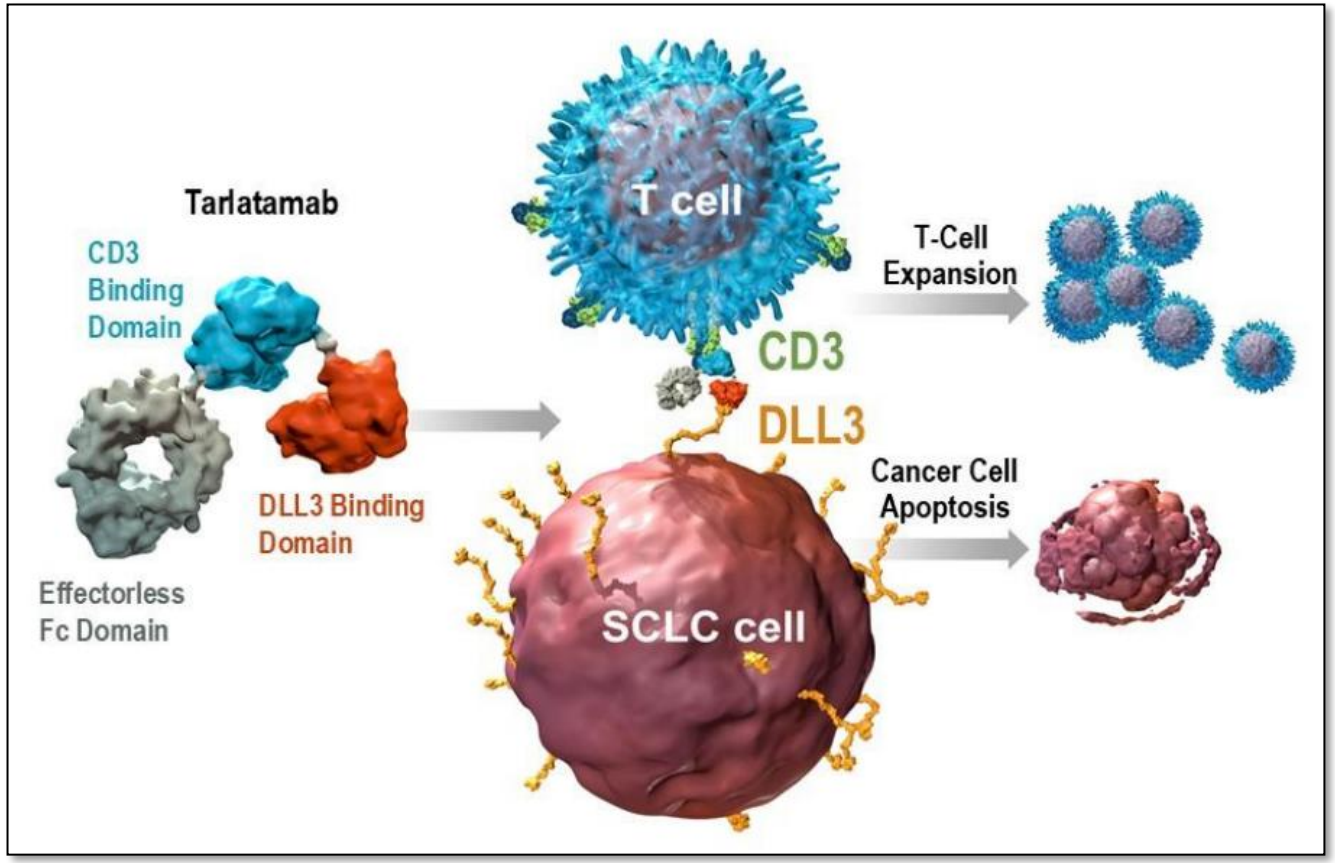
Management of Adverse Events Following Medical Treatment

고려대학교 구로병원 호흡기내과 최주환

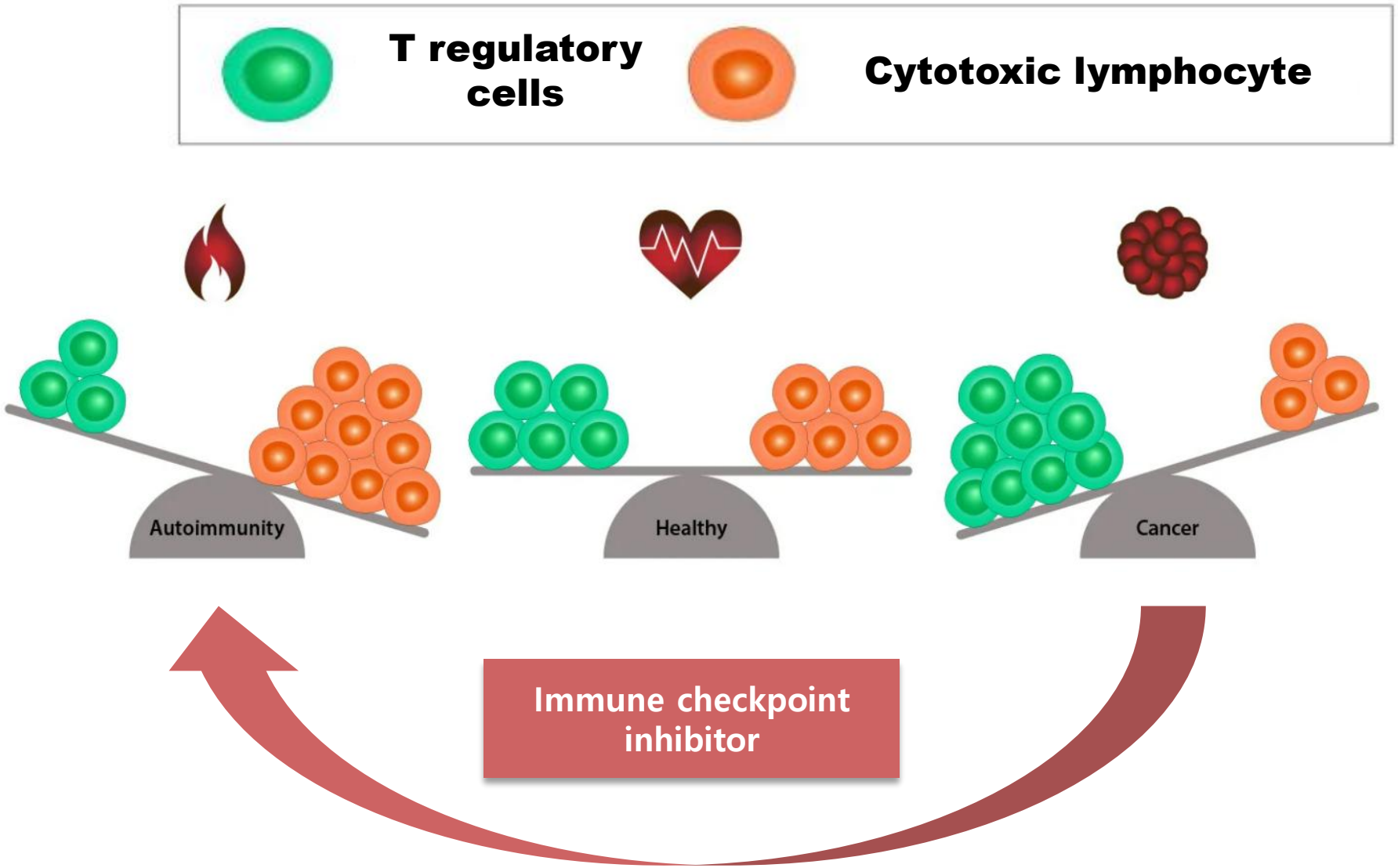
KU MC KOREA UNIVERSITY MEDICAL CENTER

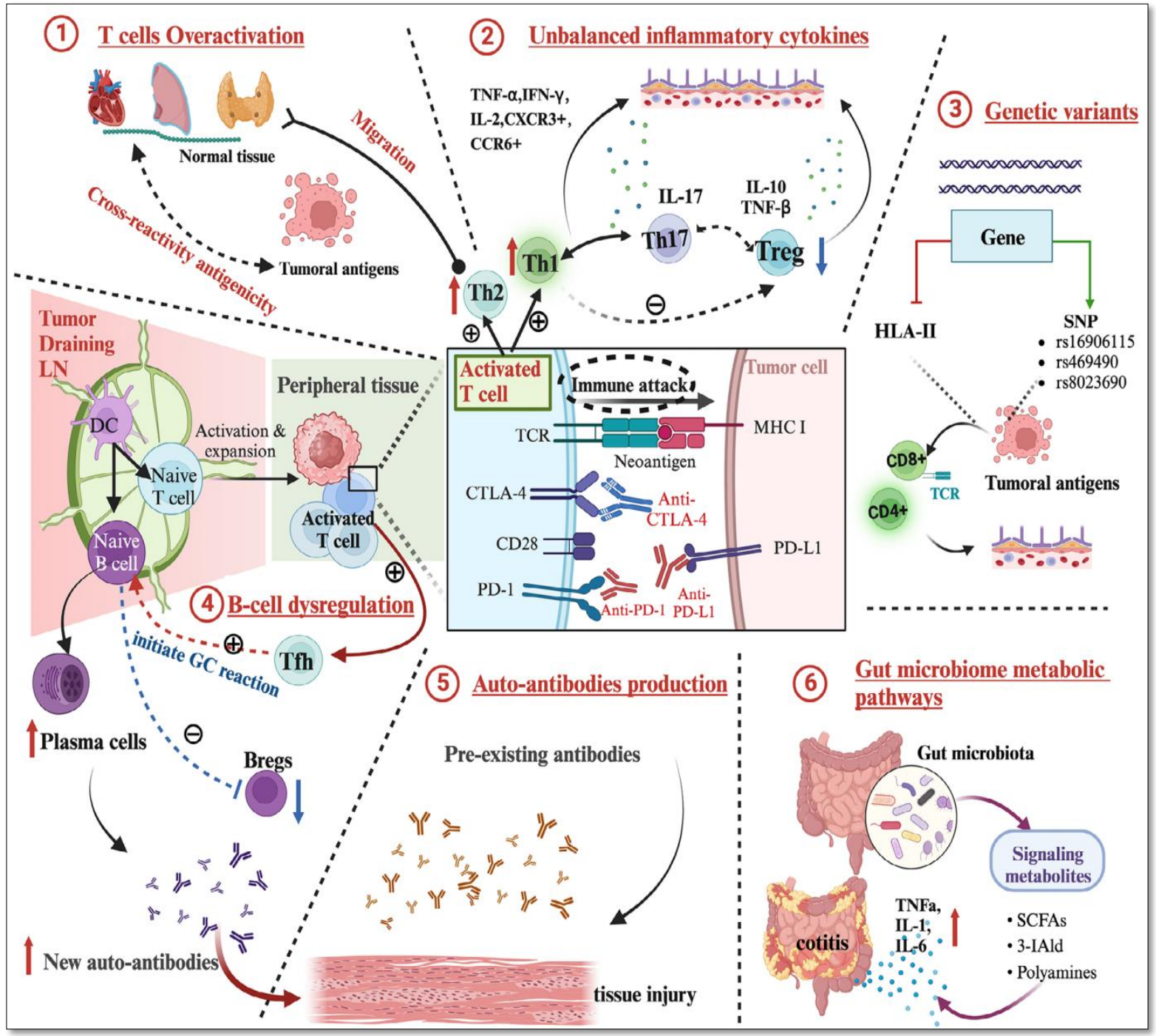


Immune checkpoint inhibitor



Tarlatamab

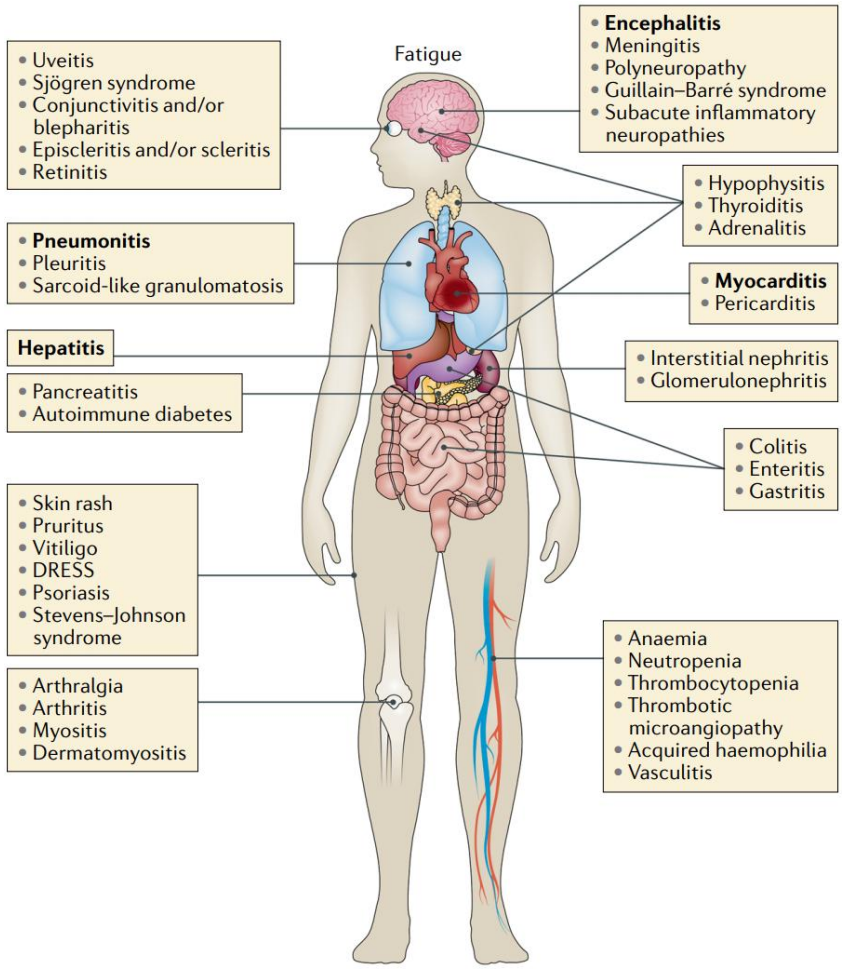

T regulatory cells
Cytotoxic lymphocyte
Autoimmunity
Healthy
Cancer
Immune checkpoint inhibitor


