Overview of Adverse Events of Lung Cancer Treatments and Management

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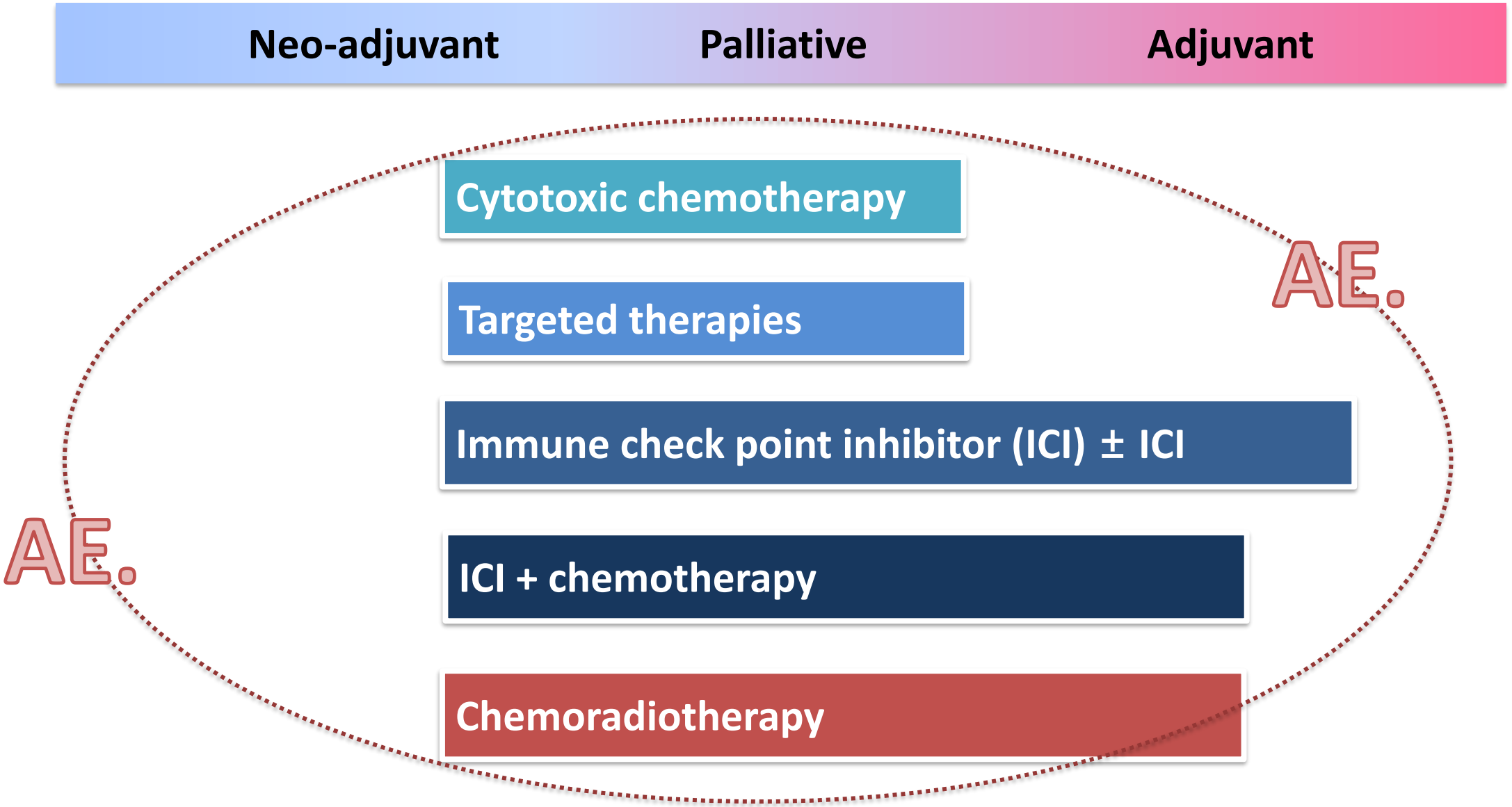
Contents

Therapeutic options for the treatment of Lung Cancer



When we encounter AEs of lung cancer treatments .....

?

- Is this *truly* related to cancer treatment ?
- How *serious* it is?
- How to *manage* these AEs?
- Will these AEs resolve or persist permanently?
- Should I stop offending Tx permanently or hold?
- Can the drug or Tx be re-challenged?

Potential and Real Impacts of AEs on Patients and/or Cancer

- May lead to temporal or permanent D/C of Tx.
- Might reduce the PFS and/or OS.
- Serious AE can be *fatal* for the patient
- Worsen patient's *QoL*.
- Sometimes, permanent medications are necessary to manage AEs.
- Might related to *improved survival* ?

Contents

Chemotherapy Induced Neutropenia (CIN) : *Definition and consequences*

AE	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia, (ANC)	ANC <LLN–1500 cells/mm3	ANC 1000–1500 cells/mm3	ANC 500–1000 cells/mm3	ANC <500 cells/mm3

- Febrile Neutropenia (FN) : a **single oral** temperature of >**38.3ºC** or a sustained temperature of ≥38ºC for >1 hour and an absolute neutrophil count (ANC) of <0.5 × 10^9/L, or expected to fall below 0.5 × 10^9/L.
- Duration and severity of neutropenia : major risk factors for FN and life-threatening infection
- Clinical consequences….
  - FN, Antibiotics use, unplanned ER visit and hospitalization, and possible death
  - Dose reduction and dose delays in chemotherapy cycle -> can adversely impact patient outcomes

Blayney DW, et al. Cancer Treatment Reviews. 2022;109, 102427.

Risk Factors for CIN and FN

Treatment-related	Patient-related	Disease-related
• Type of chemotherapy • Intensity of chemotherapy • No prior prophylactic antibiotics • No prophylactic G-CSF use • Prior chemotherapy or radiation therapy	• Age > 65 years • Female gender • Poor performance status • ≥1 comorbidity • Nutritional status • History of prior FN • Recent surgery and/or open wounds • Liver dysfunction • Renal dysfunction • Low WBC • Low hemoglobin levels • Cardiovascular disease • HIV infection	• Advanced disease • Type of cancer • Bone marrow involvement • Infection

Blayney DW, et al. Cancer Treatment Reviews. 2022;109, 102427.

Types of *Chemotherapy* and Risk of FN

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Hematopoietic Growth Factors

Disease Settings and

Chemotherapy Regimen with an

Intermediate Risk for Febrile

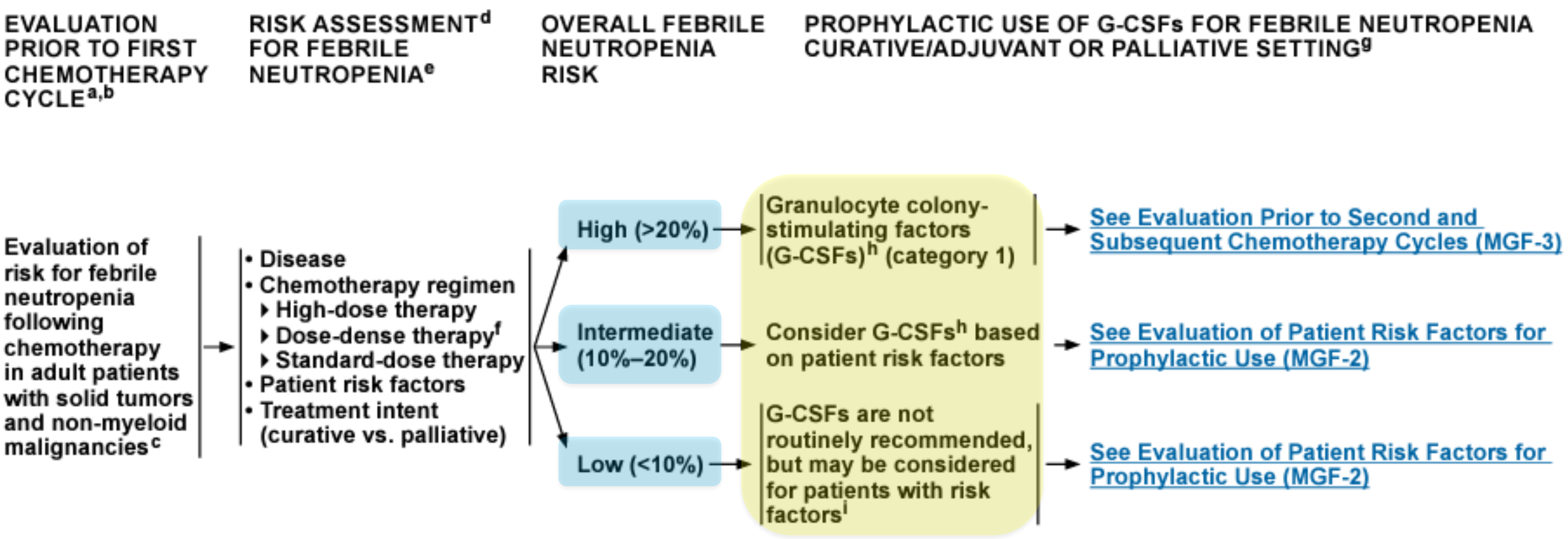
Neutropenia (10%-20%)

Non-Small Cell Lung Cancer

- Cisplatin/paclitaxel[59]
- Cisplatin/vinorelbine[60]
- Cisplatin/docetaxel[59,61]
- Cisplatin/etoposide[62]
- Carboplatin/paclitaxel[a,f,63]
- Docetaxel[61]

NCCN guidelines V2. 2023, Hematopoietic Growth Factors

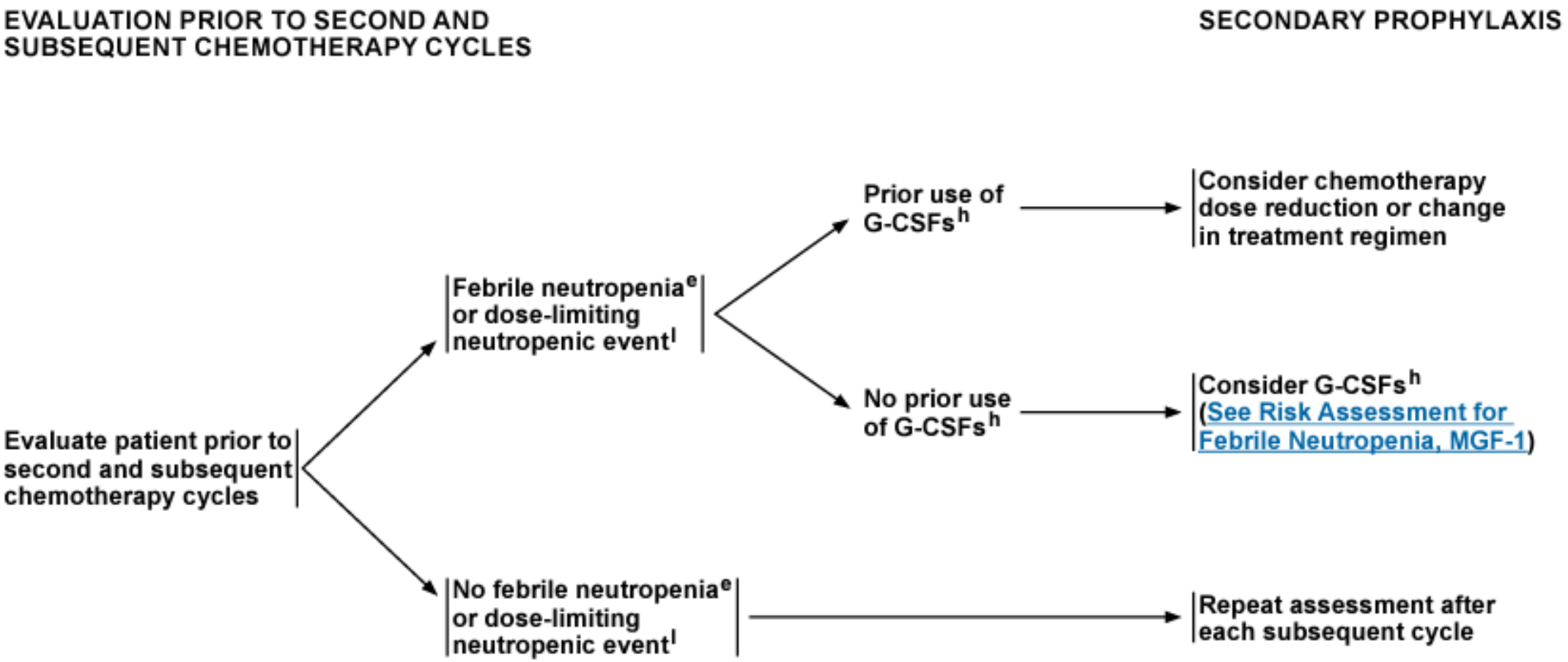
Prophylactic use of G-CSF for FN : *Primary prophylaxis*



- G-CSFs may be considered for patients receiving low-risk regimens who have *2 or more patient-related risk factors*. Use of G-CSF in this setting is based on clinical judgment.