1 T cells Overactivation
Normal tissue
Migration
Cross-reactivity antigenicity
Tumoral antigens
2 Unbalanced inflammatory cytokines
TNF-α,IFN-γ,
IL-2,CXCR3+,
CCR6+
IL-17
IL-10
TNF-β
Th1
Th17
Treg
Th2
3 Genetic variants
Gene
HLA-II
SNP
rs16906115
rs469490
rs8023690
CD8+
CD4+
TCR
Tumoral antigens
Tumor Draining LN
DC
Naive T cell
Naive B cell
Activation & expansion
Peripheral tissue
Activated T cell
Activated T cell
Immune attack
Tumor cell
TCR
MHC I
Neoantigen
CTLA-4
Anti-CTLA-4
CD28
PD-L1
PD-1
Anti-PD-1
Anti-PD-L1
4 B-cell dysregulation
initiate GC reaction
Tfh
Plasma cells
Bregs
New auto-antibodies
5 Auto-antibodies production
Pre-existing antibodies
tissue injury
6 Gut microbiome metabolic pathways
Gut microbiota
Signaling metabolites
• SCFAs
• 3-IAld
• Polyamines
TNFa,
IL-1,
IL-6
cotitis

The spectrum of immune related adverse events

Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance

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

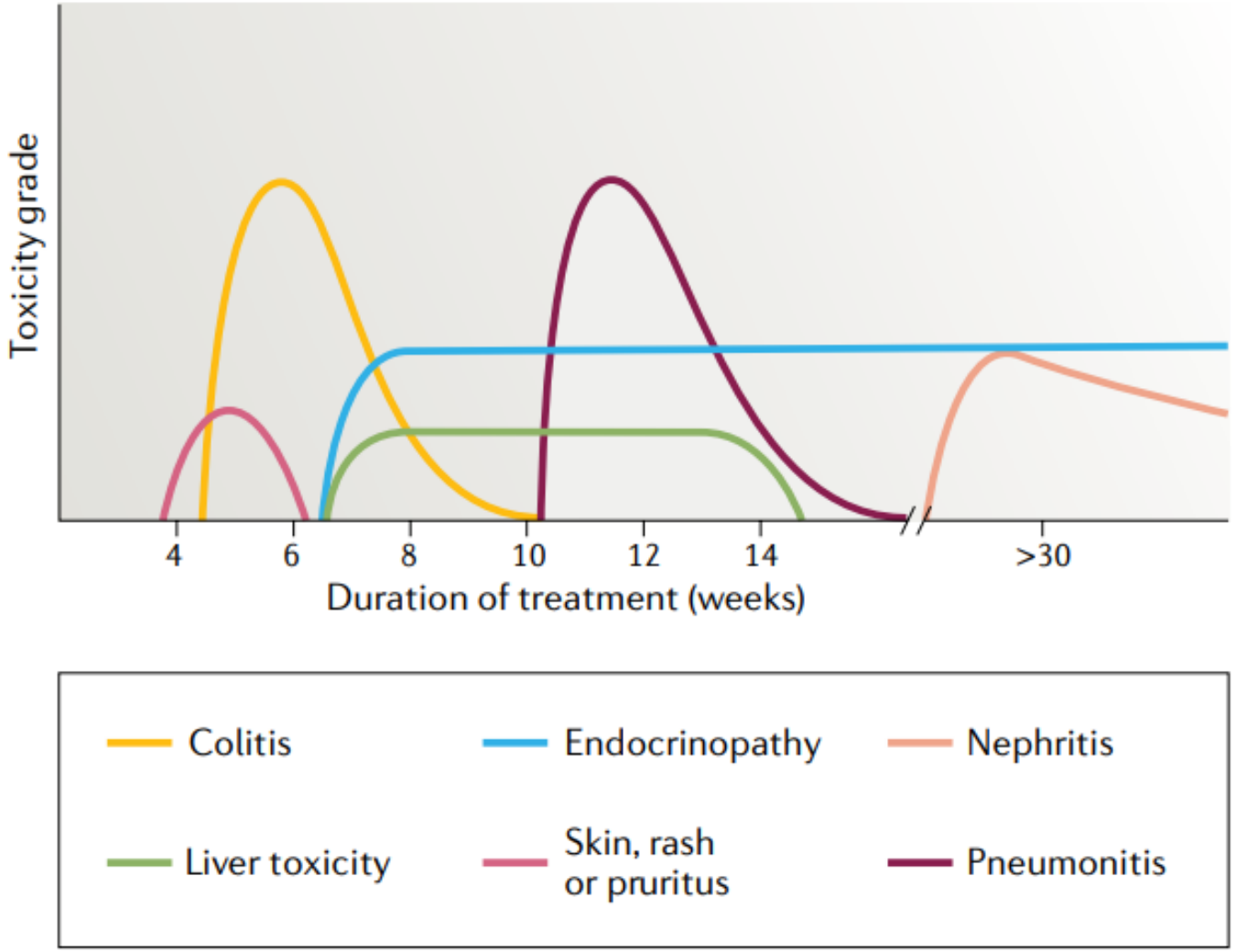


ASCO : There should always be a high level of suspicion.

Time of onset

Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance

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



Time of onset

Late-Onset Immune-Related Adverse Events After Immune Checkpoint Inhibitor Therapy

JAMA Network Open. 2025;8(3):e252668.

- **Retrospective observational cohort study : 2021~2025, 795 patients (Lung cancer 21.0%)**

Table 2. Immune-Related Adverse Event Diagnoses by Time of Admission

	Events, No. (%)			
Organ system	All	Early (0-6 mo)	Intermediate (>6-12 mo)	Late (>12 mo)
No.	898	679	128	91
Gastrointestinal	233 (25.9)	183 (78.5)	29 (12.4)	21 (9.0)
Pulmonary	128 (14.3)	91 (71.1)	21 (16.4)	16 (12.5)
Hepatic	120 (13.4)	96 (80.0)	14 (11.7)	10 (8.3)
Endocrine	115 (12.8)	91 (79.1)	17 (14.8)	7 (6.1)
Neurologic	86 (9.6)	70 (81.4)	12 (13.9)	4 (4.7)
Cardiac	64 (7.1)	53 (82.8)	7 (10.9)	4 (6.3)
Dermatologic	53 (5.9)	36 (67.9)	10 (18.9)	7 (13.2)
Kidney	32 (3.6)	18 (56.2)	4 (12.5)	10 (31.3)
Rheumatologic	26 (2.9)	17 (65.4)	5 (19.2)	4 (15.4)
Hematologic	23 (2.6)	12 (52.2)	6 (26.1)	5 (21.7)
Other[a]	18 (2.0)	12 (66.7)	3 (16.7)	3 (16.7)

Late IRAEs after ≥2 Years of ICI

Brief Report: Late Immune-Related Adverse Events (IRAEs) After ≥2 Years of Immune Checkpoint Inhibitor (ICI) Therapy: Incidence and Association with Survival in Patients with Advanced Non-Small-Cell Lung Cancer (NSCLC)

Articles in Press100851 May 25, 2025.

- **Single center retrospective study (N=76) : Median duration of treatment was 41.9m.**
- **After 2 years on ICI, 38/76 (50%) of patients experienced a late IRAE, many of whom (39%) had no prior early IRAE.**
- **Higher rates of late IRAEs was seen in patients with prior grade≥2 IRAE (p=0.020).**

IRAE Types	
<2-year IRAEs (n=44)	
Constitutional	5 (11.4%)
Dermatologic	23 (52.3%)
Ocular	2 (4.5%)
Endocrine	9 (20.5%)
GI	2 (4.5%)
Hepatobiliary	4 (9.1%)
MSK	8 (18.2%)
Pulmonary	2 (4.5%)

Late IRAEs (n=38)	
Constitutional	2 (5.3%)
Dermatologic	10 (26.3%)
Endocrine	4 (10.5%)
GI	8 (21.1%)
Hepatobiliary	4 (10.5%)
MSK	7 (18.4%)
Pulmonary	4 (10.5%)
Renal	1 (2.6%)
Neurological	1 (2.6%)

Incidence rates of immune related adverse events

Cancer and treatment specific incidence rates of immune related adverse events induced by immune checkpoint inhibitors: a systematic review

British Journal of Cancer (2025) 132:51–57.

- Systematic review : 272 studies (2017-2021), 305,879 total patients on ICI.
- General irAE occurrence across any grade was 40.0% (37.3–42.7%), and high grade was 19.7% (15.8–23.7%)
- ICI monotherapy was 30.5% (28.1–32.9%), and ICI combination therapy 45.7% (29.6–61.7%).

Study design	ICI study population	Number of patients with irAE
Cohort or observational	129,502*	16,365†
Clinical trial or subset analysis	9783	2496
Experimental, exploratory, or pilot	27,400	4367‡
Case control or matched case control	23,693§	3323
Pharmacovigilance or surveillance	54,767‖	23,705¶
Systematic review and/or meta-analysis	60,734#§	8035Δ

Clinical trial : 25.5% (2,496/9783)

Pharmacovigilance or surveillance : 43.3% (23,705/54,767)

Incidence rates of immune related adverse events

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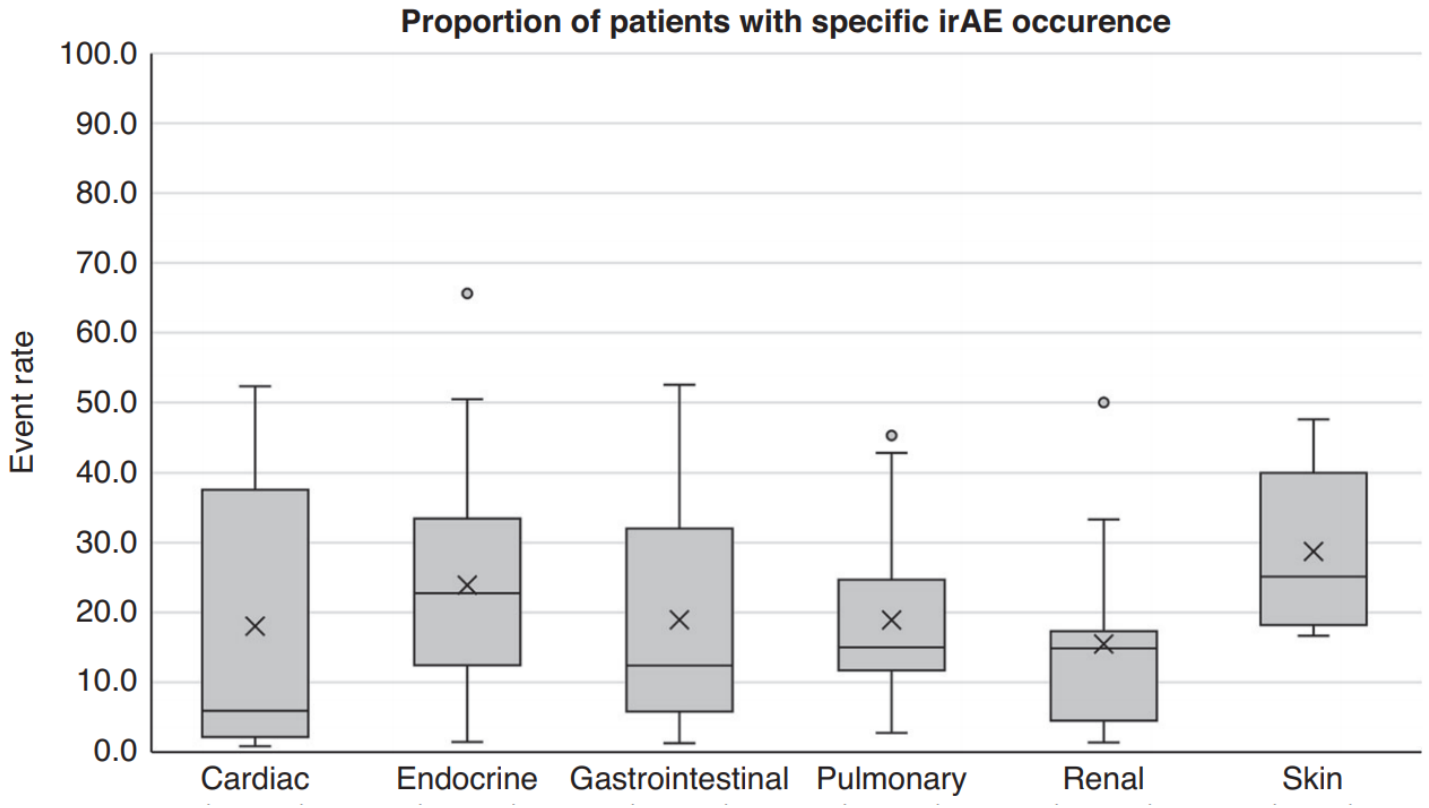
British Journal of Cancer (2025) 132:51–57.



Skin (28.7%), Pulmonary (18.9%), Cardiac (18.0%)

Incidence rates of immune related adverse events

Comparisons of adverse events associated with immune checkpoint inhibitors in the treatment of non-small cell lung cancer: a real world disproportionality analysis based on the FDA adverse event reporting system

Gao et al. BMC Cancer (2025) 25:216 .