NCCN guidelines V2. 2023, Hematopoietic Growth Factors

Prophylactic use of G-CSF for FN : *Secondary prophylaxis*



NCCN guidelines V2. 2023, Hematopoietic Growth Factors

Scoring System to predict major complications for FN
: Clinical Index of Stable Febrile Neutropenia (CISNE)

Characteristic	Points
Eastern Cooperative Oncology Group performance score ≥2	2
Stress-induced hyperglycemia (initial blood glucose ≥121 mg/dL, or ≥250 mg/dL in diabetic patients or those on steroids)	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
Mucositis grade ≥2	1
Monocytes <200 cells/mcL	1

Scoring	Interpretation
Low risk = 0	1.1%-1.5% risk of complication within 7 days
Intermediate risk = 1-2	4%-6.2% risk of complication within 7 days
High risk = ≥3	34%-95% risk of complication within 7 days

Source: Ann Emerg Med. 2017;69(6):755-64. doi: 10.1016/j.annemergmed.2016.11.007

G-CSFs : *dose and schedules of dose delivery*

Filgrastim (category 1)

- Daily dose of **5 mcg/kg** until p
  laboratory standards.
- Start the next day or up to 3-
  treat through post-nadir recc

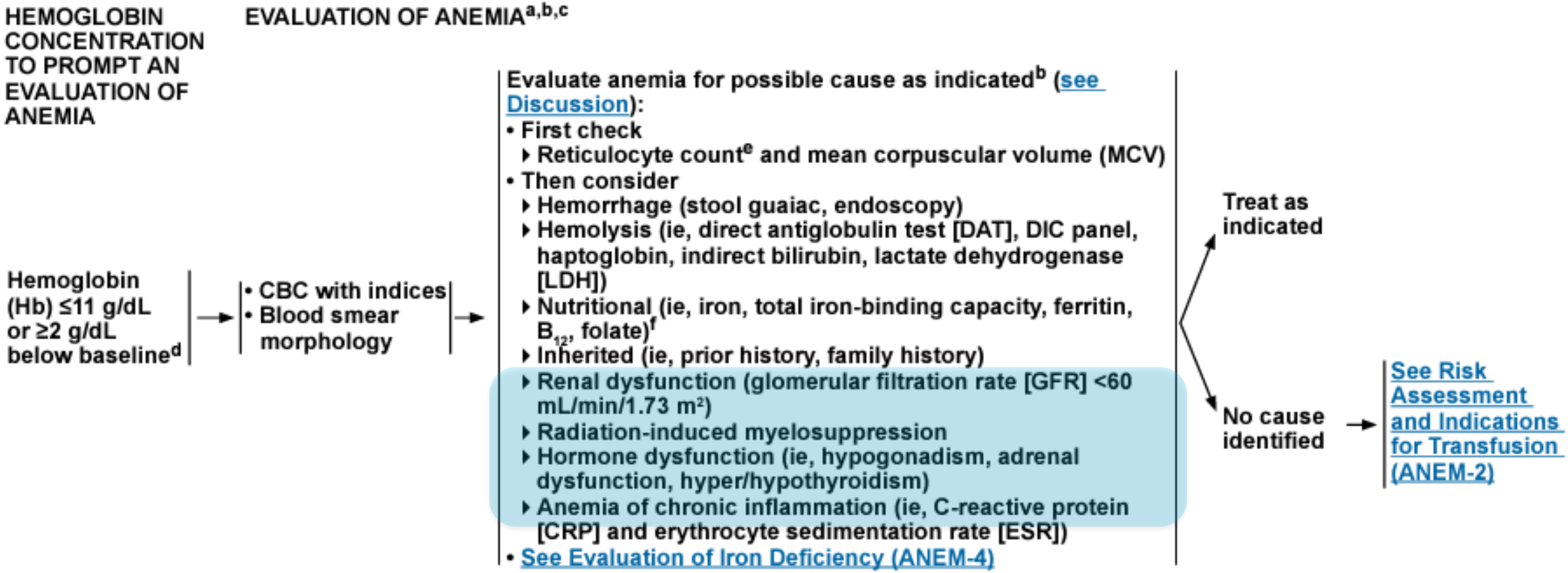
Pegfilgrastim (category 1)

- One dose of **6 mg**
- administered the day after m
- There should be **at least 12 d**
  chemotherapy.

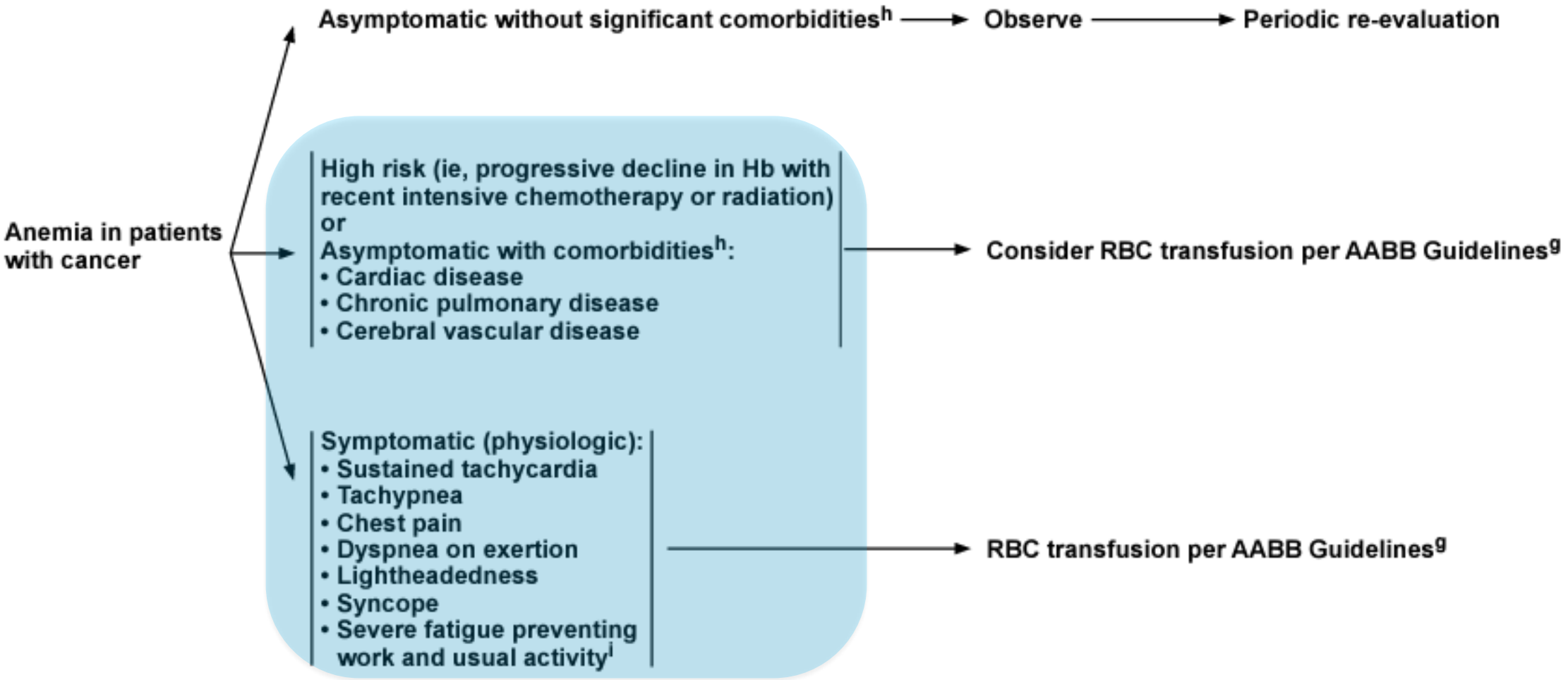
- **Toxicity**
- Warnings
  - **Allergic reactions**
    ◇Skin: rash, urticaria, facial edema
    ◇Respiratory: wheezing, dyspnea
    ◇Cardiovascular: hypotension, tachycardia, anaphylaxis
  - Splenic rupture
  - Acute respiratory distress syndrome
  - Alveolar hemorrhage and hemoptysis
  - **MDS and AML**
- Adverse reactions
  - **Bone pain**

NCCN guidelines V2. 2023, Hematopoietic Growth Factors

Anemia : *Evaluation*

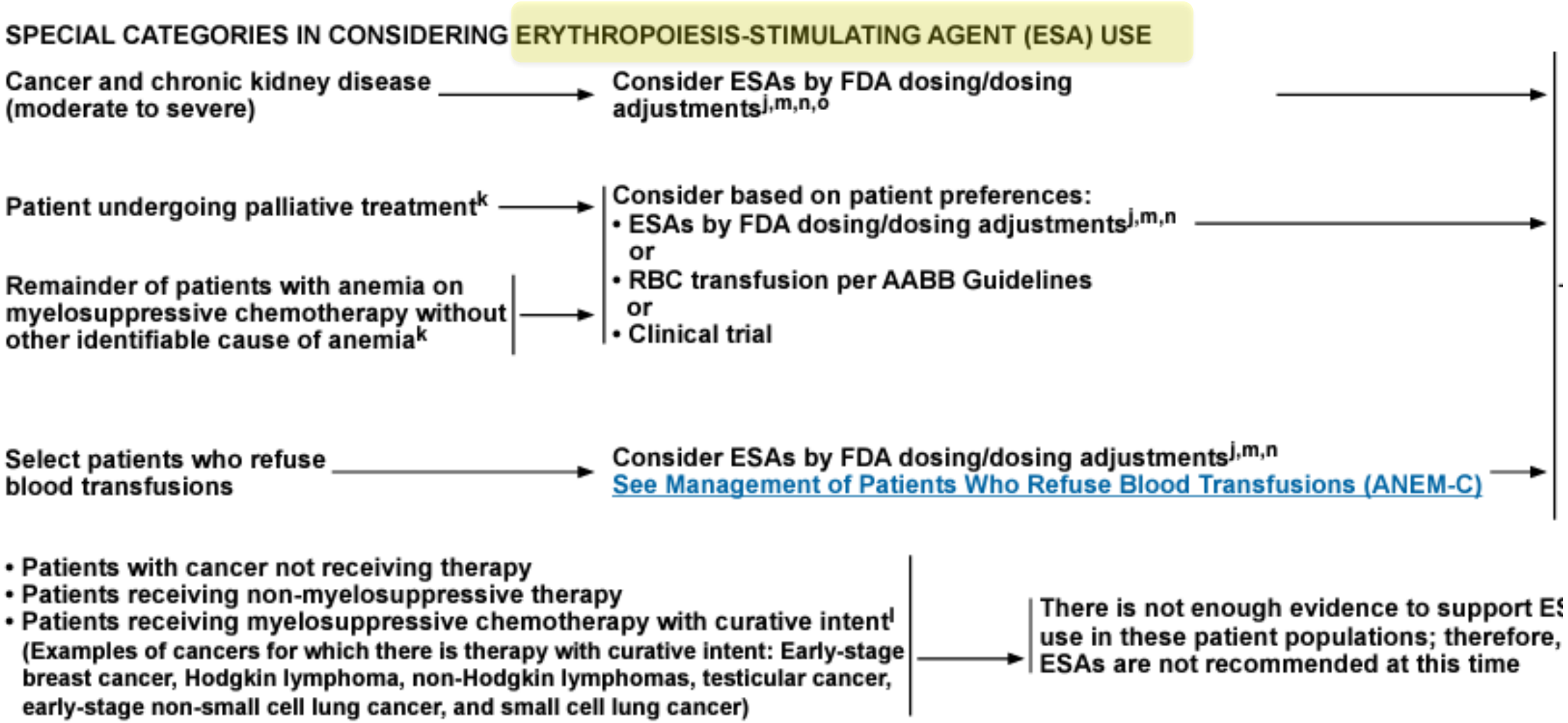


Anemia : *Risk Assessment and Indications for Initial Transfusion*



NCCN guidelines V2. 2023, Hematopoietic Growth Factors

Anemia : *Erythropoesis-Stimulating Agent (ESA) Use*

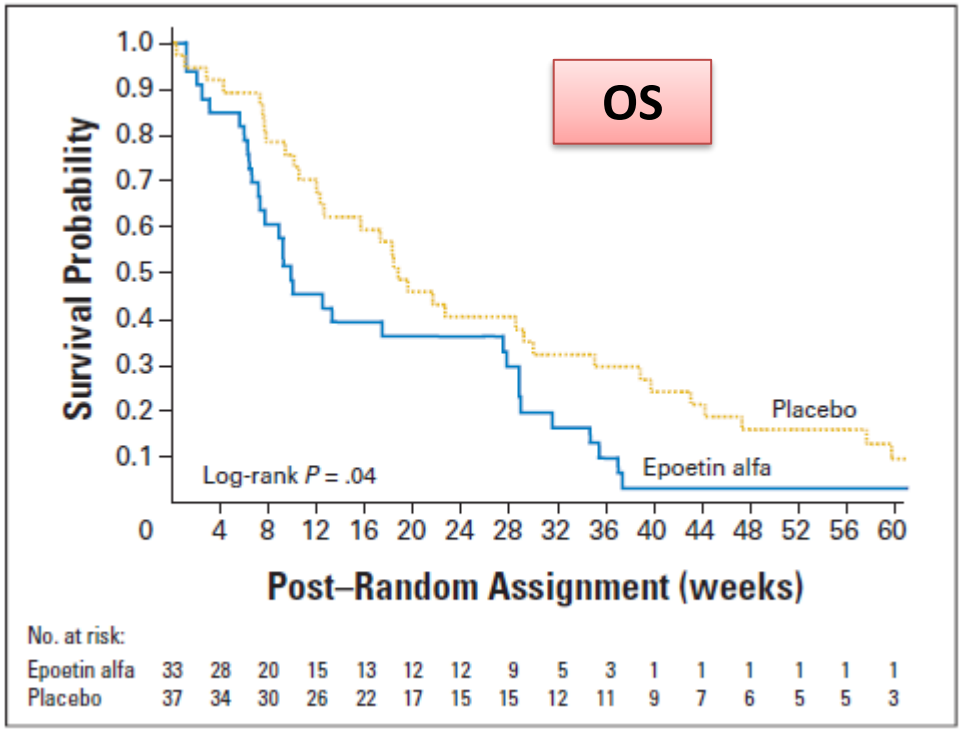


NCCN guidelines V2. 2023, Hematopoietic Growth Factors

Anemia : *Possible adverse effects of ESA*

Caution !!