- 13,580 reports of AEs associated with five ICIs. (2013-2022)

	Durvalumab	Pembrolizumab	Ipilimumab	Atezolizumab	Nivolumab
Durvalumab	1	2.48(1.72,3.59)	2.76(1.14,6.65)	1.35(0.83,2.20)	0.59(0.25,1.39)
Pembrolizumab	0.40(0.28,0.58)	1	1.11(0.45,2.75)	0.54(0.32,0.93)	0.24(0.10,0.58)
Ipilimumab	0.36(0.15,0.88)	0.90(0.36,2.23)	1	0.49(0.19,1.29)	0.21(0.06,0.71)
Atezolizumab	0.74(0.45,1.21)	1.84(1.07,3.16)	2.04(0.78,5.36)	1	0.44(0.17,1.13)
Nivolumab	1.70(0.72,4.00)	4.21(1.72,10.28)	4.67(1.41,15.51)	2.29(0.89,5.91)	1

In terms of respiratory AEs, pembrolizumab exhibited a higher risk

	Durvalumab	Pembrolizumab	Ipilimumab	Atezolizumab	Nivolumab
Durvalumab	1	0.43(0.13,1.37)	0.13(0.02,0.75)	0.27(0.06,1.28)	0.67(0.20,2.28)
Pembrolizumab	2.35(0.73,7.58)	1	0.30(0.07,1.26)	0.64(0.20,2.02)	1.57(0.80,3.08)
Ipilimumab	7.80(1.33,45.90)	3.32(0.79,13.85)	1	2.12(0.37,12.16)	5.20(1.17,23.03)
Atezolizumab	3.68(0.78,17.36)	1.58(0.50,5.02)	0.47(0.08,2.71)	1	2.46(0.73,8.30)
Nivolumab	1.50(0.44,5.12)	0.64(0.32,1.25)	0.19(0.04,0.85)	0.41(0.12,1.38)	1

In terms of endocrine and metabolic AEs, durvalumab and nivolumab exhibited a higher risk

Association between irAEs and efficacy

Association between immune-related adverse events and immunotherapy efficacy in non-small-cell lung cancer: a meta-analysis

Front. Pharmacol., 22 May 2023.

- Meta-analysis : 54 Retrospective studies (N= 35~2,503)
- IrAEs was a strong predictor of survival efficacy in patients with NSCLC treated with ICIs.
  - ① higher ORR (P<0.001), longer PFS (P<0.001), longer OS (P<0.001)
  - ② Grade ≥2 irAEs had better PFS
  - ③ Better PFS, OS : thyroid dysfunction, gastrointestinal, skin, or endocrine irAEs

    (No significant differences were observed in pneumonitis or hepatobiliary irAEs.)

Immune-related adverse events as potential surrogates of immune checkpoint inhibitors' efficacy: a systematic review and meta-analysis of randomized studies

ESMO Open. 2023 Apr;8(2):100787.

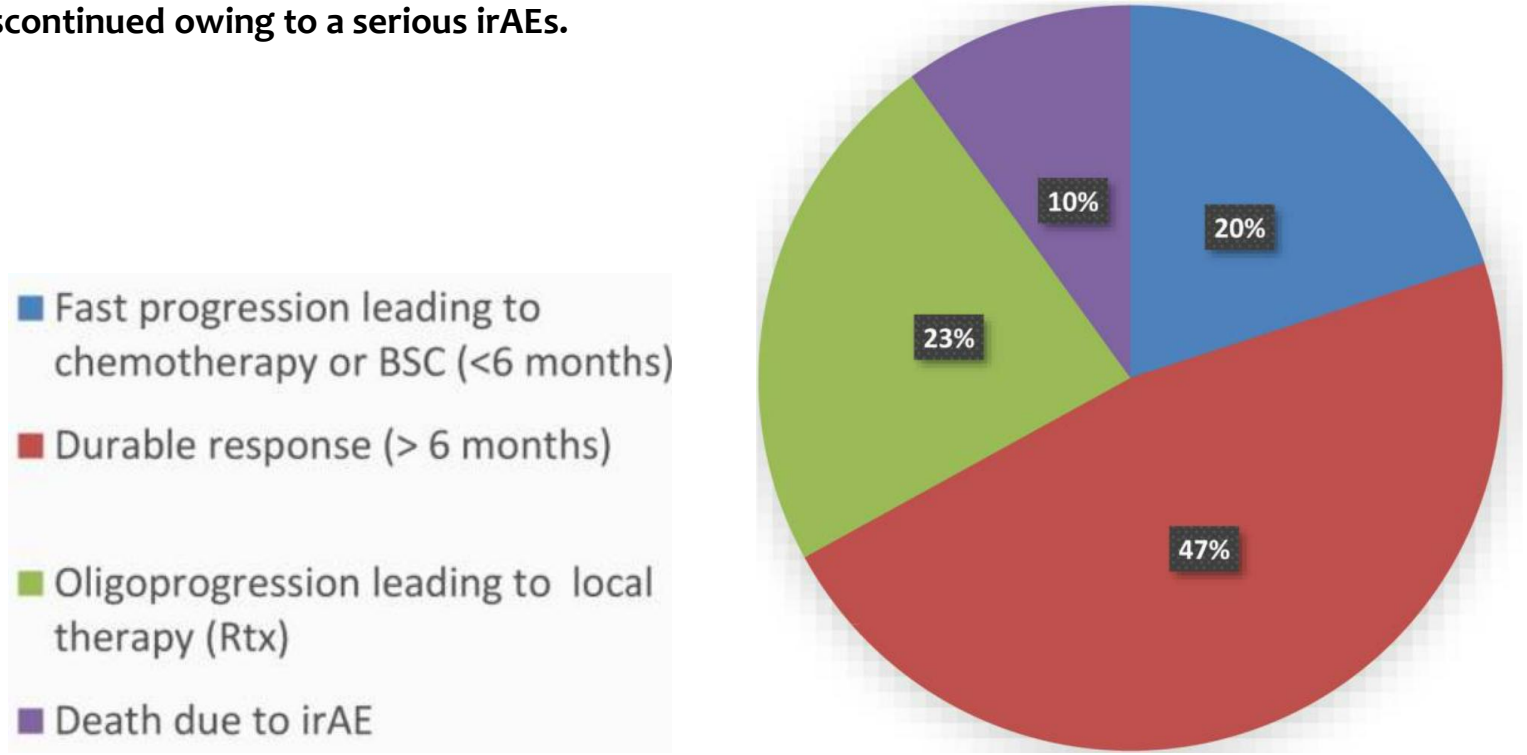
- Meta-analysis : 62 RCTs (N= 42,247); 18 NSCLC, 7 SCLC
- The analyses found no significant association between the treatment effects for overall grade 1-2 or grade 3-4 irAE rates or specific (skin, gastrointestinal, endocrine) irAE rates.

What happens if we just observe it without any additional treatment?

Clinical Outcomes of Patients With Metastatic NSCLC After Discontinuation of Immunotherapy Because of Immune-Related Adverse Effects

JTO Clin Res Rep. 2022 Nov 25;4(1):100441.

- **Small sample!!!, single-center retrospective observational study (N=30)**
- **NSCLC in whom ICI had to be discontinued owing to a serious irAEs.**



A watchful waiting approach is justified after discontinuation of ICI owing to irAEs.

ICI rechallenge / restarting

Immune Checkpoint Inhibitor Rechallenge Safety and Efficacy in Stage IV Non-Small Cell Lung Cancer Patients After Immune-Related Adverse Events

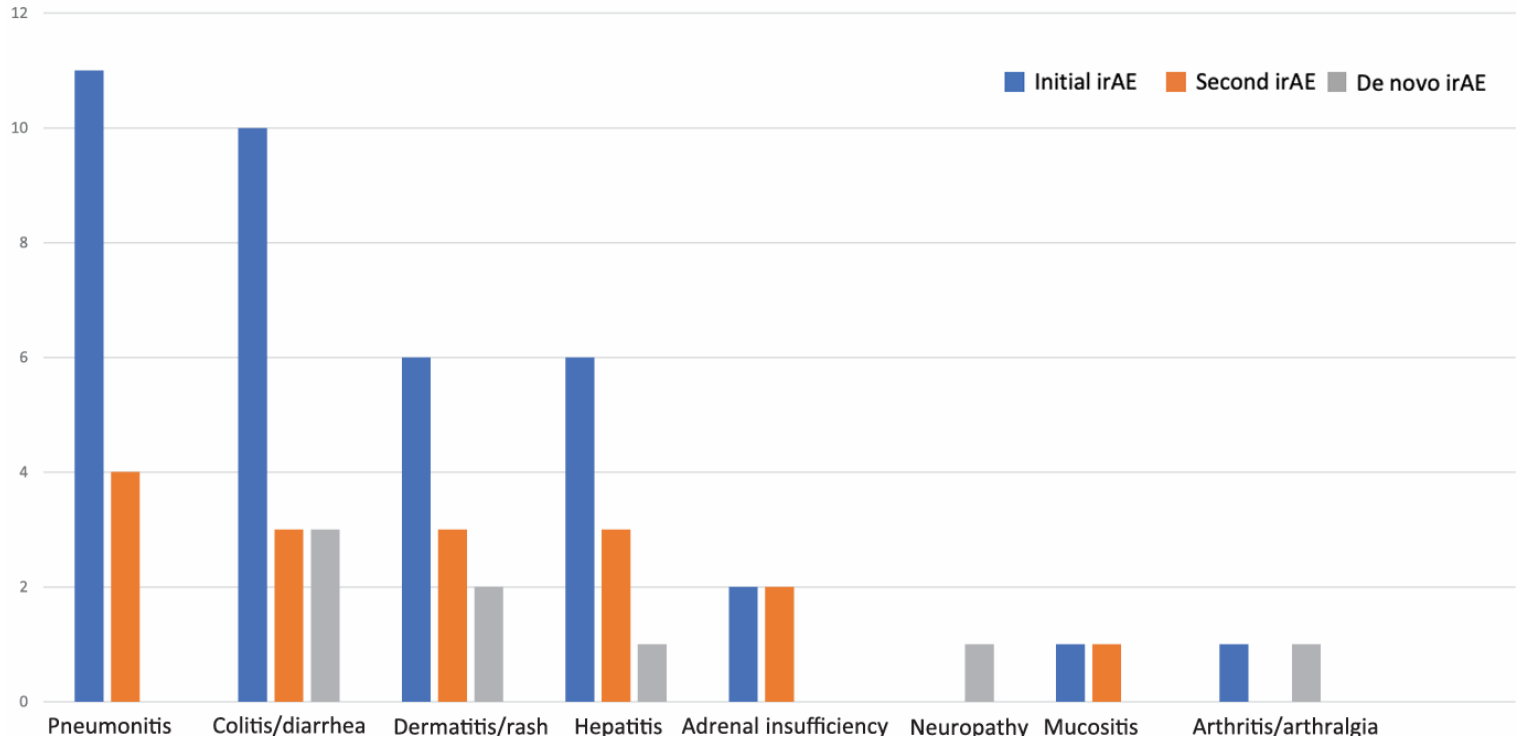
Clinical Lung Cancer, Vol. 23, No. 8, 686–693.

- Retrospective single center study (N=99/1051 (9.4%)), grade ≥2 irAEs, rechallenged group (N=40)

① After rechallenging, 24 of 40 (60%) patients had recurrence of the same or de-novo irAEs.

② Twenty (50%) developed second grade ≥2 irAEs.

③ No grade 4 irAE or irAE-related death occurred after rechallenging.



ICI rechallenge / restarting

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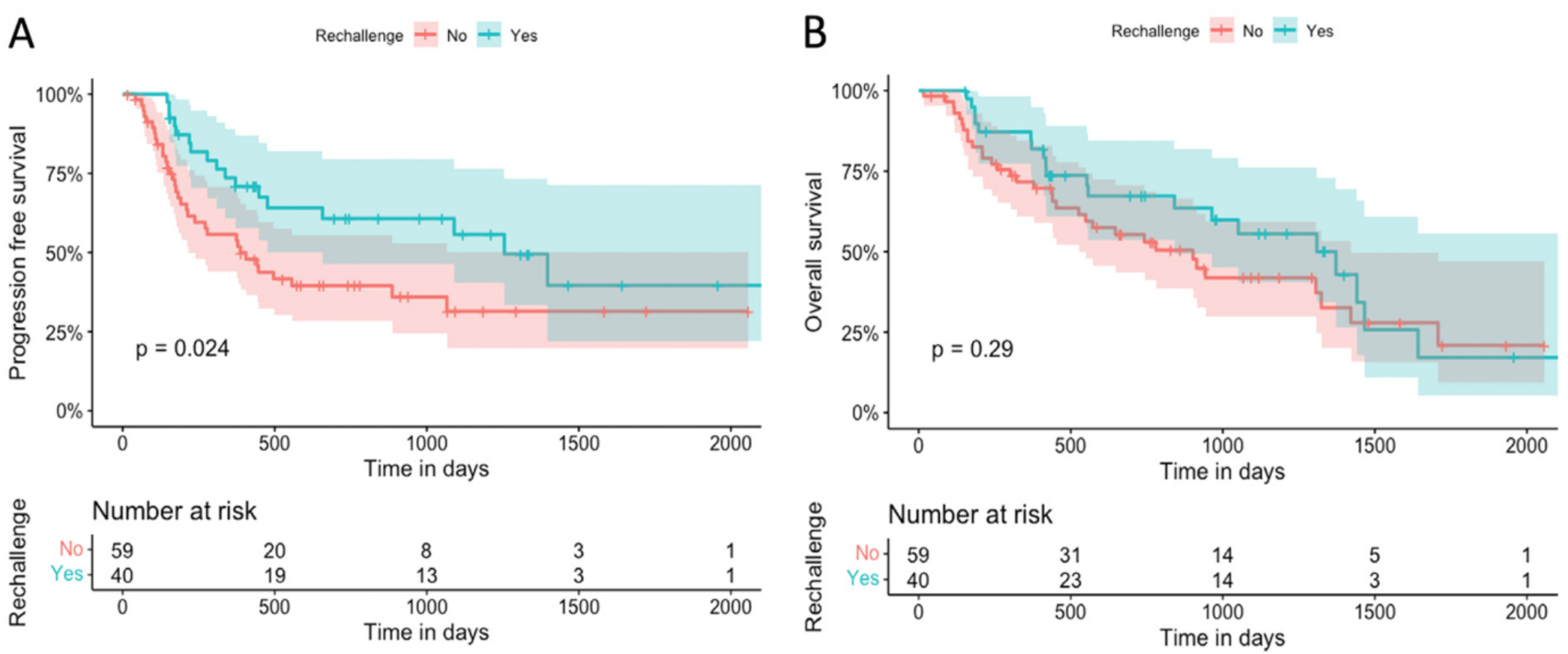


Permanent ICI discontinuation is an appropriate strategy after grade ≥2 irAEs, especially severe irAEs.