- Possible **decreased survival** in patients with cancer receiving erythropoietic drugs for correction of anemia.
- Analyses of eight studies in patients with cancer found decreased survival in patients receiving erythropoietic drugs for correction of anemia and **target Hb levels of >12 g/dL.**



NSCLC patients unsuitable for curative therapy

NCCN guidelines V2. 2023, Hematopoietic Growth Factors; Wright JR, et al. J Clin Oncol 2007;25:1027-1032

CIN and Treatment Efficacy in NSCLC

RESEARCH Open Access

Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of 6 randomized trials

- Whole population : 1572
- Landmark population : 572 (6 cycles done, survival > 180ds)
- Median FU : 23.4 months

A

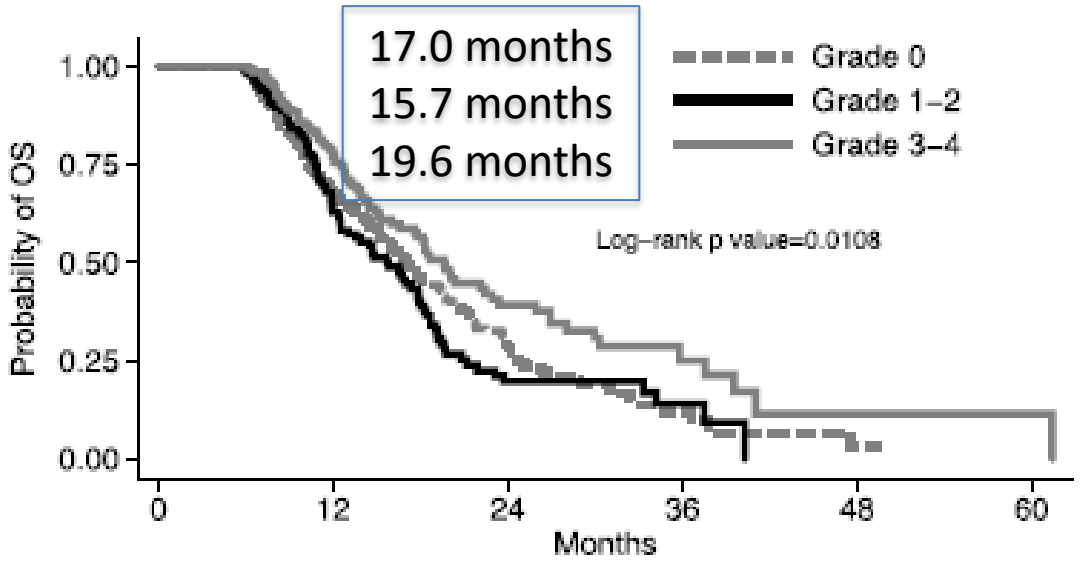


Table 3 Multivariable analysis of death in the landmark population

	Landmark population (358 events / 572 patients)		
	HR[a]	(95% CI)	*P*
Chemotherapy-induced neutropenia			0.048
Grade 1–2 vs 0	1.21	(0.92–1.58)	
Grade 3–4 vs 0	0.71	(0.53–0.95)	
Age (continuous)	1.03	(1.01–1.05)	0.002

Gargiulo P, et al. BMC Cancer 2021;21:549

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- ✓ Chemotherapy Induced Hematologic AE (neutropenia, anemia)
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- ✓ Chemotherapy Induced ILD
- ✓ Immune Related Adverse Events (irAEs)
- ✓ AEs by Targeted Therapies
- ✓ Takeaway messages

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

ASCO special articles

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

Charles L. Loprinzi, MD[1]; Christina Lacchetti, MHSc[2]; Jonathan Bleeker, MD[3]; Guido Cavaletti, MD, PhD[4]; Cynthia Chauhan, MSW[5]; Daniel L. Hertz, PharmD, PhD[6]; Mark R. Kelley, PhD[7]; Antoinette Lavino, BS Pharm, RPh[8]; Maryam B. Lustberg, MD[9]; Judith A. Paice, PhD, RN[10]; Bryan P. Schneider, MD[11]; Ellen M. Lavoie Smith, RN, PhD[6]; Mary Lou Smith, JD, MBA[12]; Thomas J. Smith, MD[13]; Nina Wagner-Johnston, MD[13]; and Dawn L. Hershman, MD[14]

Clinical manifestations

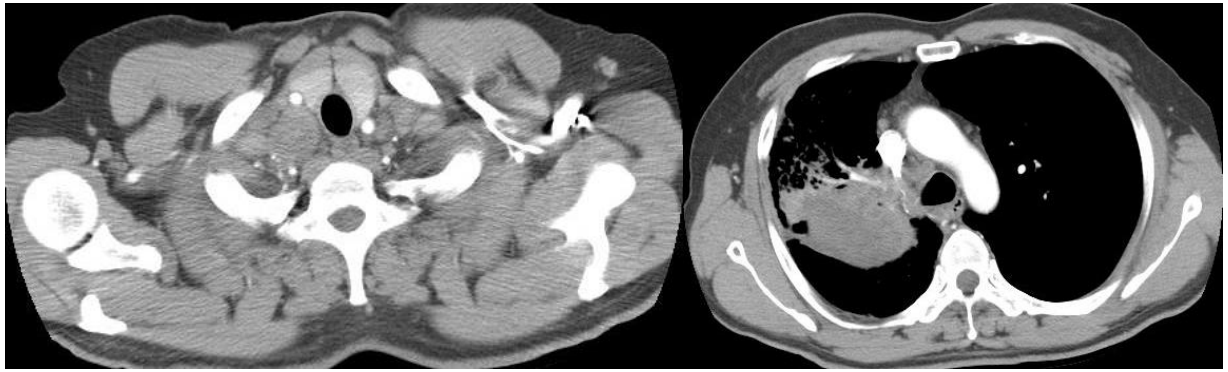
- Paclitaxel induced **acute** neuropathy
  - peaking approx. 2-3 ds after each dose
  - pain occurring in a truncal/hip distribution
  - arthralgia and myalgia feeling
  - tend to resolve more btw doses
  - not worsened in subsequent cycles
- Paclitaxel induced **chronic** neuropathy
  - primarily sensory (lower extremities >> upper)
  - numbness, tingling, and pain
  - stocking-glove distribution (from fingers and toes)

Prognosis and Impacts of chronic NP

- improve, on average, over several months
- Markedly affect the QoL of patients
- may be detrimental to cancer outcome

J Clin Oncol 2020; 38:3325-3348

CASE #1, 41/M

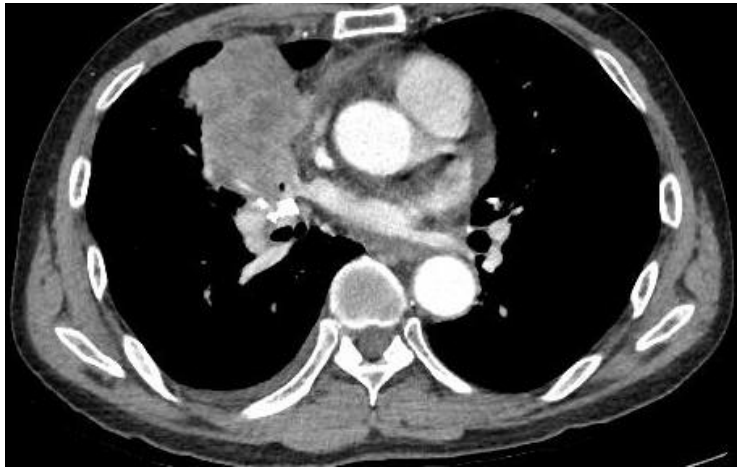


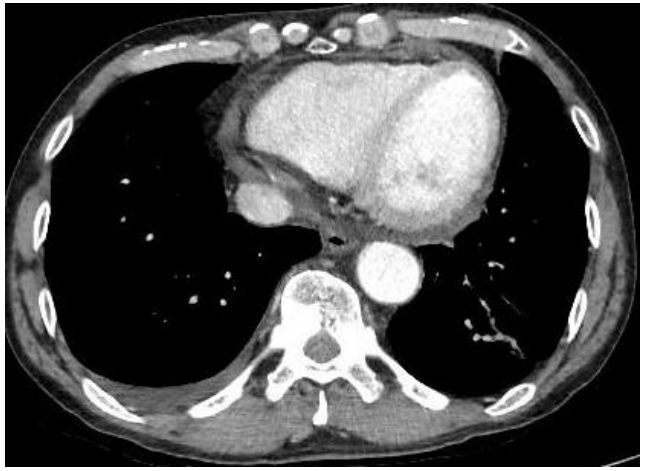
Clinical course

- 06.12 Sq. cell ca. T4N3M0 (IIIc)
  - Docetaxel/cisplatin CCRT and consolidation chemo : 2006.12-07.3
  - 2007.7-10 Gemcitabine/carboplatin #5
  - Severe neuropathic pain

	*		주▶ C34.09 Malignant neoplasm of main bronchus, unspecified sid
	*		E78.8 Other disorders of lipoprotein metabolism
			◆주치의 ☞MED62 이현경
1	M	1	Targin CR 10/5mg/T(마약,먼디파마) 1 TB <원내:45> 마약
			*04 아침 점심 저녁식후 30분, 자기전 PO for 168 Days
		2	Gabapentin 400mg/C(동아ST) 1 CP <원외>
	+		Sensival 25mg/T(일성신약) 0.50 TB <원외>
			*03 아침 점심 저녁식후 30분 PO for 168 Days
		3	Mago 500mg/C(한국파마) 1 CP <원외>
			*02 아침 저녁식후 30분 PO for 168 Days
		4	Nucynta ER 50mg/T(얀센) 1 TB <원내:45> 마약
			*02 아침 저녁식후 30분 PO for 168 Days
2	R	1	Chest-Low dose CT 예약:2023.08.21 14:20
			(2023-08-21)
			☞lung cancer, CR 상태
		2	Chest P-A view
			(2023-08-28)
			☞lung cancer, CR 상태

CASE #2, 66/M





Clinical course

- 2021.4 Sq. cell ca. cT3N3M1a
  - 2021.4-8 Gem/cis #6
  - 2021.11 Tecentriq #1 : hyperPD
  - 2022.3. Paclitaxel/carbo 2nd cycle
  - 손발저림, 다리 감각저하가 심함
  - 2022.7 산책하다 넘어져서 발목골절 발생

1	M	1	Cymbalta 60mg/C(릴리) 1.00 CP <원외>
			*01 아침식후 30분 PO for 35 Days
		2	Trileptal 필름코팅 150mg/T(노바티스) 1 TB <원외>
			*02 아침 저녁식후 30분 PO for 35 Days
		3	Lyrica 150mg/C(비아트리스) 1 CP <원외>
			*02 아침 저녁식후 30분 for 35 Days
		4	M-cobal 500mcg/C(동화) 1 CP <원외>
			*02 아침 저녁식후 30분 for 35 Days

Evaluation of the CIPN : *CTC-AE ver 5.0 and Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group-Neurotoxicity (Ntx)*

Grade	Description
Grade 1	Asymptomatic (E.g., Loss of deep tendon reflexes)
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	-

ADL: Activities of daily living

CTCAEv5.0 grading for peripheral sensory neuropathy

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Calhoun EA, et al. Int J Gynecol Cancer. 2003 Nov-Dec;13(6):741-8

CIPN : *Prevention (ASCO guideline 2020)*

Recommendation

1.1 **Assess the risks and benefits** of agents known to cause CIPN

- among patients with ***underlying neuropathy***
- with conditions that ***predispose to neuropathy*** such as diabetes and/or a family or personal history of hereditary peripheral neuropathy (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

1.2 Clinicians **should not offer**, and should discourage use of, **acetyl-L-carnitine** for the prevention of CIPN in patients with cancer (Type of recommendation: evidence based, harms outweigh benefits; Evidence quality: high; Strength of recommendation: **strong**

1.3 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the prevention of CIPN:

- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

1.4 Clinicians should not offer to prevent CIPN

- ATRA. Amitriptyline, Ca/Mg, Gabapentin/pregabaline, Goshajinkigan (우차신기환), Omega 3, Vit B,E, Venlafaxine(Efexor)

J Clin Oncol 2020; 38:3325-3348

CIPN : *Treatment (ASCO guideline 2020)*

Recommendation

2.1 Clinicians should assess, and discuss with patients, the appropriateness of **dose delaying, dose reduction, or stopping chemotherapy** (or substituting with agents that do not cause CIPN) in patients **who develop intolerable neuropathy and/or functional nerve impairment** (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

3.1 For patients with cancer experiencing painful CIPN, clinicians may offer **duloxetine** (Type of recommendation: evidence based, benefits equal harms; Evidence quality: intermediate; Strength of recommendation: **moderate**).

3.2 Outside the context of a clinical trial, **no recommendations** can be made on the use of the following interventions for the treatment of CIPN:

- Exercise therapy
- Acupuncture
- Scrambler therapy
- Gabapentin/pregabalin
- Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine
- Tricyclic antidepressants
- Oral cannabinoids

J Clin Oncol 2020; 38:3325-3348

CIPN : Duloxetine (SNRI)

- For Neuropathy

  - start 60mg, maximum 120mg qd (can be started with 30 mg)

- AE of Duloxetine (very common ≥ 10%)

  - insomnia

  - nasopharyngitis

  - weight loss and appetite

  - Somnolence, headache, dizziness

  - Nausea, abdominal pain, diarrhea, constipation, dry mouth

https://www.drugs.com/sfx/duloxetine-side-effects.html

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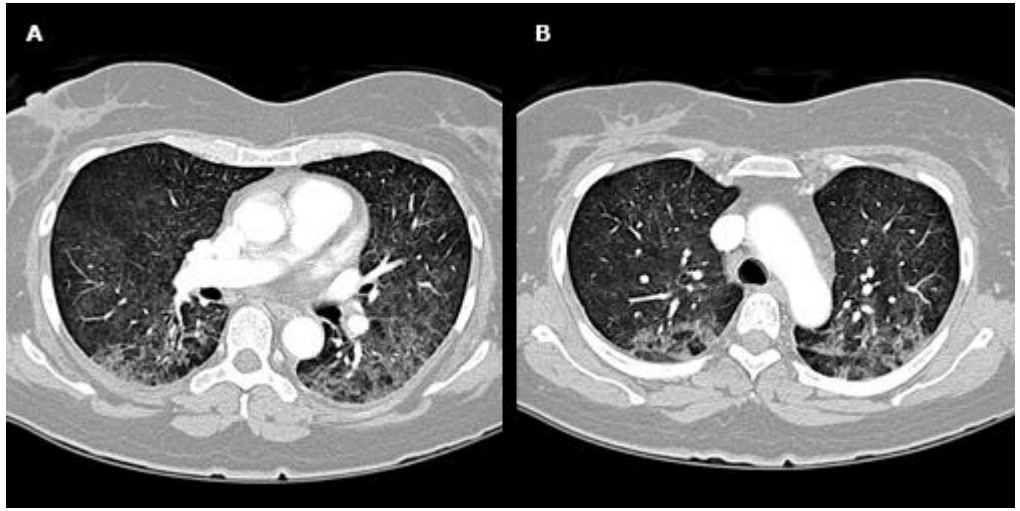
Chemotherapy Induced ILD

- Taxane (paclitaxel, docetaxel) : 1-5%, usually more frequent in weekly setting
- Pemetrexed
- Gemcitabine
- Irinotecan

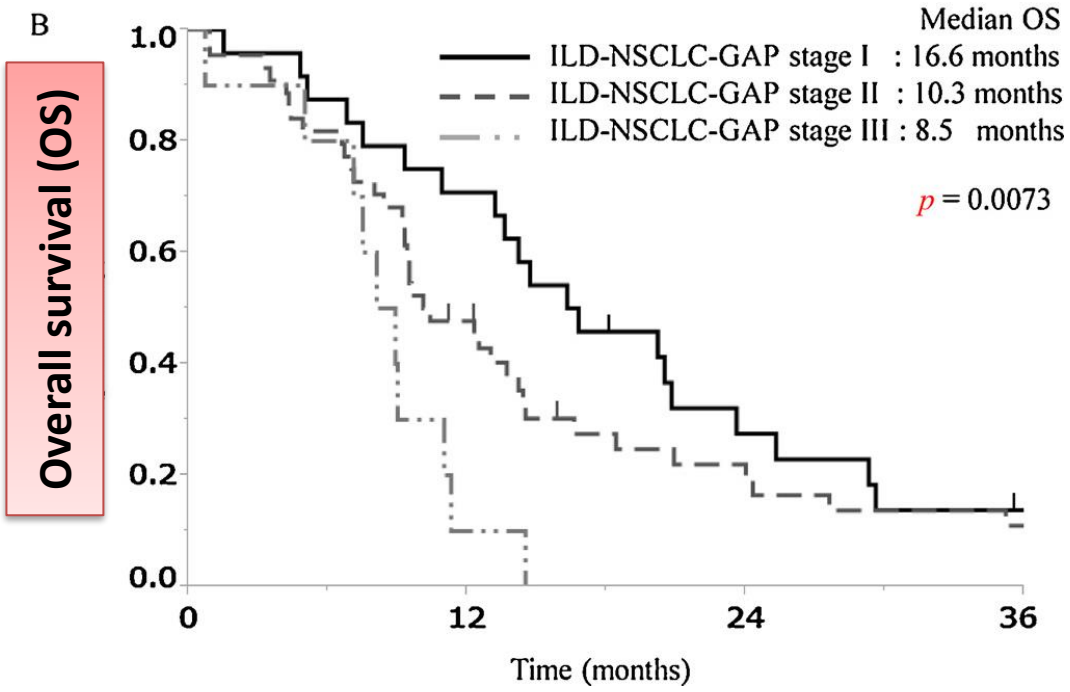


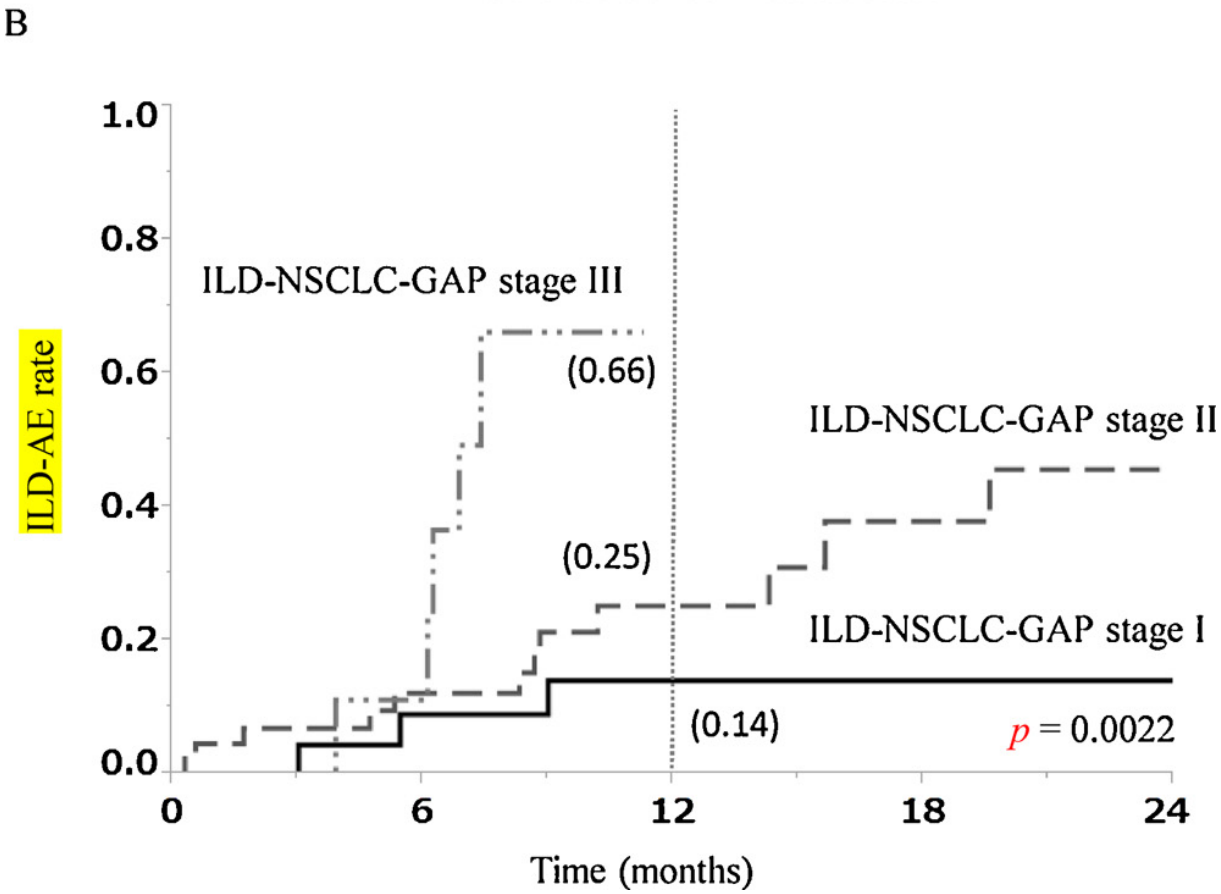
Uptodate.com accessed on July 2023

Prediction of AE-IPF and Survival on platinum based chemotherapy

ILD-NSCLC-GAP Index

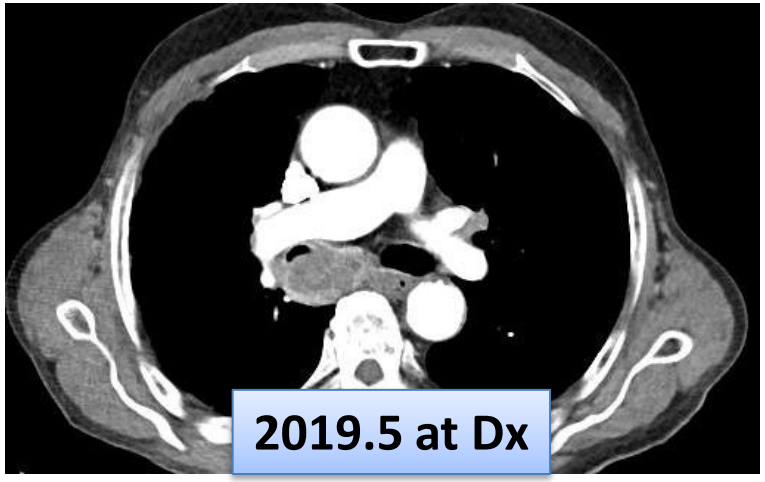
- Gender (female, 0; male, 1)
- Age (≤60,0; 61-65,1; >65, 2)
- FVC (%) (>75%,0; 50-75%, 1; <50%, 2)
- ILD subtype (IPF/UC-ILD, 0; non-IPF, -2)