Moving Immunotherapy Into the Treatment of Resectable Non–Small Cell Lung Cancer

Adverse events in Neo-adj/adj

Treatment-related adverse events, including fatal toxicities, in patients with solid tumours receiving neoadjuvant and adjuvant immune checkpoint blockade: a systematic review and meta-analysis of randomised controlled trials

Lancet Oncol 2024; 25: 62–75.

- **Meta-analysis : 28 RCTs (16,976 patients), Lung cancer RCTs (N=5)**
- **The addition of ICIs was not significantly associated with increased treatment-related deaths (OR 1·76, 95% CI 0·95–3·25; p=0·073).**

① **40 fatal toxicities (0.4%) were identified in ICIs group (N=9,864)**

② **13 fatal toxicities (0.2%) were identified in non-ICIs group (N=7,112)**

Cardiovascular	
Myocarditis	5 (12·5%)
Atrial fibrillation	2 (5·0%)
Gastrointestinal	
Colitis	3 (7·5%)
Bowel perforation	1 (2·5%)
Liver failure	1 (2·5%)
Peritonitis	1 (2·5%)

Respiratory	
Pneumonitis	6 (15·0%)
Acute respiratory distress syndrome	2 (5·0%)
Pulmonary embolism	2 (5·0%)
Alveolitis	1 (2·5%)
Interstitial lung disease	1 (2·5%)

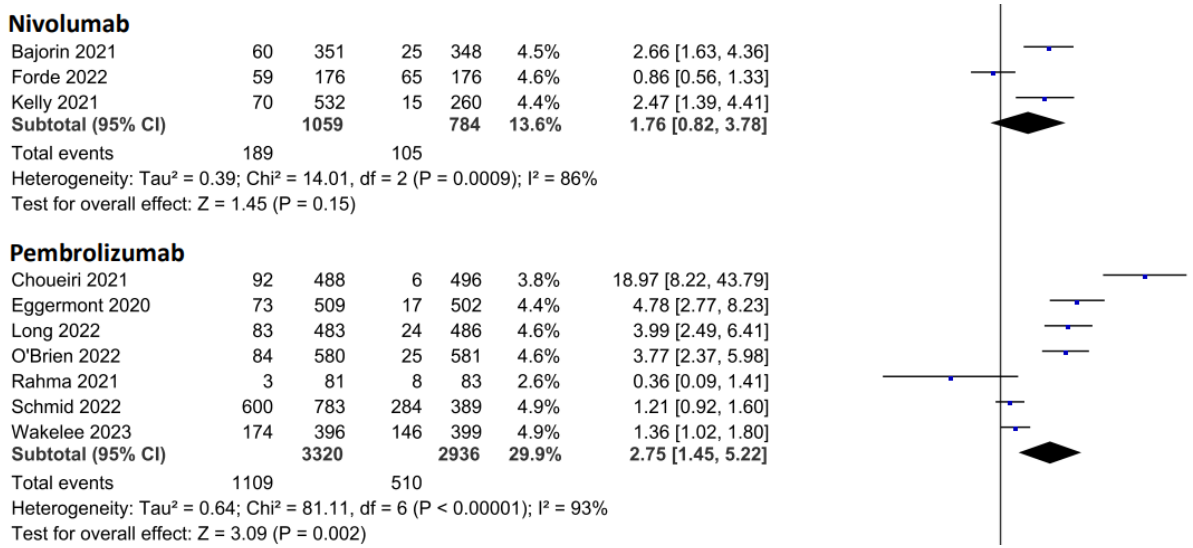
Adverse events in Neo-adj/adj

Treatment-related adverse events, including fatal toxicities, in patients with solid tumours receiving neoadjuvant and adjuvant immune checkpoint blockade: a systematic review and meta-analysis of randomised controlled trials

Lancet Oncol 2024; 25: 62–75.

- The addition of ICIs increased the incidence of grade 3–4 treatment-related adverse events (OR 2·73, 95% CI 1·98–3·76; p<0·0001), adverse events leading to treatment discontinuation (3·67, 2·45–5·51; p<0·0001), and treatment-related adverse events of any grade (2·60 [1·88–3·61], p<0·0001).

- Grade 3-4 trAEs (sub-group analysis)



Clinicians should closely monitor patients for treatment-related adverse events to prevent treatment discontinuations and morbidity from these therapies in earlier-stage settings

Side effects that may be dangerous during surgery

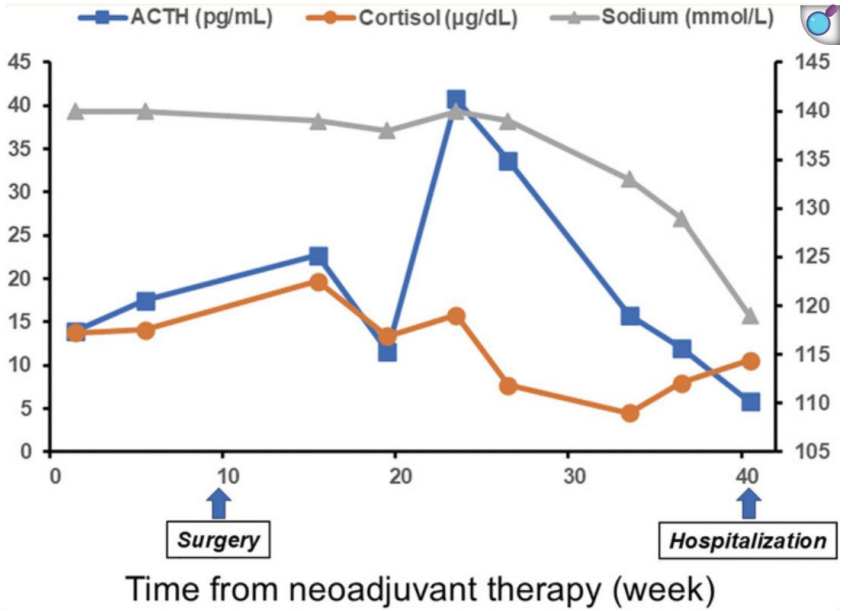
ICI-induced adrenal insufficiency

① Occurs in 1-2% (Stage IV)

② Adrenal insufficiency is a rare but potentially serious complication that can occur after major surgery.

③ Mimicked prolonged postoperative fatigue : nonspecific, anorexia, fatigue, hyponatremia.

④ 8AM cortisol : 3ug/dL (AI), 15uld/L (r/o)

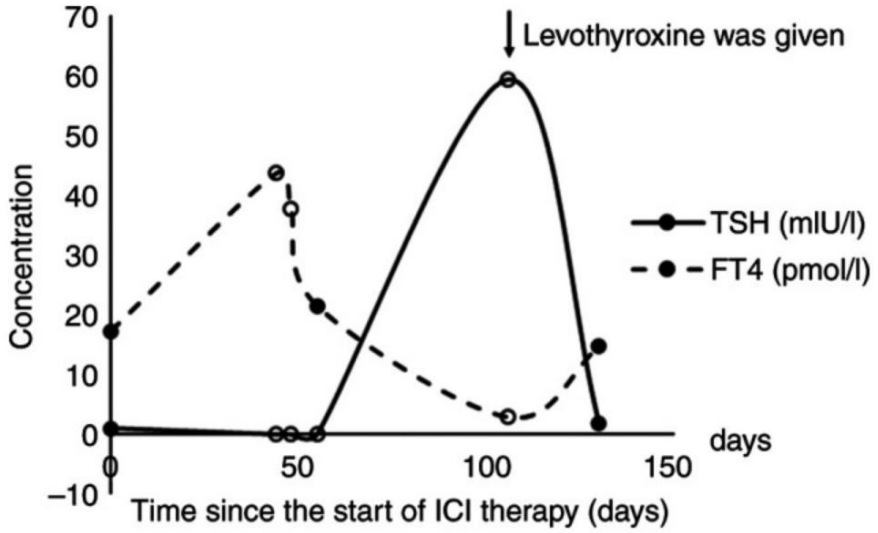


Surg Case Rep. 2025 Feb 1;11(1):24-0044.

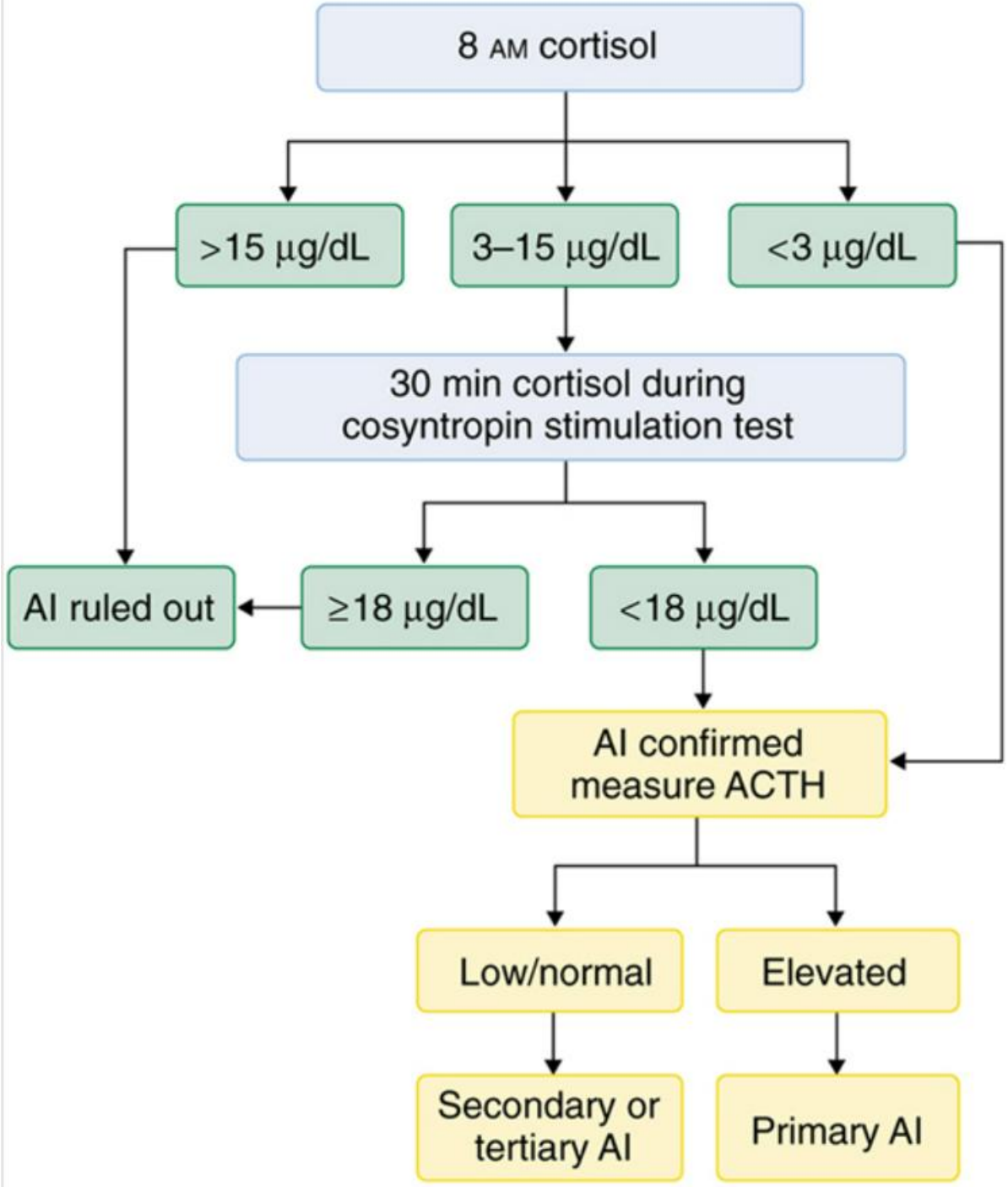
ICI-induced hypothyroidism

① The most commonly affected endocrine organ is the thyroid

② Wound healing



Oncol Lett. 2023 Sep 29;26(5):496.


8 AM cortisol
>15 µg/dL
3–15 µg/dL
<3 µg/dL
30 min cortisol during cosyntropin stimulation test
AI ruled out
≥18 µg/dL
<18 µg/dL
AI confirmed measure ACTH
Low/normal
Elevated
Secondary or tertiary AI
Primary AI

Routine monitoring (NCCN)

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Patient and relevant family history of any autoimmune/ organ-specific disease, endocrinopathy, or infectious disease (ID) • Neurologic examination • Bowel habits (typical frequency/consistency) • ID screening (human immunodeficiency virus [HIV]; hepatitis A, B, C) as indicated	Clinical examination at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General blood work • Complete blood count (CBC) (with differential if indicated) • Comprehensive metabolic panel (CMP)	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Consider dermatology referral. Monitor affected skin and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (FT4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	ICI_ENDO-2 and ICI_ENDO-3

CMP : Glucose (4 weeks – 6/12 weeks)
TSH, free T4 : (4-6 weeks – 12 weeks) + T3 -> AM cortisol levels
Amylase, lipase : no routine monitoring

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Pituitary/Adrenal (ICI_ENDO-4) • Consider serum cortisol (morning preferred) and thyroid function as above	Consider repeating every 4–6 weeks during immunotherapy (immuno-oncology [IO]-only regimens[c]), then follow-up every 12 weeks as indicated	Morning serum cortisol, adrenocorticotropic hormone (ACTH), TSH, FT4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol (premenopausal individuals), and cosyntropin stimulation test only as indicated
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for patients who are high risk (eg, interstitial lung disease on imaging, chronic obstructive pulmonary disease [COPD], previous suspected treatment-related lung toxicity) • In the absence of prior imaging, consider a chest x-ray	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes
Cardiovascular (ICI_CARDIO-1) • Consider baseline electrocardiogram (ECG) • Consider high-sensitivity troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms[d]	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine kinase (CK)

Consider AM cortisol levels
Consider PFT with DLCO
Consider ECG, troponin, pro-BNP

Management : ASCO, ESMO, NCCN

Management

ESMO Clinical Practice Guideline

1. Diagnosis and grading of irAEs
2. Ruling out differential diagnoses (consultation specialist, biopsy)
3. Selecting the appropriate immunosuppression strategy for grade 2 events
4. Active evaluation at 72r h to adapt treatment

ASCO Guideline

Grade I : ICI is to be continued with close monitoring (Except for some neurological, hematological and cardiac toxicities, such as myocarditis.)

Grade 2 : ICIs are temporarily discontinued + Corticosteroids (0.5–1 mg/kg prednisone or equivalent) can be administered

Grade 3 : ICI suspension + Administration of high-dose corticosteroids (1–2 mg/kg prednisone or methylprednisolone, tapered over 4–6 weeks)

Grade 4 : Permanent discontinuation of ICI is recommended.

For grades 1–3, if symptoms and/or lab values revert to grade 1 or less, an ICI rechallenge can be done

Mechanism-based therapeutic managements

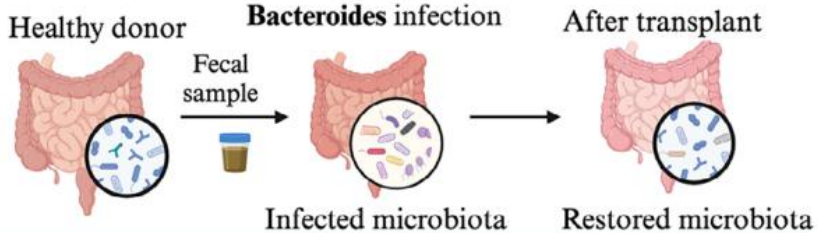
Immune-related adverse events in non-small cell lung cancer: Occurrence, mechanisms and therapeutic strategies

Clin. Transl. Med. 2024;14:e1613.

Strategy 1#: Modulation of T cells activity and migration

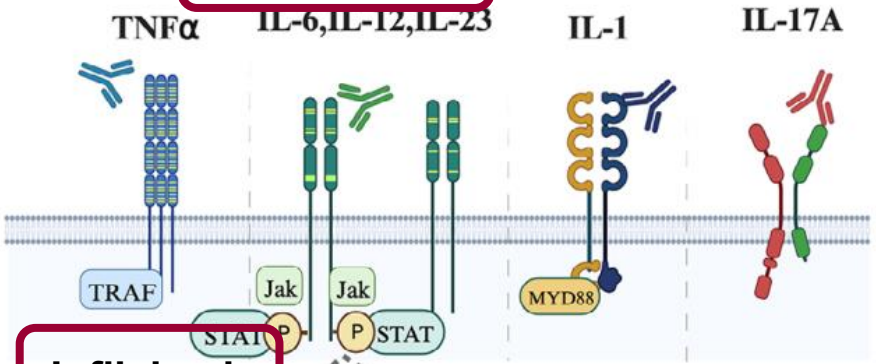
Mycophenolate
Cyclophosphamide

- Corticosteroids
- Immunosuppressants
- Fecal microbiota transplant and Perspective



Strategy 3#: Targeting cytokines receptors

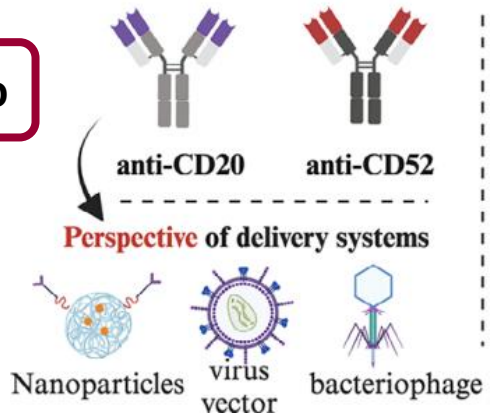
Tocilizumab

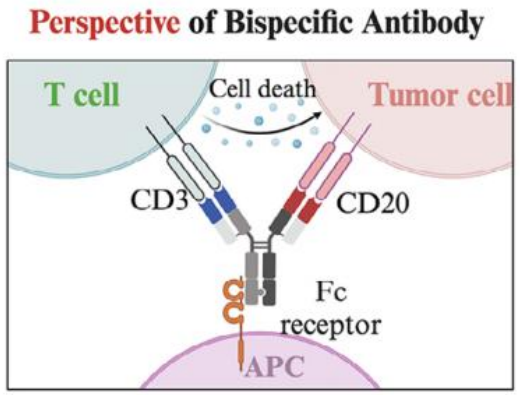


Infliximab

Strategy 2#: Lymphocyte-targeted monoclonal antibodies

Rituximab

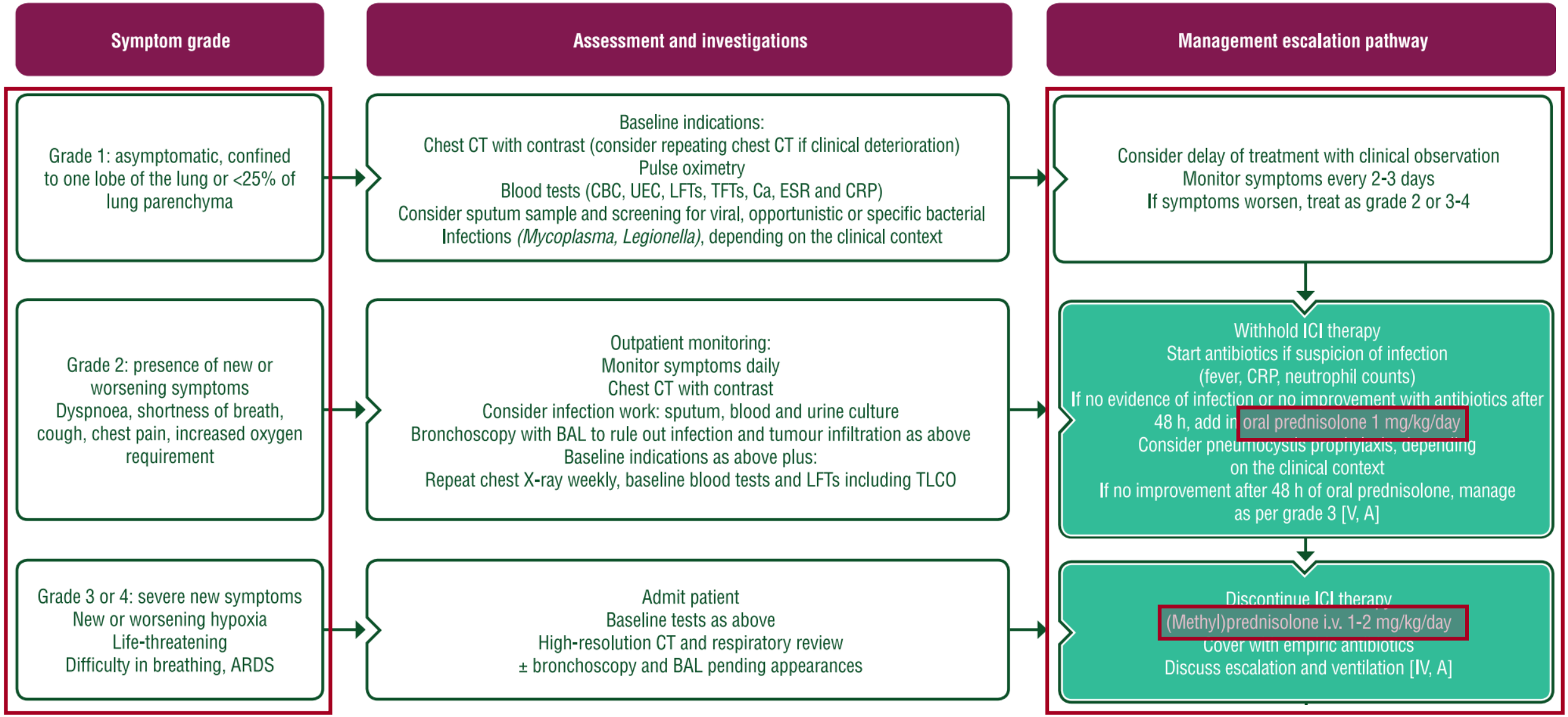




Strategy 4#: Targeting signaling pathways

- JAK-STAT pathway
- PI3K pathway
- CDK4/6 pathway
- MNK1/2 pathway

ESMO Clinical Practice Guideline



ESMO Clinical Practice Guideline

If not improving or worsening after 48 h

Add tocilizumab 8 mg/kg or infliximab 5 mg/kg ± IVIG
Consider MMF or cyclophosphamide on individual basis
Continue with i.v. CSs; wean as clinically indicated [V, A]

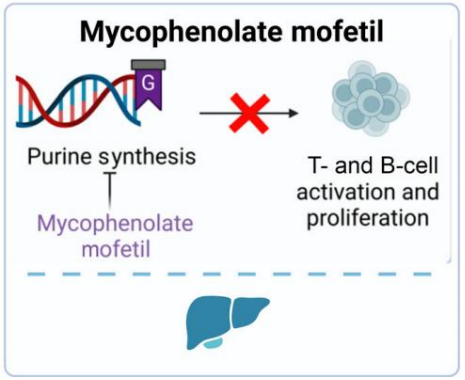
Once improved to baseline:

- Grade 2: wean oral CSs over 4-6 weeks, titrate to symptoms
- Grade 3-4: wean CSs over at least 6-8 weeks

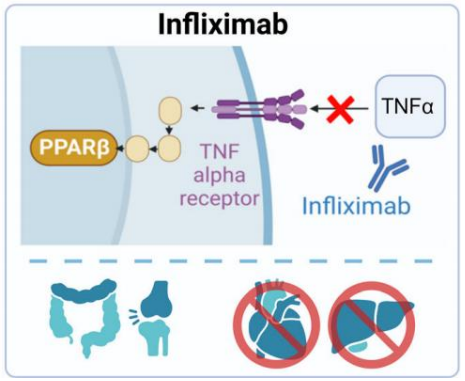
Steroid considerations:

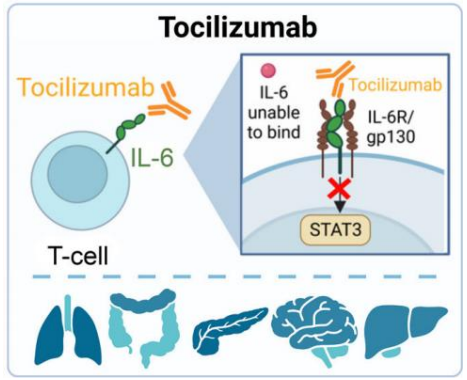
- Calcium and vitamin D supplementation as per local guidelines
- Pneumocystis prophylaxis - cotrimoxazole 480 mg b.i.d. M/W/F or inhaled pentamidine if cotrimoxazole allergy

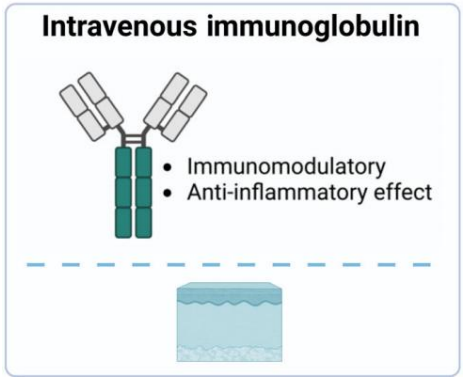
Strategy 1#: Modulation of T cells activity and migration