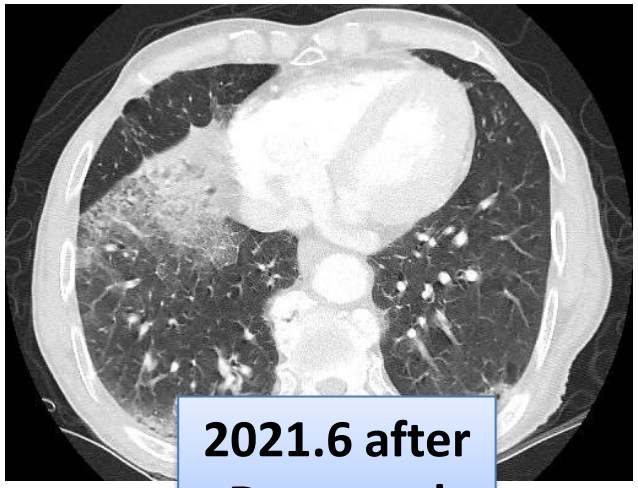


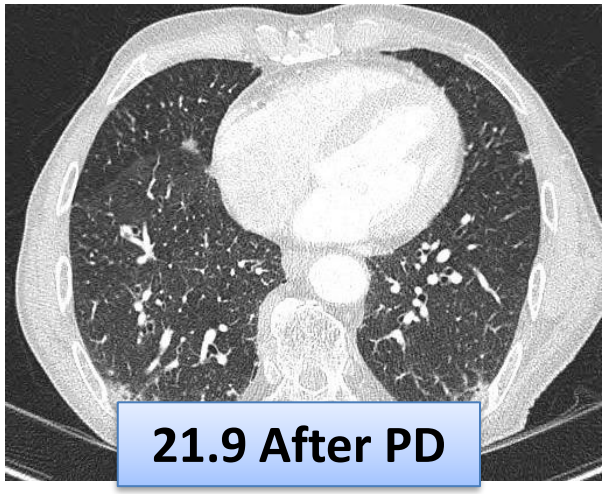


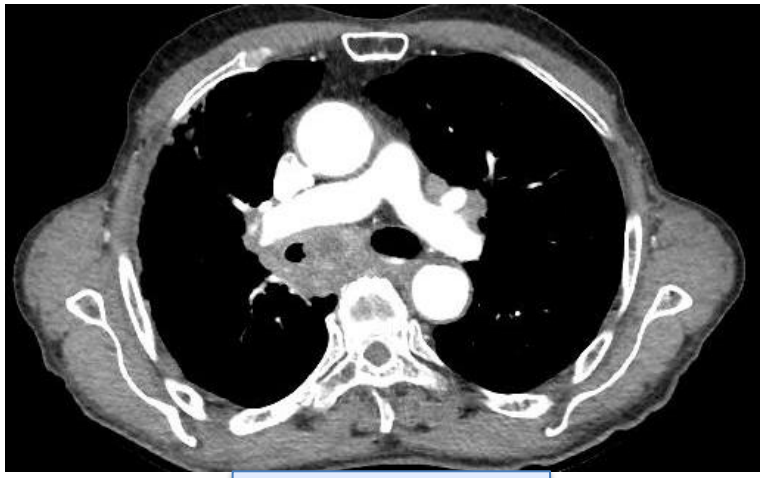
Kobayashi H et al, Lung Cancer 2018

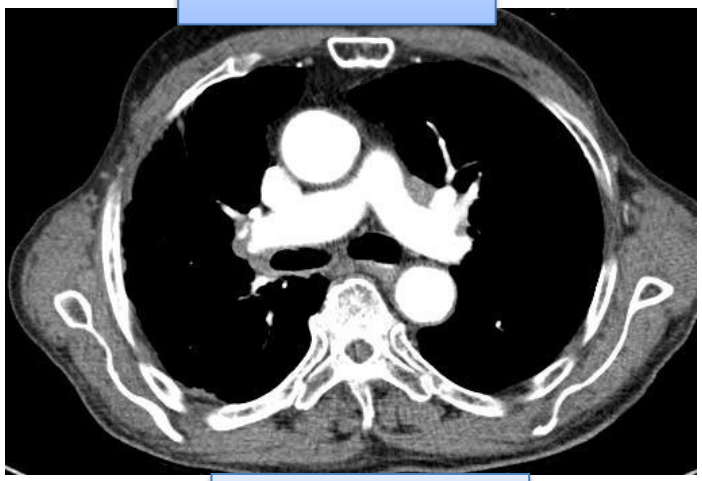
CASE #3, 87/M











Clinical course

- 2019.5 Sq. cell ca. cT2bN3M1a (left adrenal)
  - 2019.7.-20.1 Gem/carbo #5
  - 2020.9-21.2 Nivolumab #12
  - 2021.3-6 Docetaxel #4

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

Oct.2022

SPECIAL ARTICLE

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

J. Haanen[1†], M. Obeid[2,3,4†], L. Spain[5,6,7], F. Carbonnel[8,9], Y. Wang[10], C. Robert[11,12], A. R. Lyon[13,14], W. Wick[15,16], M. Kostine[17], S. Peters[4], K. Jordan[18,19] & J. Larkin[20], on behalf of the ESMO Guidelines Committee*

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

2021

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[6]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[1]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6]; Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19]; Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[20]; and Kathryn Bollin, MD[26]

The Spectrum of irAEs by organ systems

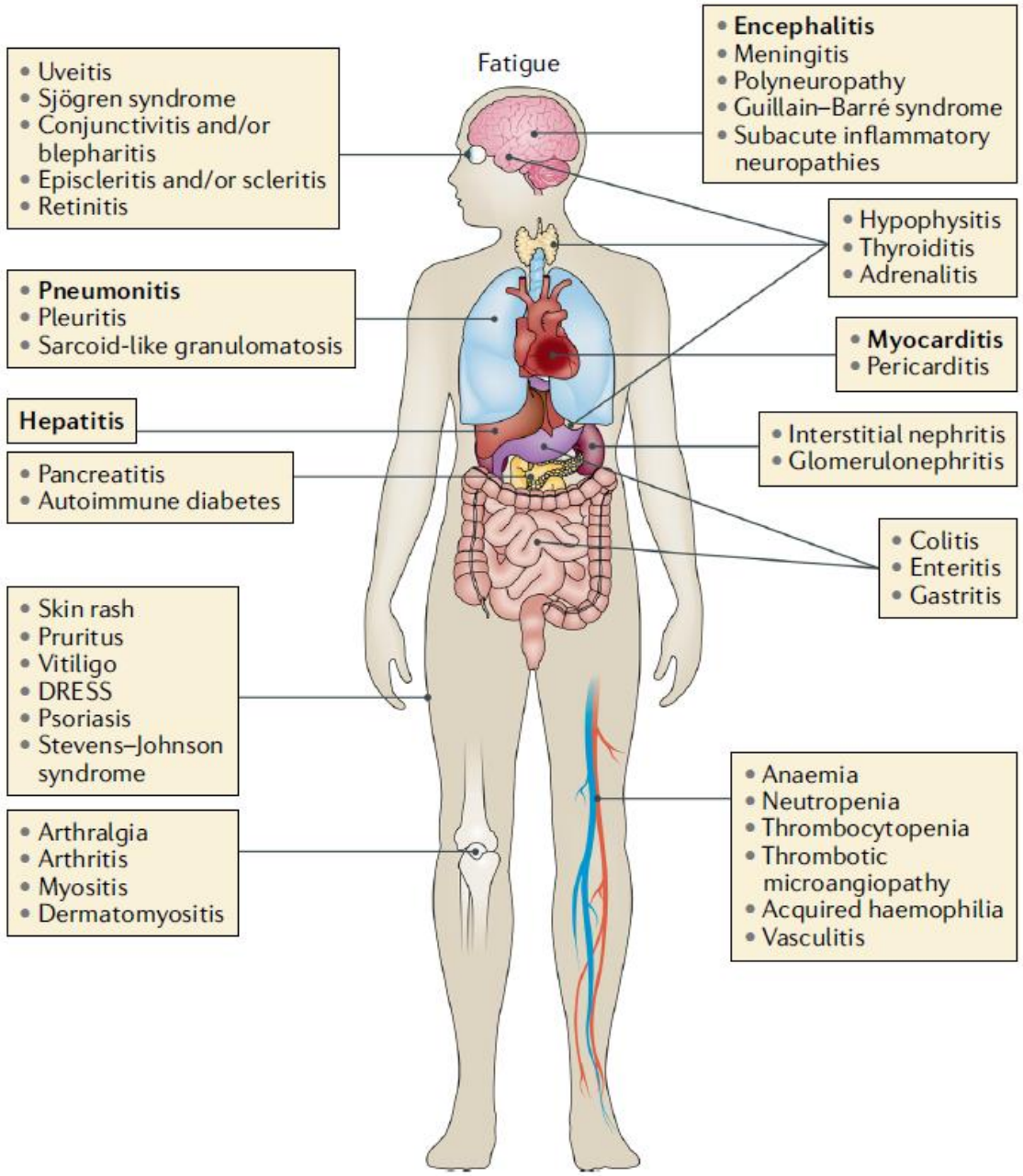
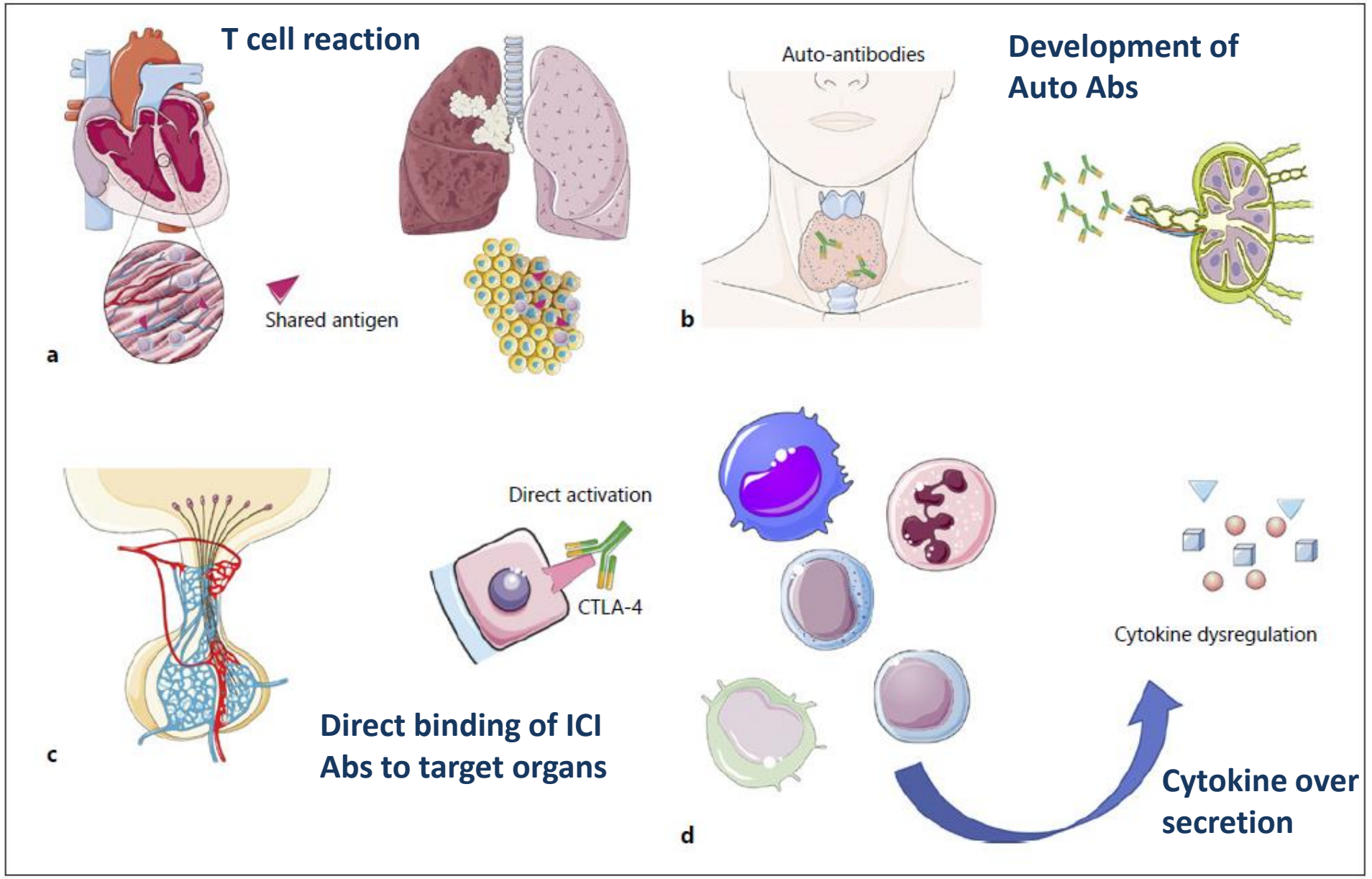


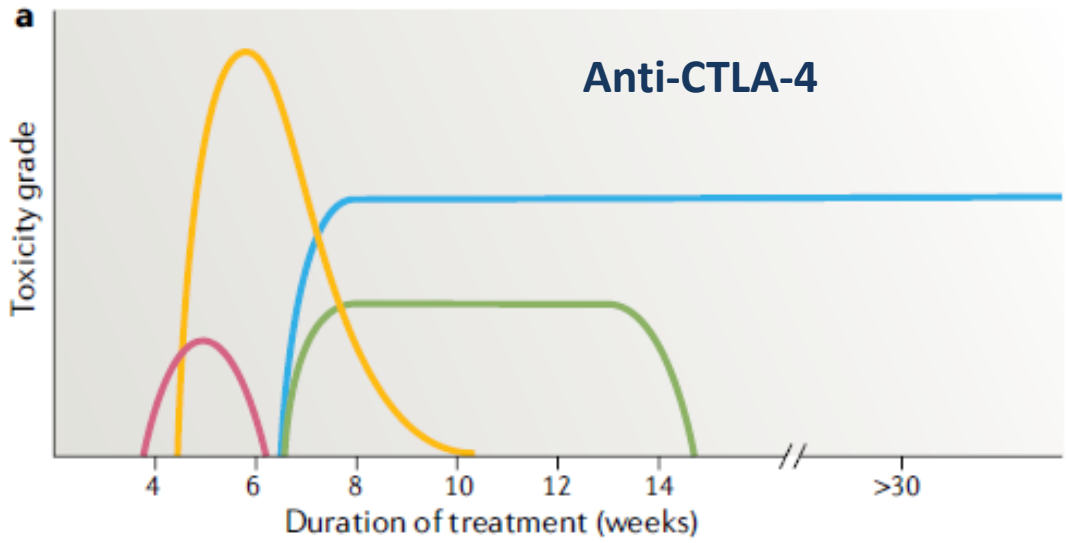
Fig. 2 | **The spectrum of irAEs by affected organ or organs.** Immune-checkpoint inhibitors (ICIs) promote the activation and expansion of T cells. Owing to the diversity of the T cell population and the ability of these cells to infiltrate most organs, ICIs can cause a wide range of immune-related adverse events (irAEs), and these can affect virtually any organ. The most frequently affected organs and the most common specific irAEs are highlighted in boxes. irAEs contributing to most fatalities are highlighted in bold. DRESS, drug rash with eosinophilia and systemic symptoms.