Strategy 3#: Targeting cytokines receptors



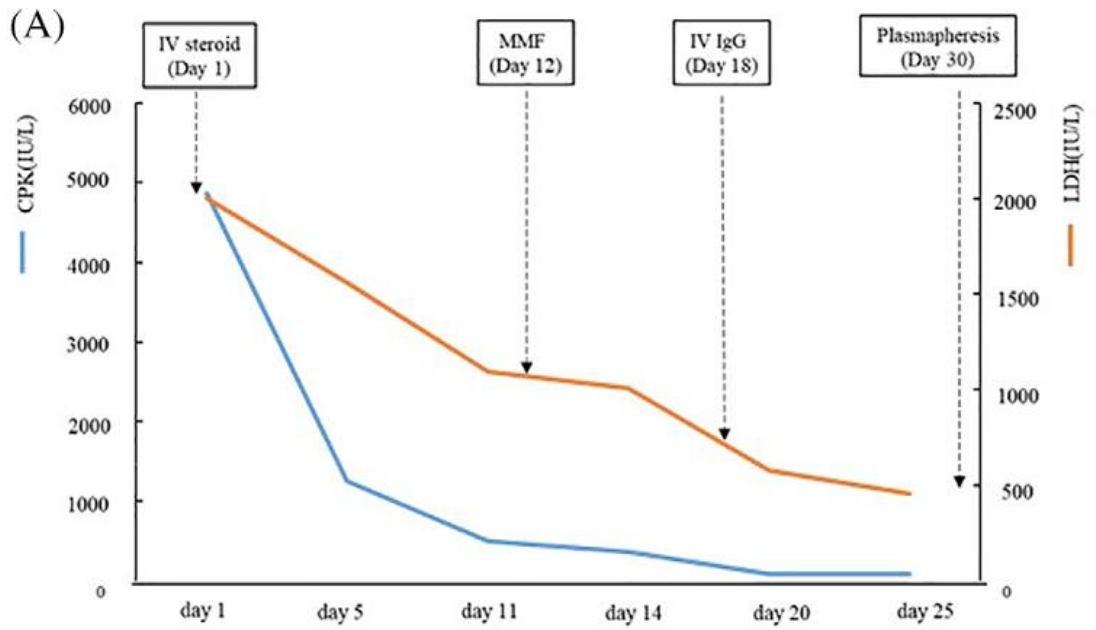


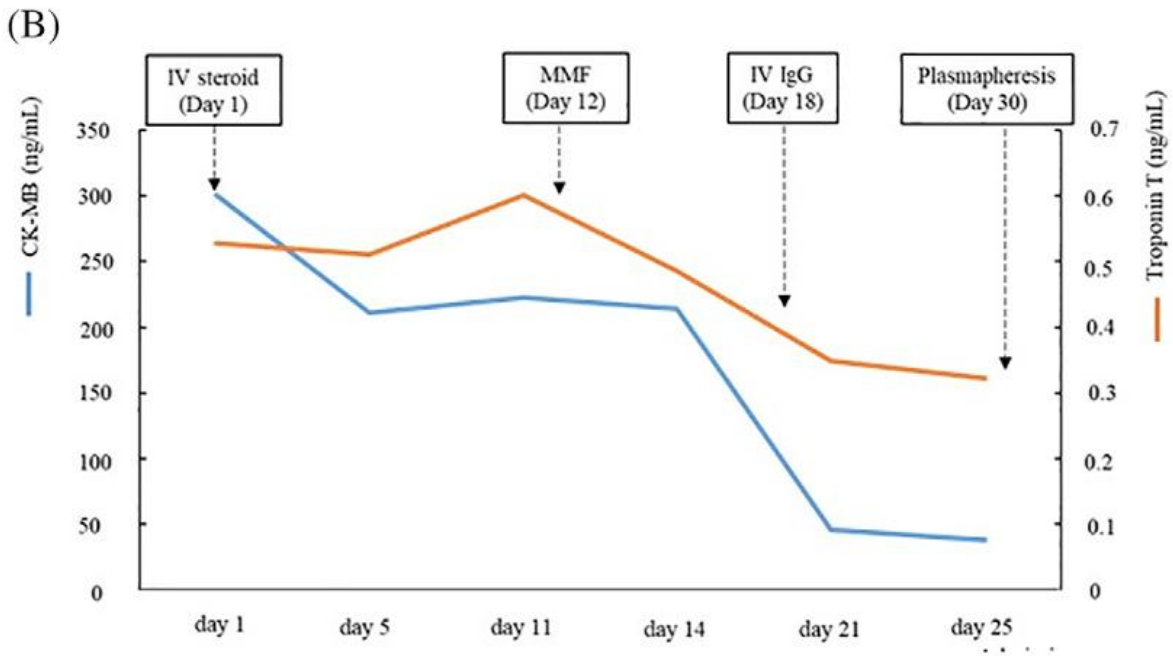


Case report

Early development of pembrolizumab-induced fulminant myositis and cardiotoxicity in a patient with metastatic thymoma

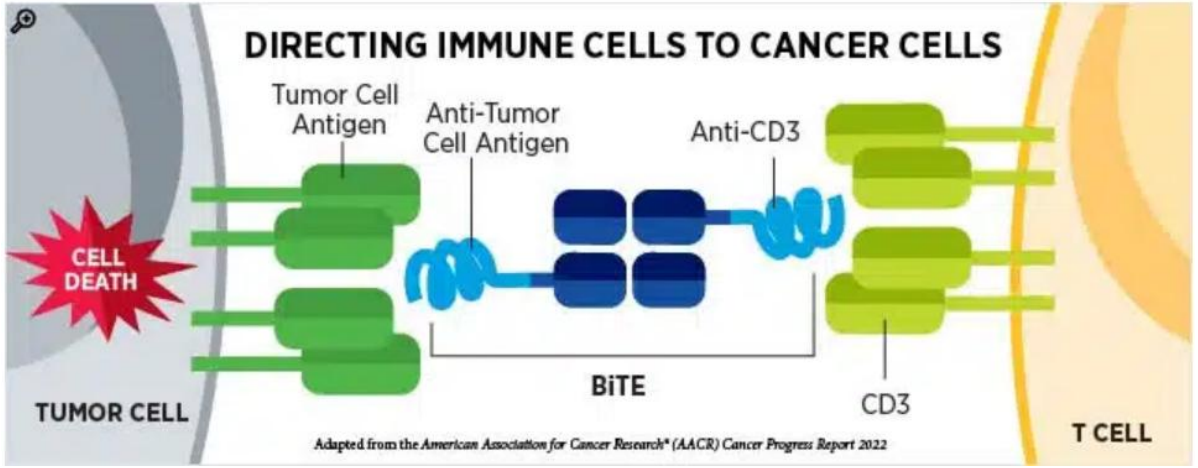
Respirol Case Rep. 2022 Aug 24;10(9):e01025.

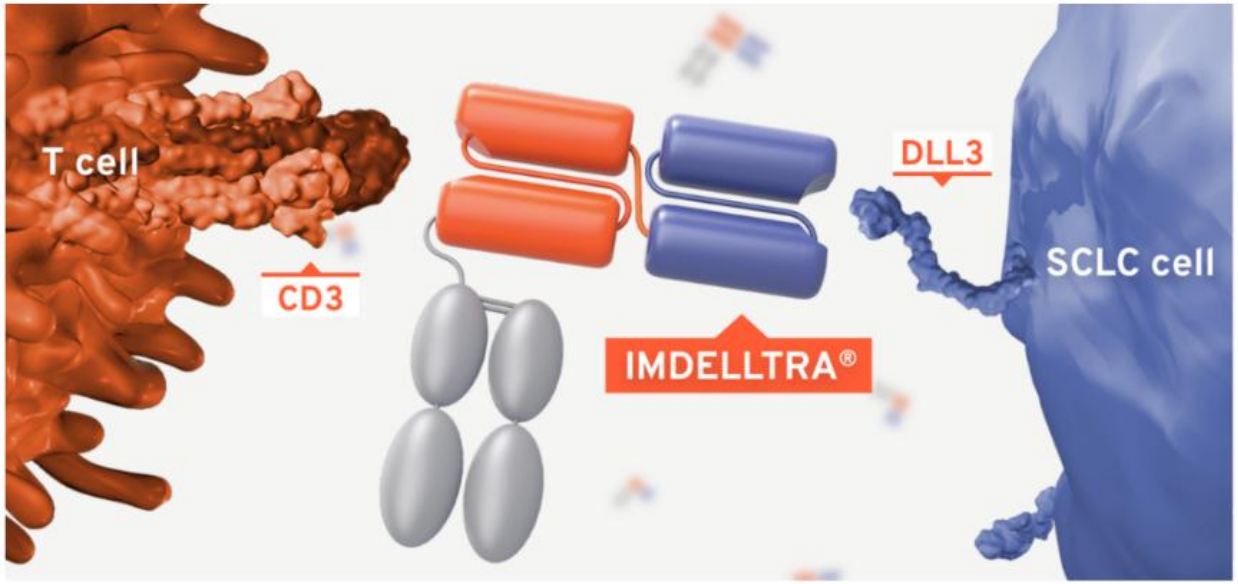


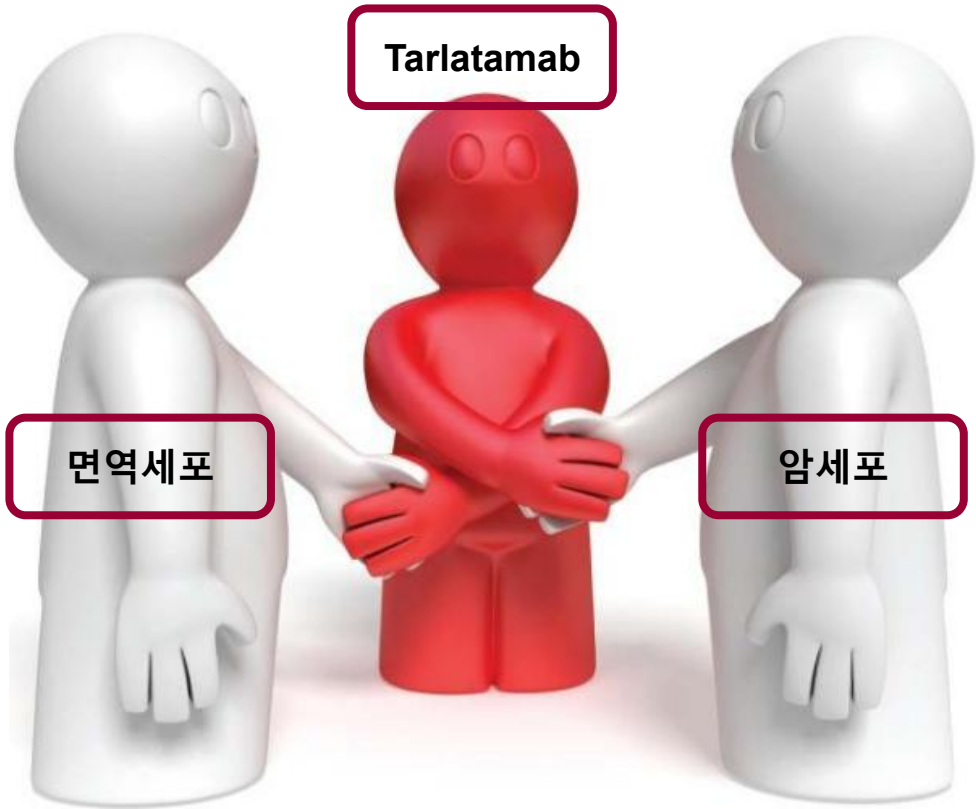


Tarlatamab (DLL3 × CD3 T cell engager)

Bispecific T-cell Engager therapy (BiTE)







Delta-Like Ligand 3 (DLL3)

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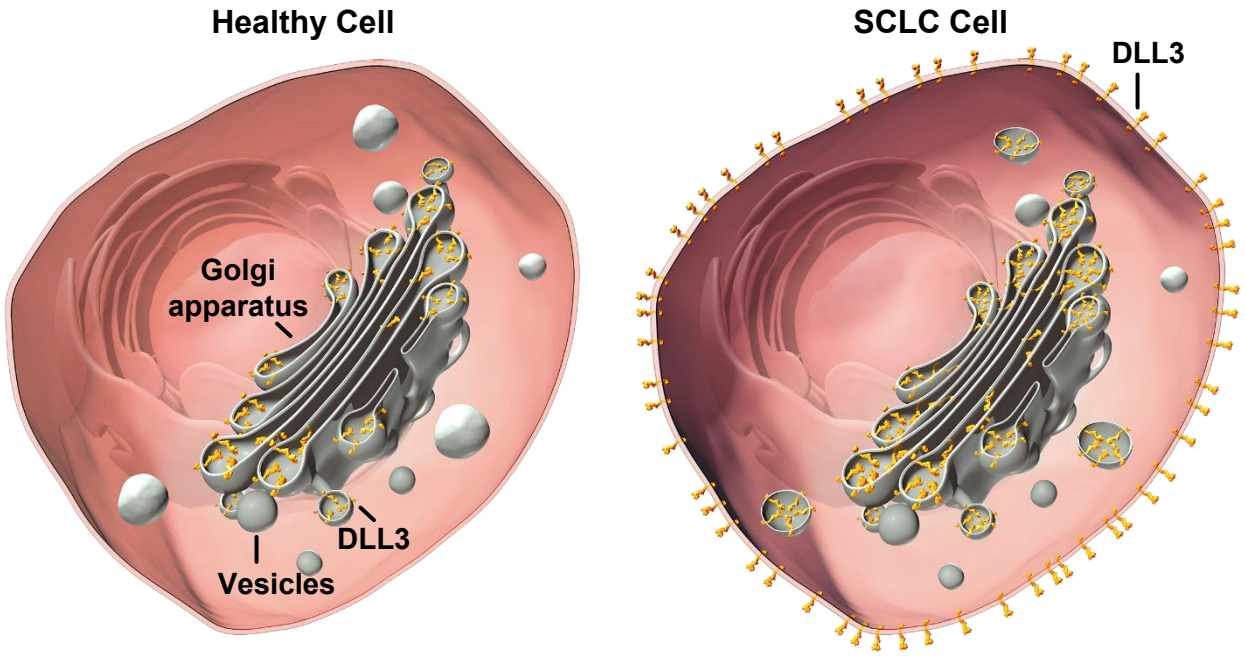
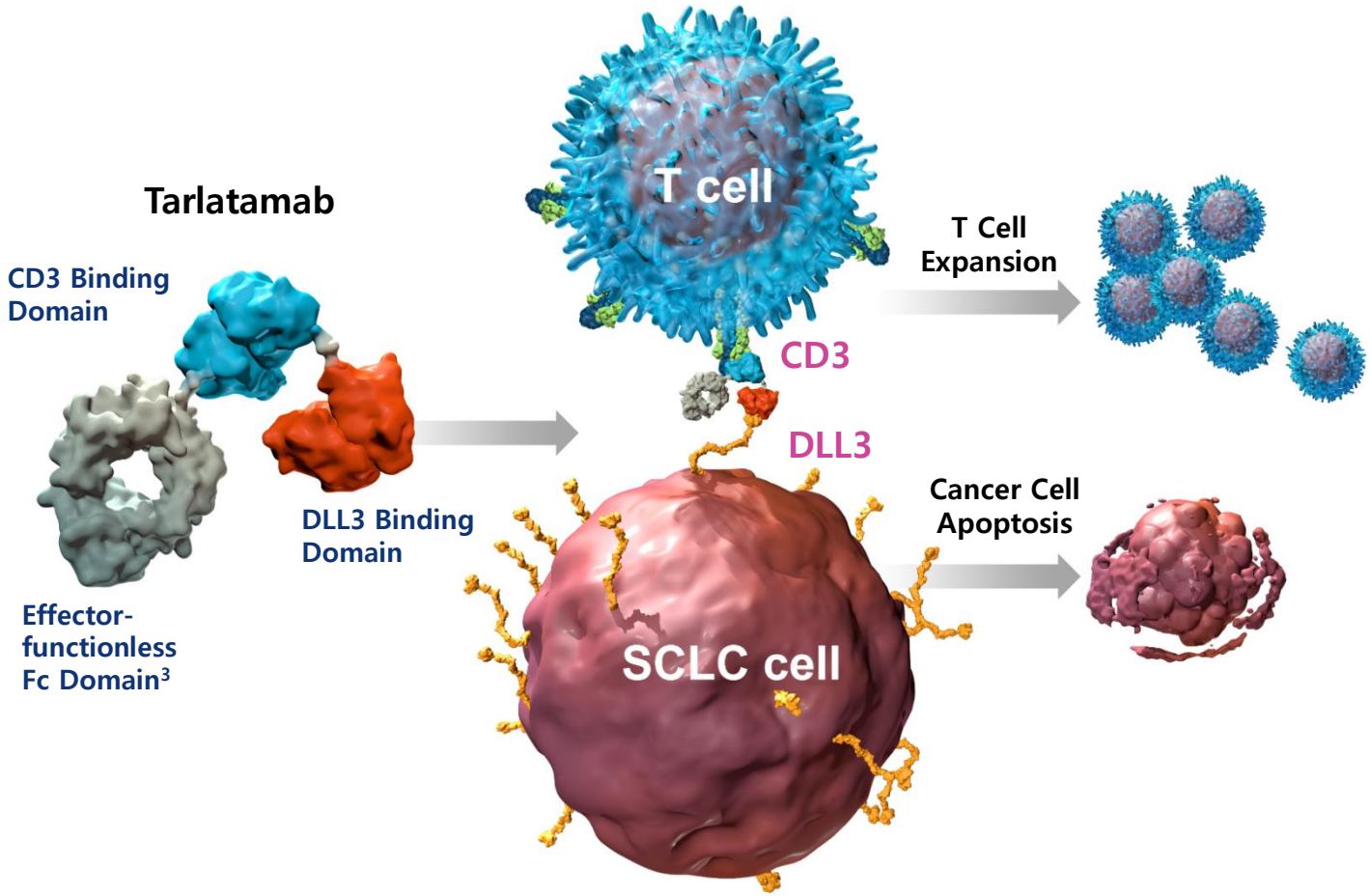
DLL3 Expression



Characteristic	Specimens With Evaluable DLL3 Expression[a] n = 1050		
	No. in Each Category	Negative 0%–24 %	Positive[b] 25 %–100 %
All patients, n (%)	1050	155 (15)	895 (85)
SCLC stage, n (%)			
Limited	335	57 (17)	278 (83)
Extensive	667	92 (14)	575 (86)
Missing	48	6 (13)	42 (88)
No treatment received	218	23 (11)	195 (89)
First-line	442	74 (17)	368 (83)
Second-line	244	38 (16)	206 (84)
Third-line or greater	146	20 (14)	126 (86)

Leonetti A, et al. Cell Oncol (Dordr). 2019;42:261-273
Lung Cancer. 2020 Sep:147:237-243.

Tarlatamab



Fever

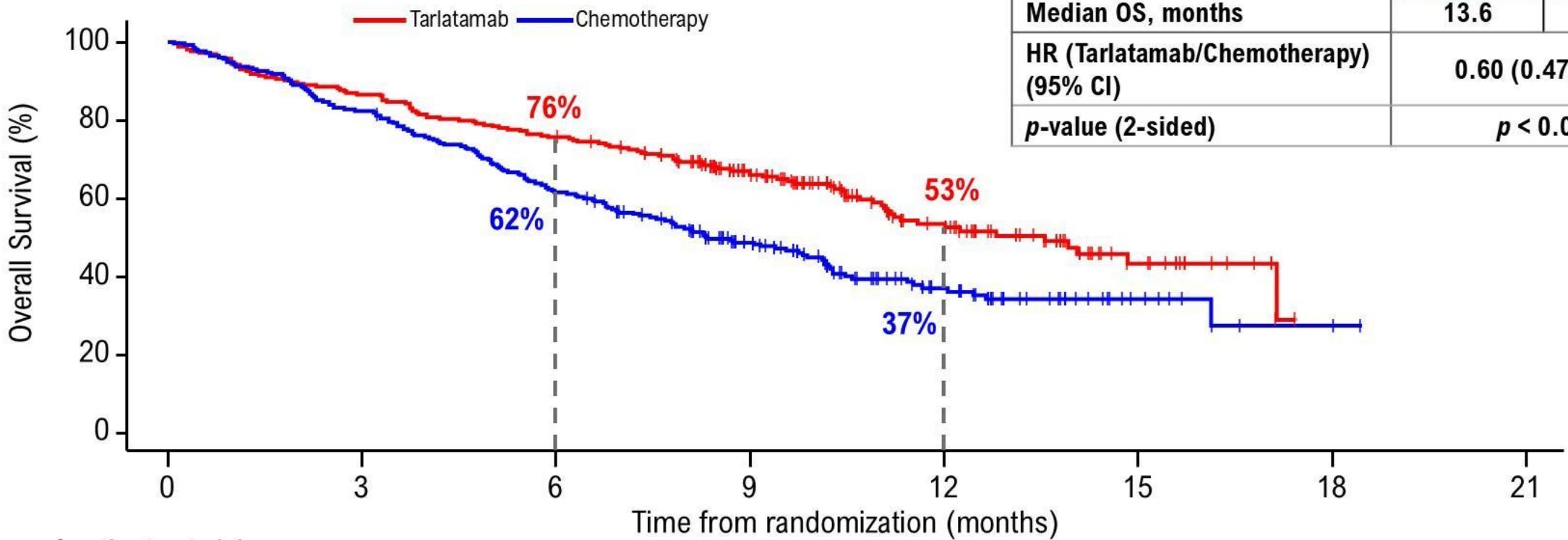
: Cytokine Release Syndrome (CRS)

Mental change

: Immune effector cell–associated neurotoxicity syndrome (ICANS)

DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy

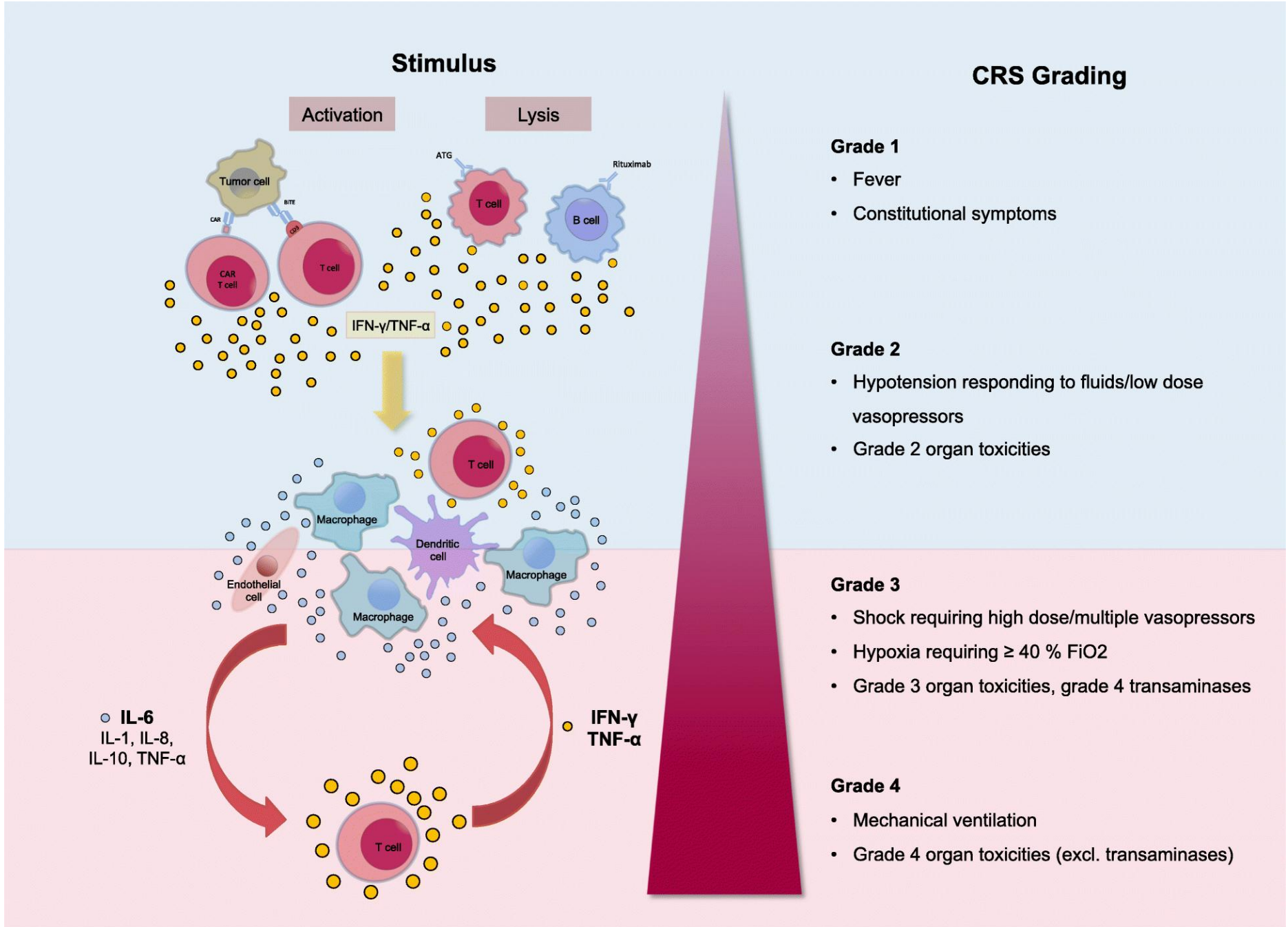
	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median OS, months	13.6	8.3
HR (Tarlatamab/Chemotherapy) (95% CI)	0.60 (0.47, 0.77)	
p-value (2-sided)	$p < 0.001$	



Number of patients at risk:

Tarlatamab	254	220	192	131	60	17	0
Chemotherapy	255	210	156	97	42	9	2	0

Median follow-up time: 11.2 months for the tarlatamab group and 11.7 months for the chemotherapy group. *p*-value was calculated using a stratified log-rank test.
HR, hazard ratio; **OS**, overall survival.



Journal for ImmunoTherapy of Cancer volume 6, Article number: 56 (2018)

Cytokine Release Syndrome

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CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	≥ 38°C	≥ 38°C‡	≥ 38°C‡	≥ 38°C‡
		With		
Hypotension	None	Not requiring vasopressors	Requiring vasopressor§ with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or††		
Hypoxia	None	Requiring low-flow nasal cannula** or blow-by	Requiring high-flow nasal cannula**, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

While there have been a variety of grading scales used across different clinical trials prior to 2019 , the ASTCT grading scale aims to standardize definitions and grading system

Cytokine Release Syndrome

- **Common symptoms: fever, hypotension, and hypoxia**
- **Timing**
  - **Median Onset: 13 hours (IQR: 8-27 hours)**
  - **Median Duration: 4 days**
  - **Resolution in 98% of cases**

CRS, n (%)	Parts 1-3 Tarlatamab 10 mg (n = 133)	Part 1 Tarlatamab 100 mg (n = 87)
All Grades	68 (51)	53 (61)
Grade 1	40 (30)	28 (32)
Grade 2	27 (20)	20 (23)
Grade 3	1 (1)	5 (6)