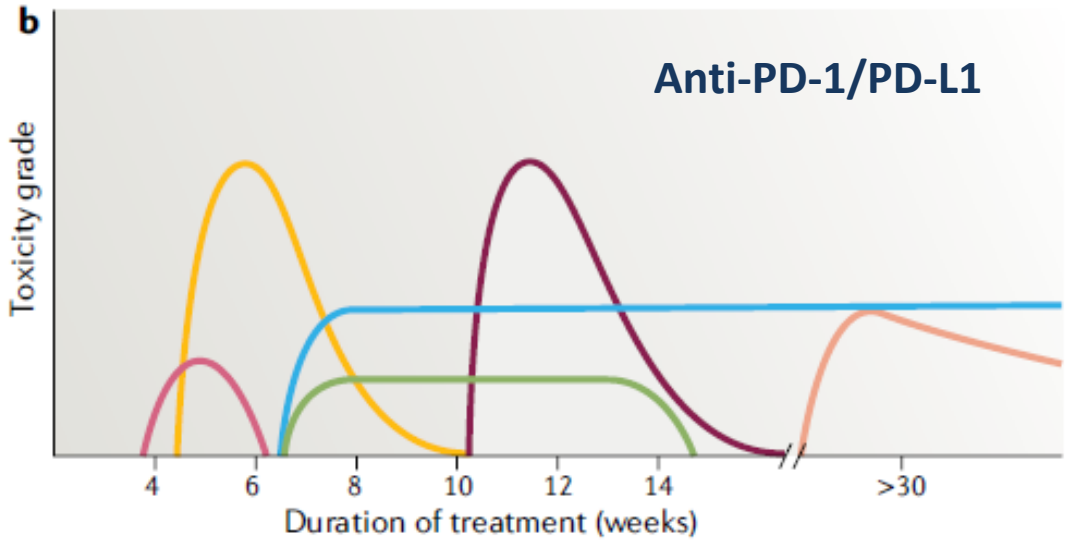
Nature Reviews 2020; https://doi.org/10.1038/s41571-019-0218-0

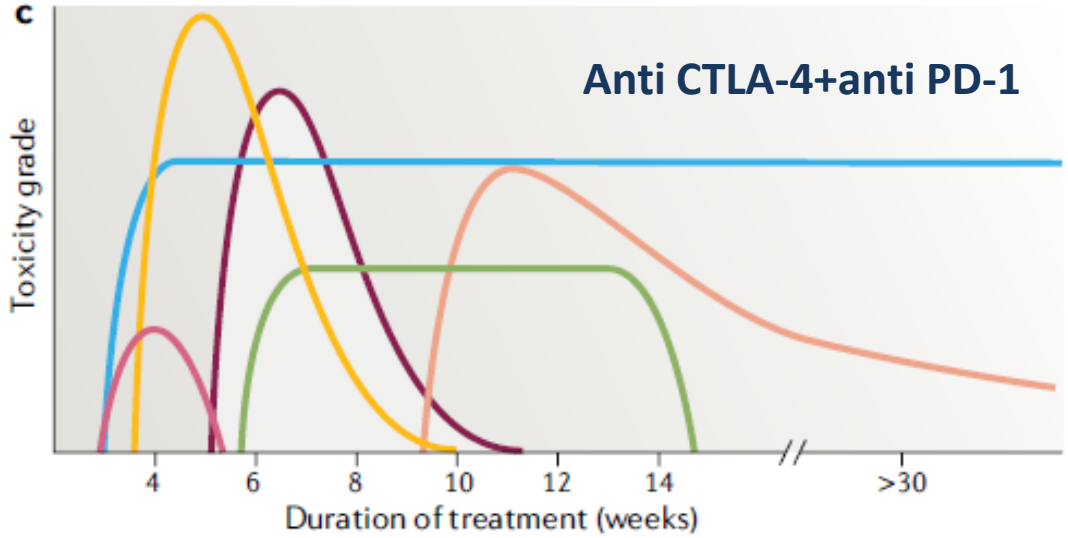
Proposed Mechanisms of irAEs

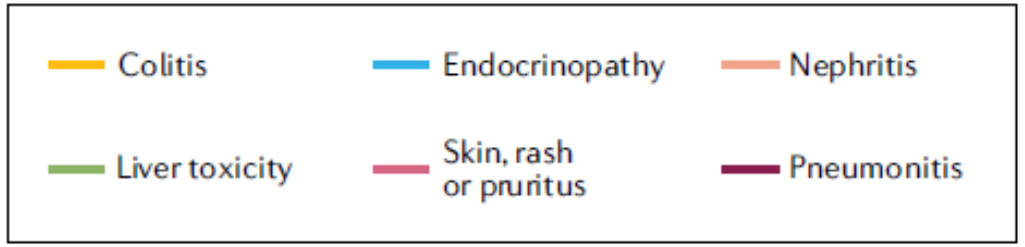


Time sequence of irAEs





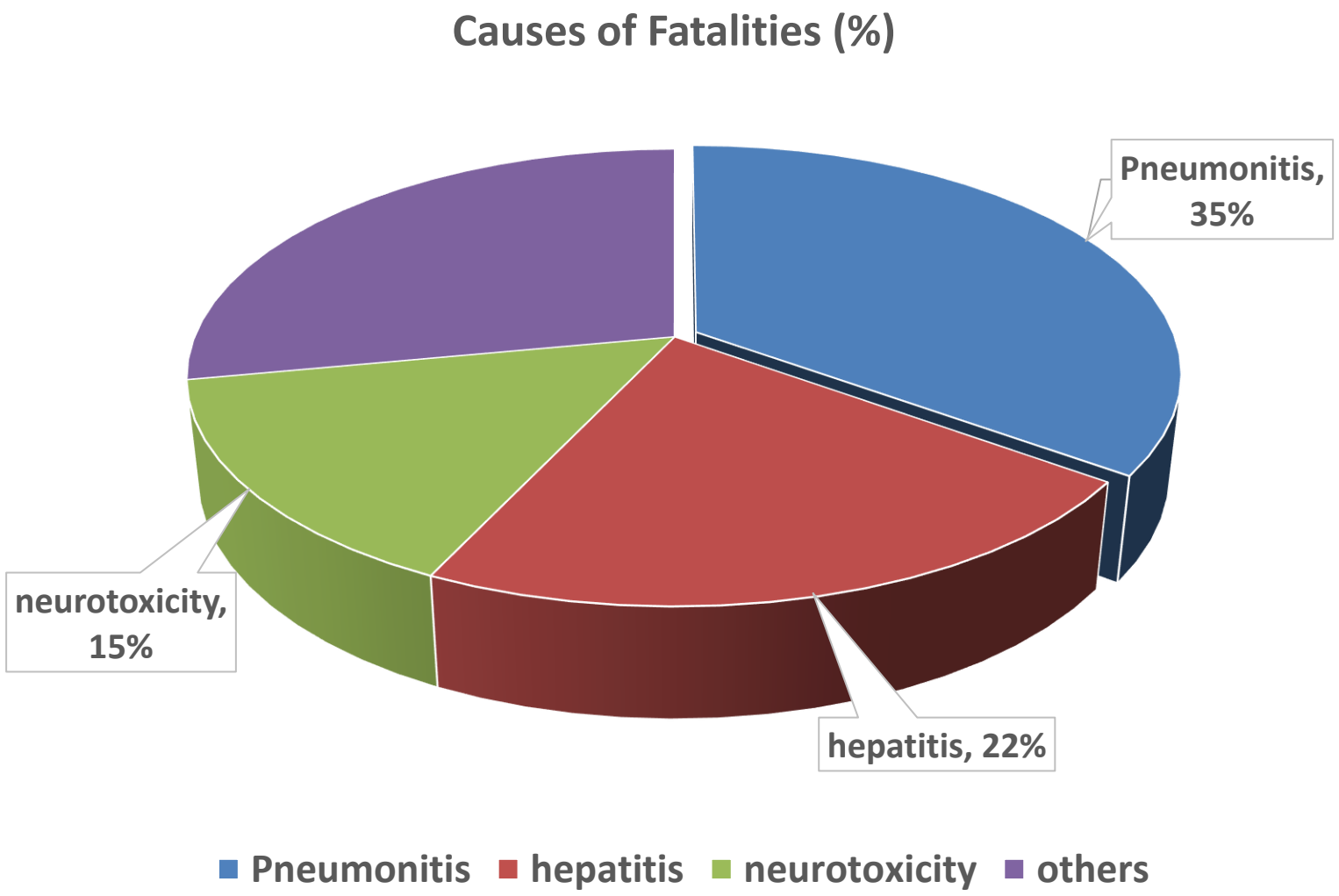




- Chemo+IO combination vs chemotherapy (KN-407)
  : rate of Gr3 and above AEs were similar

Nature Reviews 2020; https://doi.org/10.1038/s41571-019-0218-0

Most common causes of Fatality among anti-PD1 or anti-PDL1 Abs



Most irAEs occur within the first 6months

Nature Reviews 2020; https://doi.org/10.1038/s41571-019-0218-0

General Recommendations for irAEs

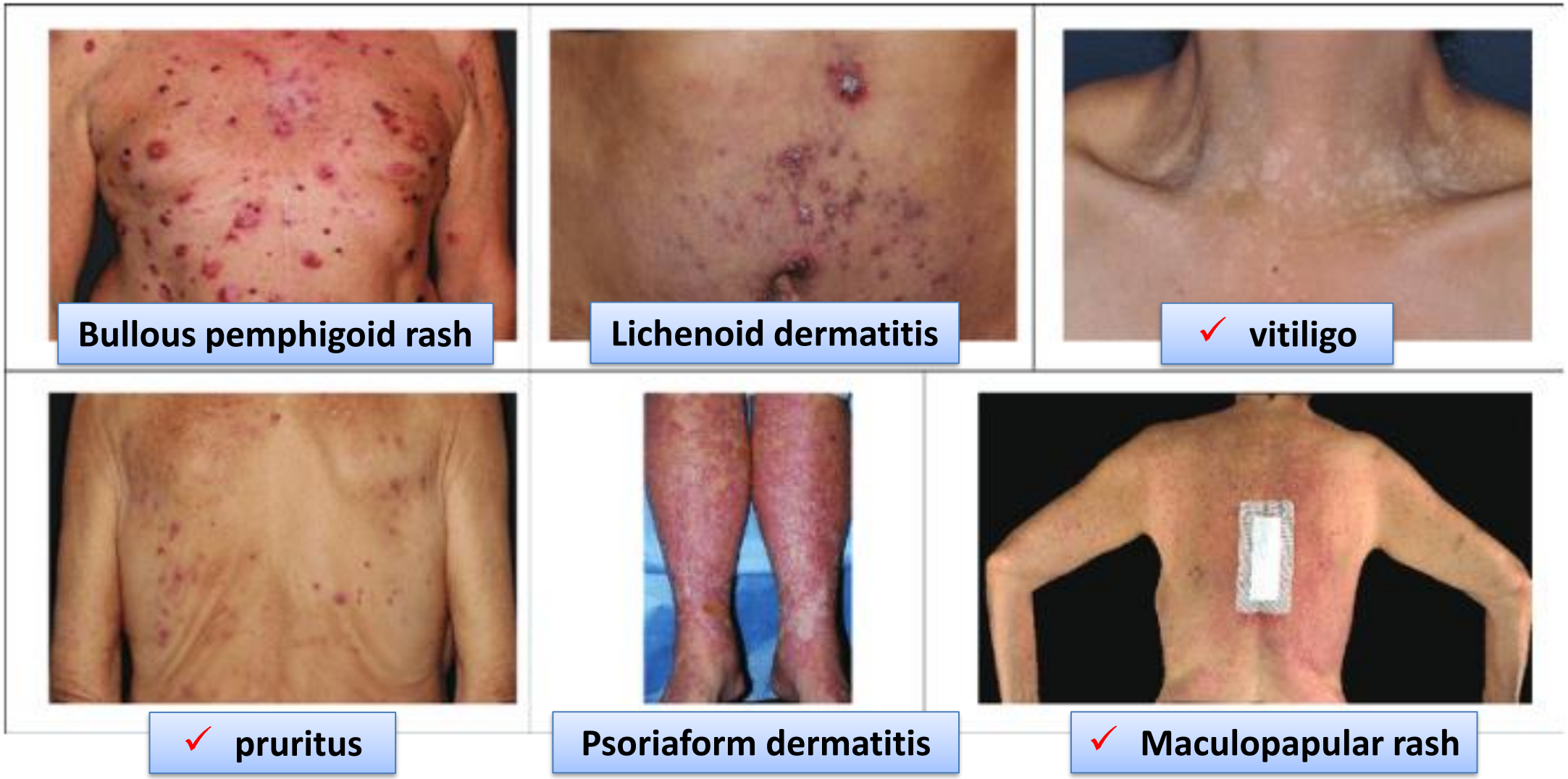
- **EDUCATE** to patient about immunotherapy, their mechanism of action, and possible irAEs
- **General consensus** of management for irAEs
  - Early recognition to limit the need for treatment interruption
  - Preserve QoL
  - Avoid or minimize the risk of rare fatal outcomes

- **Gr 1** : **CONTINUE** ICIs (except some neurologic, hematologic, and cardiac toxicities)
- **Gr 2** : **HOLD** and resume when symptoms and/or lab values ≤ Gr 1.

  Corticosteroids : 0.5-1 mg/kg/d of prednisolone
- **Gr 3** : **HOLD** and high-dose CS 1-2 mg/kg/d and taper over at least 4-6 wks
- RECHALLENGE : may be offered with caution when symptoms and/or lab values ≤ Gr 1
- **Gr 4** : **Permanent DISCONTINUE** of ICIs except endocrinopathies

Schneider BJ, et al. J Clin Oncol 2021; 39:4073-4126

Cutaneous Toxicities (1)



Brahmer JR, et al. Journal for ImmunoTherapy of Cancer 2021;9:e002435

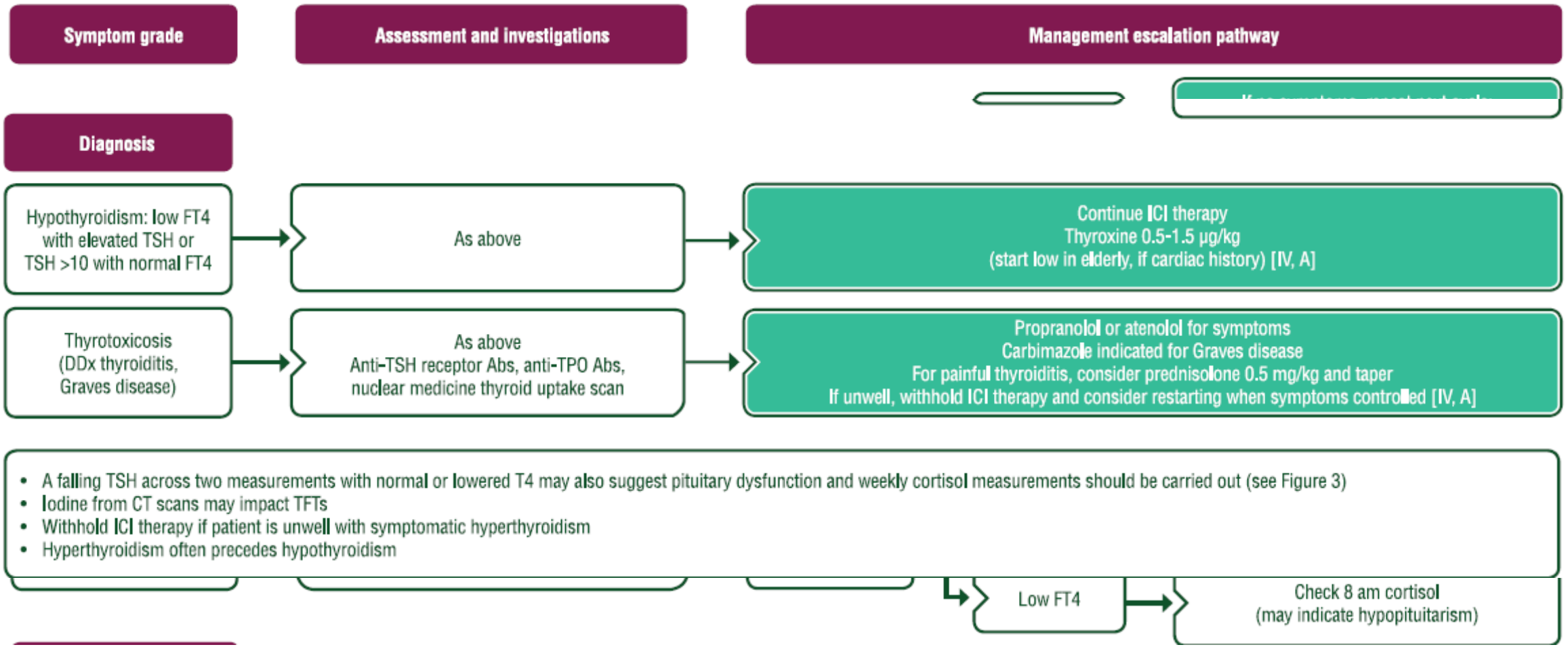
Cutaneous Toxicities (2)

- **Rash or inflammatory dermatitis**
  - G3 (>30% BSA) : hold but can be resumed if downgraded to ≤ G1
  - G4 : admission, urgent consult to dermatologist

    switch to alternative antineoplastic therapy > restart
- **Bullous Dermatoses**
  - G4 (> 30% BSA with fluid or electro. abnl.) : permanently D/C ICIs
- **SCAR** (severe cutaneous adverse reaction) : SJS, TEN, DRESS, etc. <u>No G1,2</u>
  - G3 (skin sloughing covering < 10% BSA with mucosal involved signs) : Hold ICIs
  - G4 ≥ 10% : permanent D/C of ICIs

Schneider BJ, et al. J Clin Oncol 2021; 39:4073-4126

Endocrinopathy: Thyroid disorders



Haanen J, et al. Ann Oncol 2022; 33 (12)

Gastrointestinal Toxicities : Colitis

Grading	Management
All patients	**TALK to HCP immediately if …** Abdominal pain, nausea, cramping, blood or mucus in stool, or changes in bowel habits, fever, abdominal distension, or constipation
G1: increased of < **4 stools/d** over baseline; mild increased in ostomy output	**Continue ICIs** or may be held temporarily and resume Loperamide (if infection R/O)
G2 : **4-6 stools/d**, moderate increase	HOLD ICI until recovery to G1 / Loperamide (if infection R/O) Corticosteroids (1 mg/kg/d) / Consider adding anti-TNF (infliximab) or anti-integrin (vedolizumab) **Resuming ICIs may be considered** Consider **permanently D/C CTLA- agents for grade ≥ 2**
G3: **≥ 7 stools/d,** incontinence, hospitalization indicated, severe increased, limiting self-care ADL	Corticosteroids 1-2 mg/kg/d PD until improved to G1 Consider early introduction of infliximab or vedolizumab in addition to steroids in patients with high risk endoscopic features on initial endoscopy examination or inadequate response to steroids (persistent symptoms after 3 days)
G4:life-threatening; urgent intervention indicated	**Permanently discontinue treatment**. Should provide inpatient care. Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1 Consider early biologics (infliximab or vedolizumab) if inadequate response to steroids after 3 days.

Schneider BJ, et al. J Clin Oncol 2021; 39:4073-4126

Immune-Related Hepatotoxicity

	Symptom grade	Assessment and investigations	Management escalation pathway
3X	Grade 1: ALT or AST >ULN to 3x ULN	Monitor liver enzymes every 1-2 weeks	Continue ICI therapy [IV, A]
3-5X	Grade 2: ALT or AST 3-5x ULN	Check LFTs, INR and albumin twice weekly Review medications and alcohol history Carry out hepatitis B, C and E (and sometimes A) testing, PCR, anti-ANA, SMA, LKM, SLA/LP, LCI and iron studies Consider imaging for metastases and/or clot	Withhold ICI therapy Avoid hepatotoxic drugs If rising ALT and/or AST when re-checked, start CSs 0.5-1.0 mg/kg/day Upon improvement, resume ICI therapy after tapering CSs to <10 mg/day If no improvement despite steroid use, increase dose of CSs 1-2 mg/kg/day and discontinue ICI therapy [V, B]
5-20X	Grade 3: ALT or AST 5-20x ULN	Same work-up as for grade 2 Daily LFTs, INR and albumin Carry out liver US, CT scan or MRI Consider inpatient care and early hepatologist consultation Consider liver biopsy	Discontinue ICI therapy If ALT and/or AST <400 U/l with normal bilirubin, INR and albumin: CSs 1-2 mg/kg/day If ALT and/or AST >400 U/l or raised bilirubin/INR/low albumin: i.v. methylprednisolone 2 mg/kg [IV, B]
>20X	Grade 4: ALT or AST >20x ULN	As above	Discontinue ICI therapy i.v. methylprednisolone 2 mg/kg [IV, B]

CS wean:
- Grade 2: once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once tapering CSs to <10 mg/day
- Grade 3-4: once improved to grade 2, change to oral prednisolone and wean over 4 weeks; for grade 3, rechallenge only at consultant discretion

Worsening despite steroids:
- If on oral, change to i.v. methylprednisolone
- If on i.v., consider MMF 1000 mg b.i.d., tocilizumab 8 mg/kg, tacrolimus, azathioprine, cyclosporine or anti-thymocyte globulin (ATG, 100 mg divided over 2 days). Infliximab should not be used in patients with ICI-induced liver toxicity

G4: MMF, tacrolimus, tocilizumab, azathioprine, CsA, ATG, not infliximab

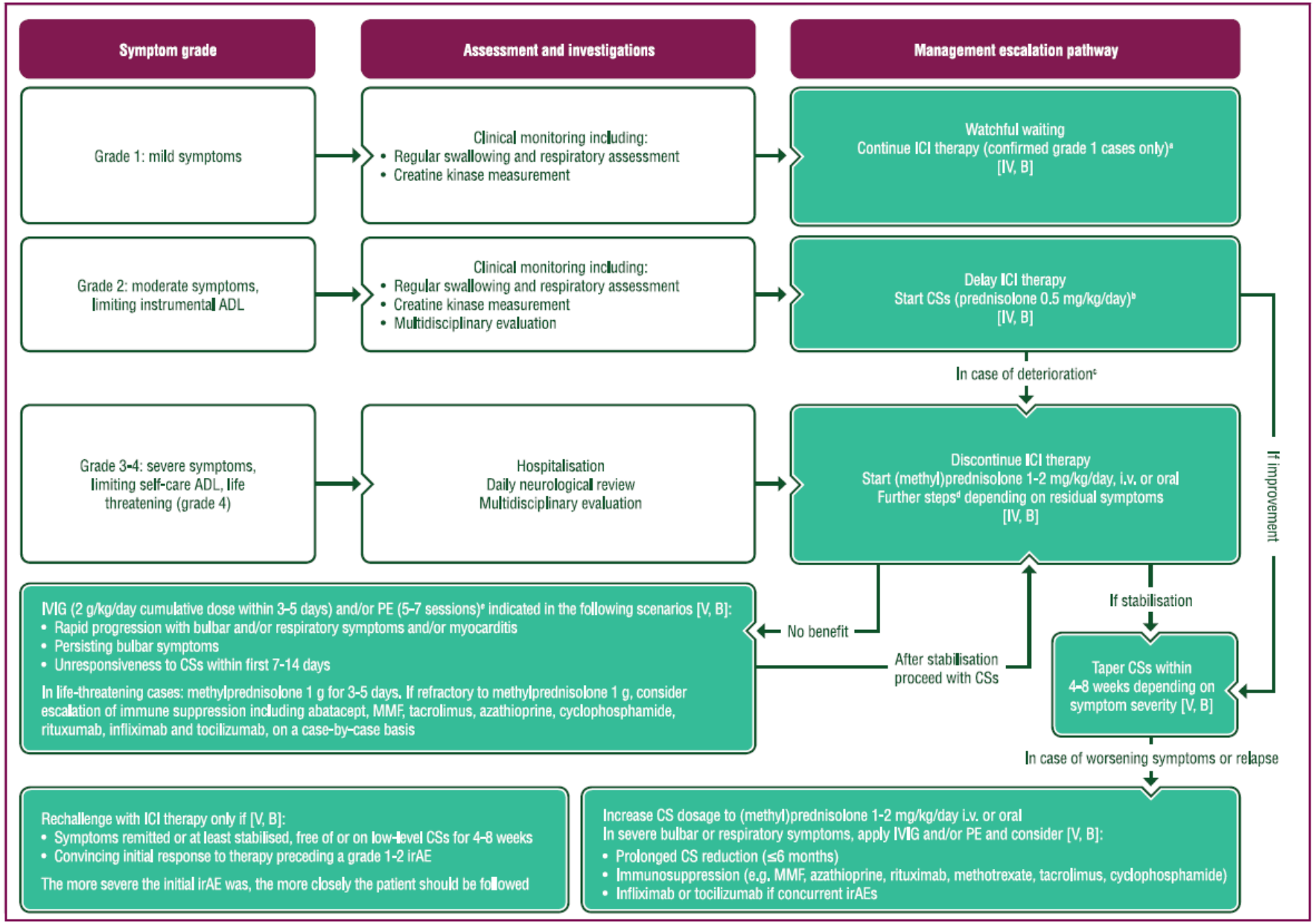
Haanen J, et al. Ann Oncol 2022; 33 (12)

Immune-Related (IR) Neurological Toxicity

- IR-Myasthenia Gravis-like syndrome
- Myasthenia-myositis-myocarditis overlap
- IR-peripheral neuropathy (GBS)
- IR-central neurological toxicity

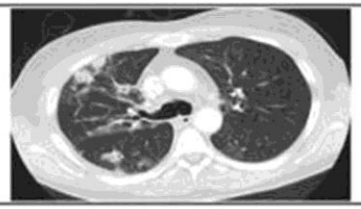
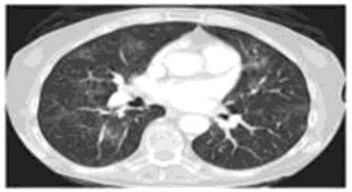
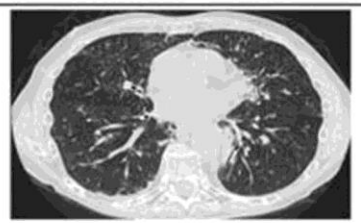
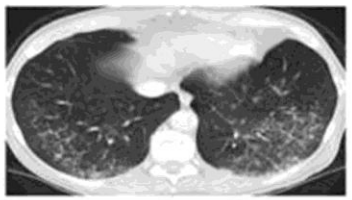
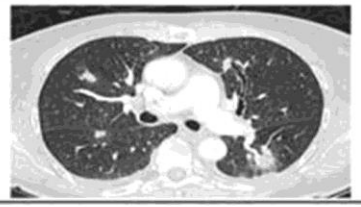
Haanen J, et al. Ann Oncol 2022; 33 (12)