CRS was predominately grade 1 or 2 in severity

Cytokine Release Syndrome

DeLLphi 301

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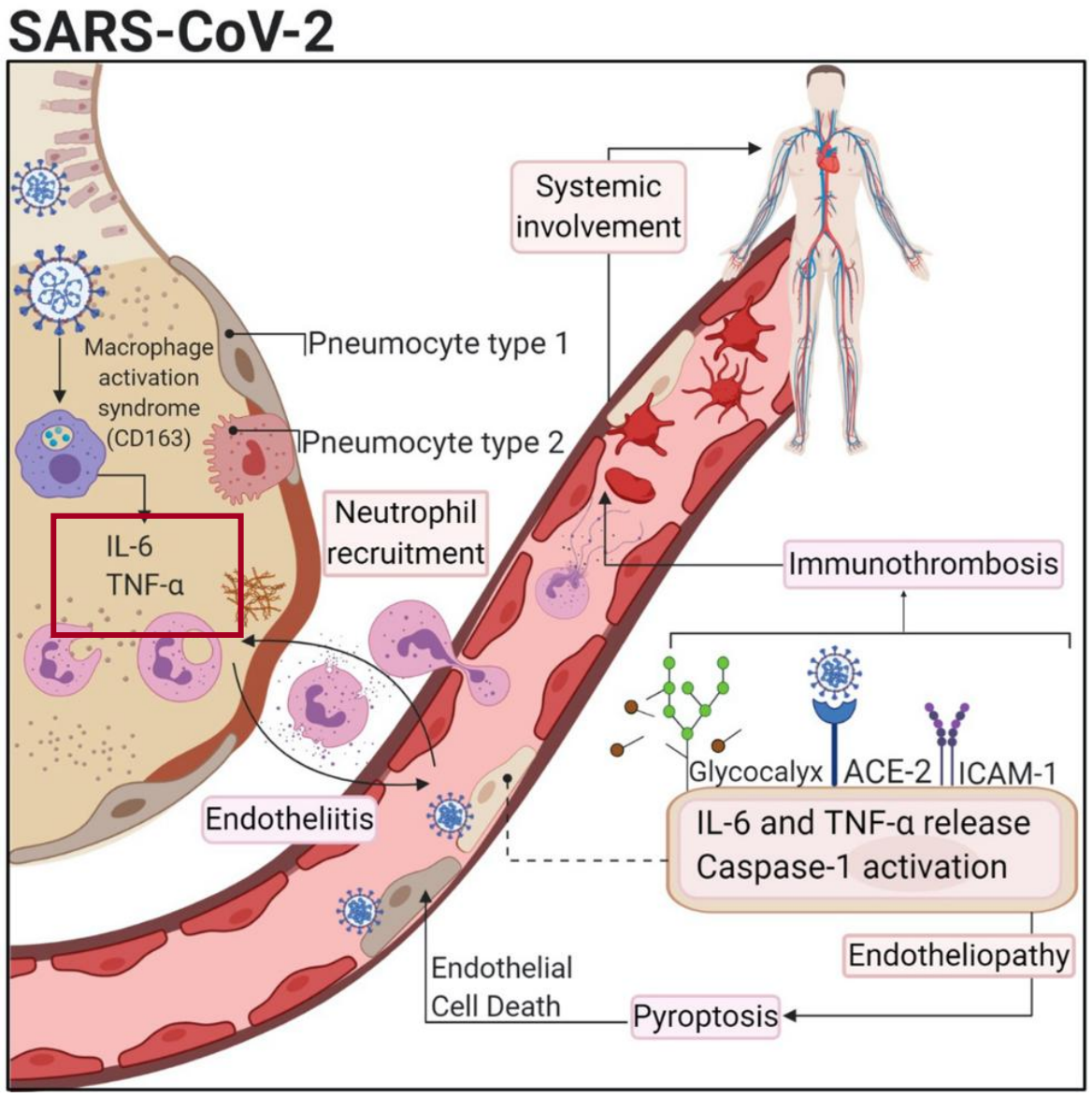
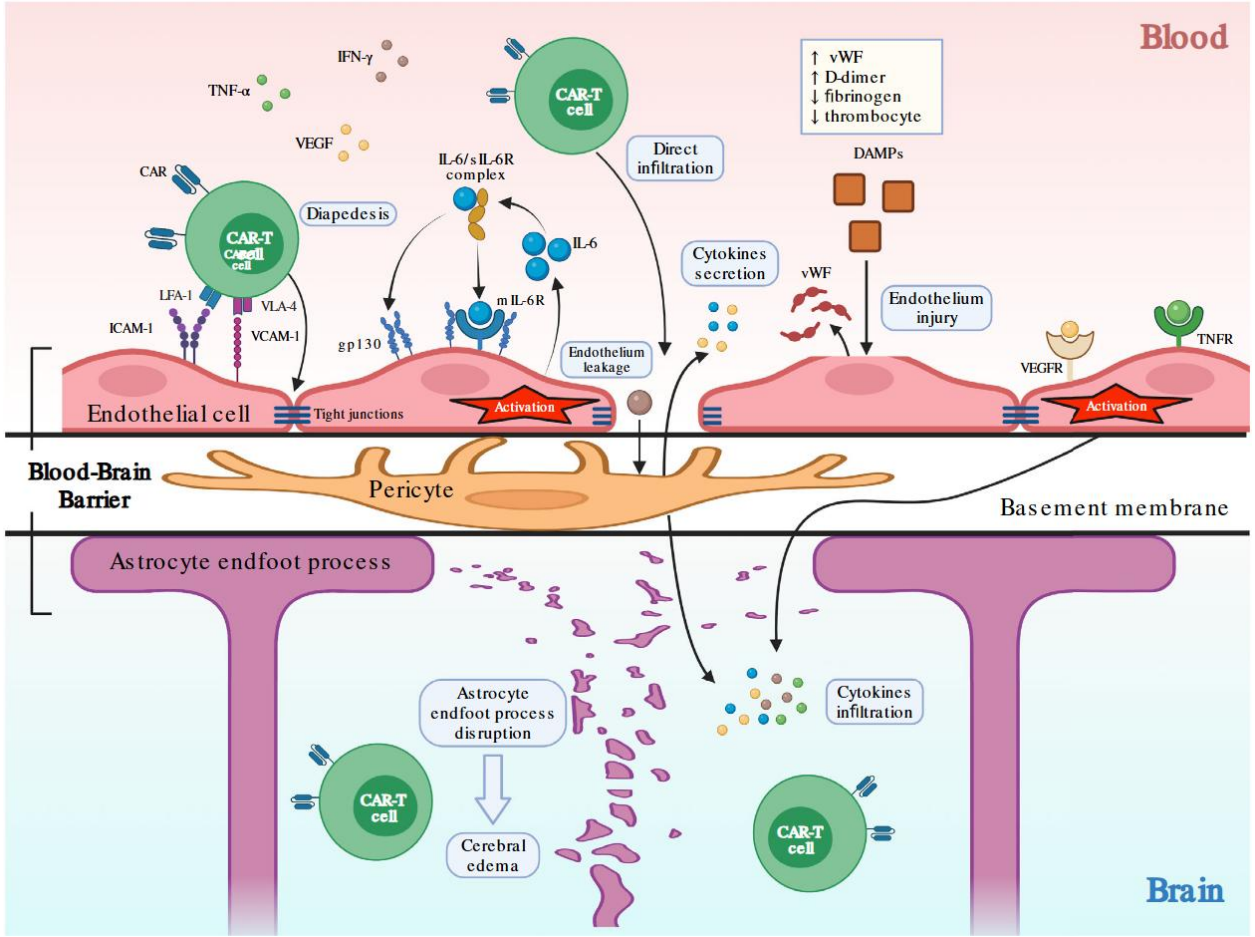
Management per protocol

- **Supportive care such as acetaminophen, IV hydration, and glucocorticoids**

Additional interventions for CRS, n (%)	Parts 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
Tocilizumab	5 (5)	9 (10)	2 (6)
IV fluid	8 (8)	8 (9)	1 (3)
Supplemental oxygen	7 (7)	8 (9)	4 (12)
Vasopressor support	1 (1)	1 (1)	0

CRS was generally managed with supportive care; additional interventions were infrequently utilized





Tarlatamab, is also expected to have limited BBB penetration under normal conditions.

WIREs Mech Dis. 2022;14:e1576.
Arterioscler Thromb Vasc Biol. 2020 Oct;40(10):2404-2407.)

Immune effector cell–associated neurotoxicity syndrome

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Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score†	7–9	3–6	0–2	0 (patient is unarousable and unable to perform the tests for grading ICE)
Depressed level of consciousness‡	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse Stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor weakness (any age)§	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging**	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy, papilledema, and Cushing's triad

Immune effector cell–associated neurotoxicity syndrome

ICANS Symptoms

- **Confusion, impaired attention, tremor, and motor findings, weakness, or both**

Timing

- **Median Onset: 5 days**
- **Median Duration: 6.5 days**

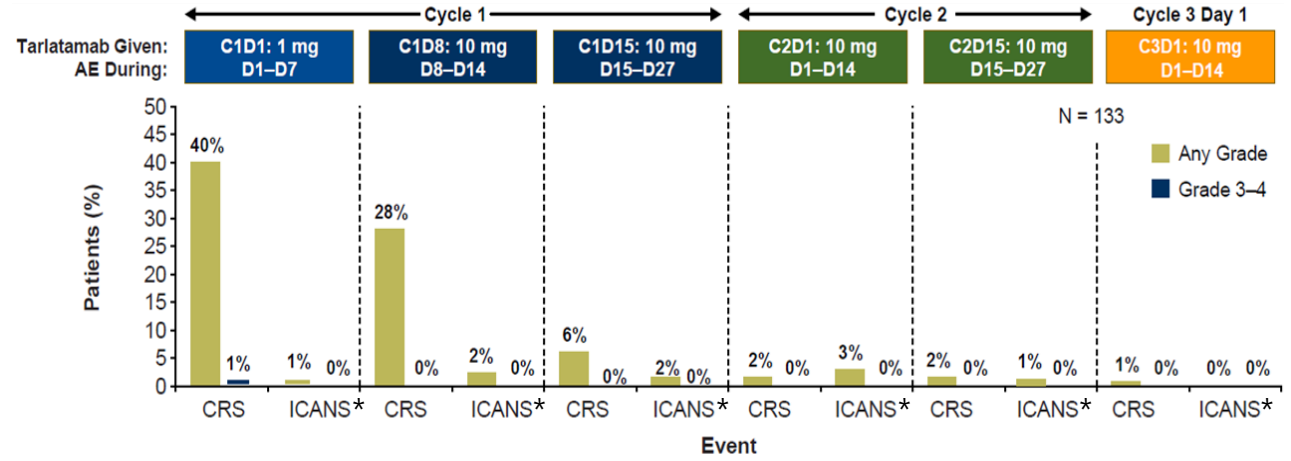
Management per protocol

- **Follow institutional guidelines**
- **All grades: supportive care**
- **≥ Grade 2: glucocorticoid therapy**
- **Grade 4: high-dose glucocorticoid treatment**

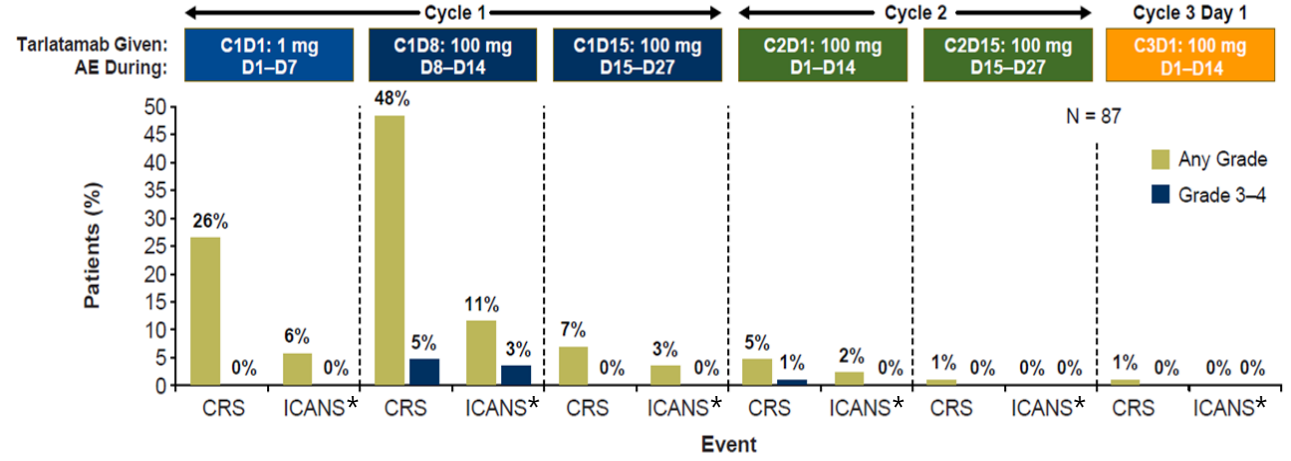
AEs of interest, n (%)	Parts 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 10 0 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
ICANS and associated neurologic events			
Overall	7 (7)	24 (28)	4 (12)
Grade ≥ 3 severity	0	4 (5)	0
Serious	2 (2)	11 (13)	2 (6)
Leading to tarlatamab discontinuation	1 (1)	1 (1)	0
Fatal	0	0	0

Timing of CRS and ICANS and associated neurologic events

10 mg Tarlatamab



100 mg Tarlatamab



- CRS was largely confined to the first or second dose
- ICANS occurred infrequently overall and was predominantly observed with tarlatamab 100 mg

Table 3. Comparison of CRS clinical features between days 1 and 8 of the first cycle

	Total CRS events (N=10)	Day 1 of the first cycle (N=5)	Day 8 of the first cycle (N=5)	P-value
Hours to fever	18.4±12.2	9.0±2.1	27.8±10.5	0.004
CRS duration	55.3±60.4	75.0±73.4	35.6±43.2	0.044
Peak fever	38.8±0.5	38.9±0.4	38.8±0.6	0.317
CRS grade				
1	5 (50.0%)	1 (20.0%)	4 (80.0%)	0.103
2	5 (50.0%)	4 (80.0%)	1 (20.0%)	
3≥	0 (0.0%)	0 (0.0%)	0 (0.0%)	
CRS grade defining events				
Hypotension	4 (40.0%)	3 (60.0%)	1 (20.0%)	0.262
Inotropic used	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Oxygen supplementation	1 (10.0%)	1 (20.0%)	0 (0.0%)	0.500
Intubation	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ICU admission	0 (0.0%)	0 (0.0%)	0 (0.0%)	

*Numbers are presented as N (%) or mean ± Standard deviation

Abbreviations: CRS, cytokine release syndrome; ICU, intensive care unit.

Take home message

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- Immune-checkpoint inhibitors
  - There should always be a high level of suspicion.
  - A watchful waiting approach is justified after discontinuation of ICI owing to irAEs.

- Tarlatamab
  - CRS was predominately grade 1 or 2.
  - CRS was generally managed with supportive care.
  - ICANS occurred infrequently overall and was predominantly observed with tarlatamab 100 mg

감사합니다