Management of IR Neuro(muscular) Toxicity



Haanen J, et al. Ann Oncol 2022; 33 (12)

Radiologic Manifestations and Risk Factors of Checkpoint Inhibitor Pneumonitis (CIP)

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

RISK FACTORS of CIPs

- 1st line setting
- NSCLC > melanoma
- Chemotherapy induced inflammation
- Previous RT
- Underlying lung disease
- smoking

Nature Reviews 2020; https://doi.org/10.1038/s41571-019-0218-0 Julie R Brahmer et al. J Immunother Cancer 2021;9:e002435

Checkpoint Inhibitor Pneumonitis (CIP) : meta-analysis

- **Possibly safer regarding pneumonitis**

  Atezolizumab > nivolumab > pembrolizumab

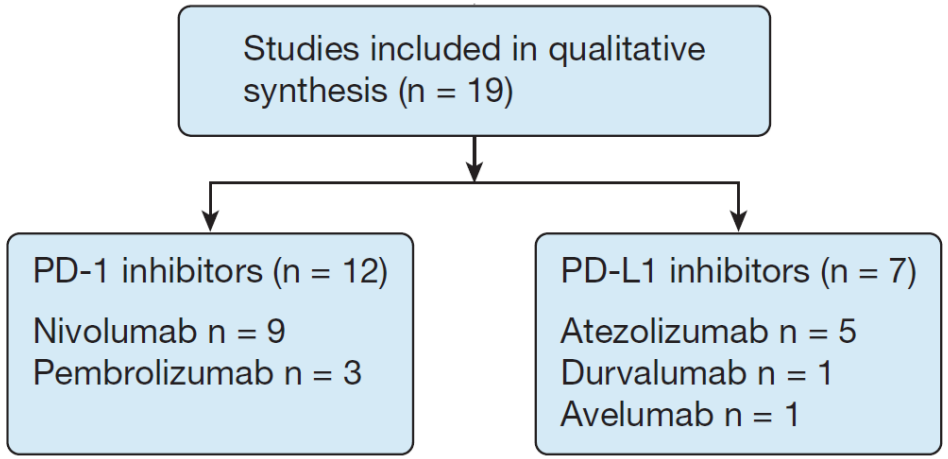
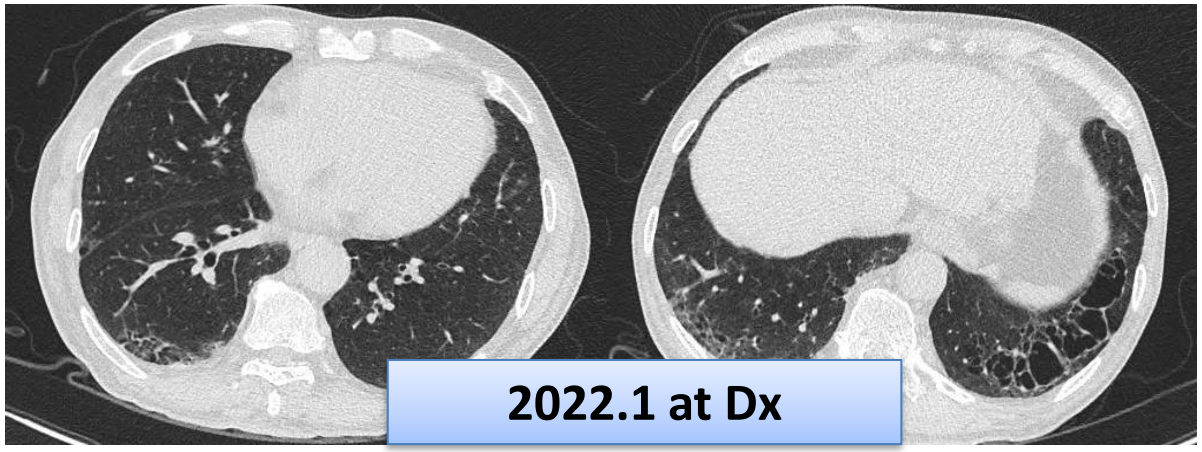


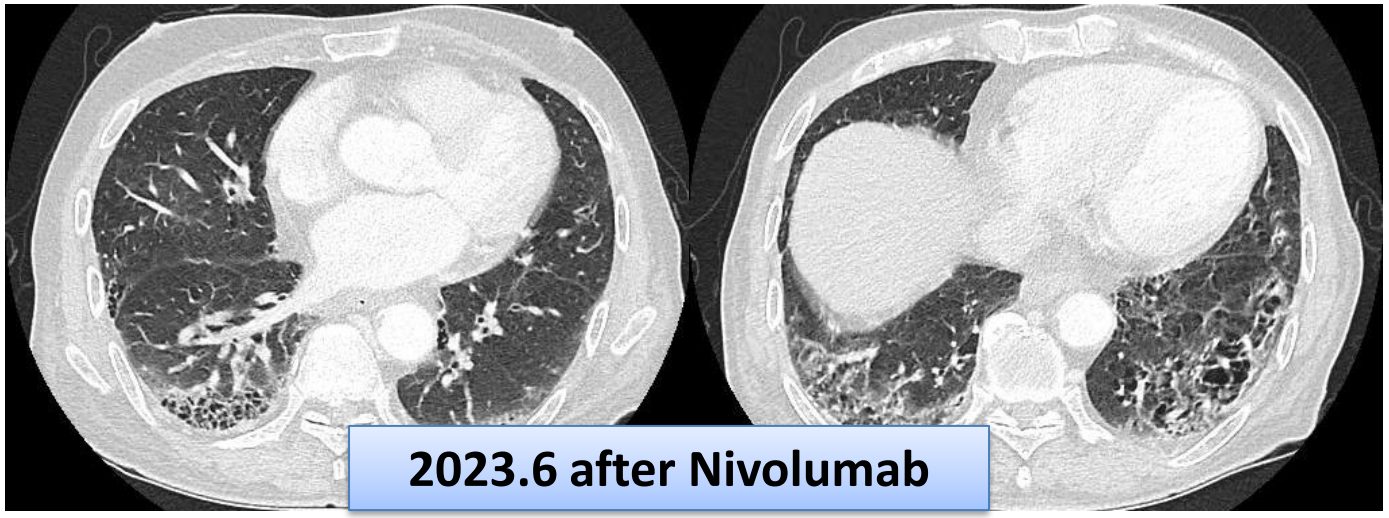
TABLE 2] Incidence of All Grade and Grade 3 or 4 Pneumonitis With PD-1 and PD-L1 Inhibitors and in All Treatment Naive and Previously Treated Patients

Patients	All Grade Pneumonitis (95% CI)	Grade 3-4 Pneumonitis (95% CI)
All patients treated with PD-1 inhibitors	3.6% (2.4%-4.9%)	1.1% (0.6%-1.7%)
All patients treated with PD-L1 inhibitors	1.3% (0.8%-1.9%)	0.4% (0%-0.8%)
P value, PD-1 vs PD-L1 inhibitor	.001	.02
All treatment naive patients	4.3% (2.4%-6.3%)	0.5% (0%-1.1%)
All previously treated patients	2.8% (1.7%-4%)	1% (0.5%-1.5%)
P valve, treatment naive patients vs previously treated patients	.03	.10

Khunger M et al, Chest, 2017

CASE #4, 74/M





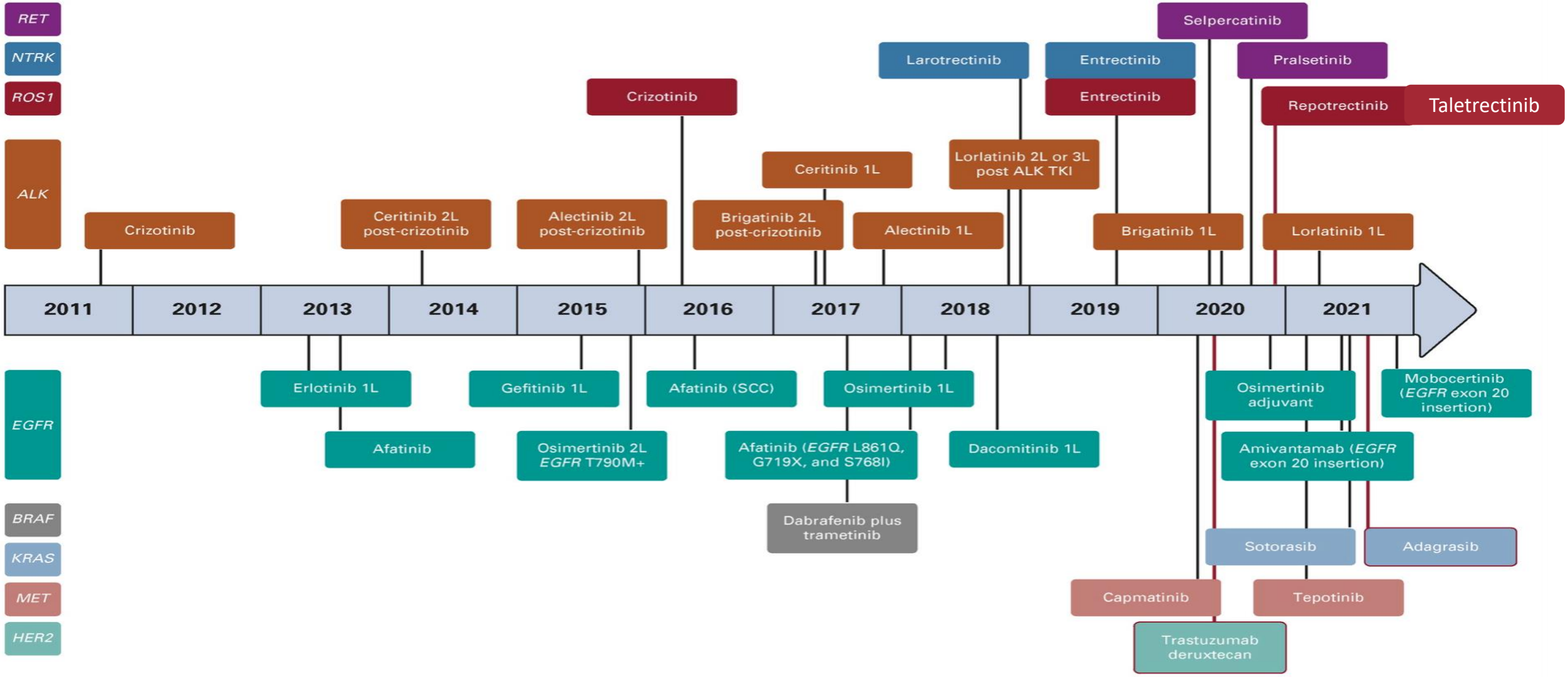
Clinical course

- 2022.2 adenoca, cT2bN2M1c
  - 2022.2.11 -9 Pem/carbo #10
  - 2022.9-23.5 Nivolumab #17

Contents

- ✓ Introduction
- ✓ Chemotherapy Induced Hematologic AE (neutropenia, anemia)
- ✓ Chemotherapy Induced Peripheral Neuropathy (CIPN)
- ✓ Chemotherapy Induced ILD
- ✓ Immune Related Adverse Events (irAEs)
- ✓ AEs by Targeted Therapies
- ✓ Takeaway messages

Timeline of FDA-approved Targeted therapies for oncogene-driven NSCLC



Tan AC. et al. J Clin Oncol 2022

* The red lines indicate breakthrough therapy designation.

Things to Remember at AEs by Targeted Therapies

- Dose modification (transient or permanent) is possible (vs ICIs).
- Don’t be hesitate to dose-reduction
  - evidences of comparable efficacy with the reduced dose are present.
- Shared decision making is essential
  - to alleviate anxiety of the patient
- Consider to improve QoL of the patient and PFS as well.
- Get help from experts of other areas
  - ex. dermatology, nephrology, cardiology, etc

Dose Modification : Afatinib (GIOTRIF®)

EGFR-TKI : 2G

GILOTRIF
40 mg tablet
Not actual size

GILOTRIF
30 mg tablet
Not actual size

GILOTRIF
20 mg tablet
Not actual size

Initiate

- Initiate therapy at the recommended 40-mg dose
- The recommended dosage of GILOTRIF in patients with pre-existing severe renal impairment is 30 mg orally once daily.*

Evaluate

- Evaluate patients for adverse reactions within 2 weeks and periodically thereafter

Pause

- Pause treatment for ≥grade 3 adverse reactions†
- Or ≥grade 2
  - diarrhea (prolonged)‡
  - cutaneous reactions (prolonged or intolerable)§
  - renal impairment

Resume

- Resume treatment at 10-mg less per day when adverse reaction fully resolves, returns to baseline, or improves to grade 1

Permanently discontinue GILOTRIF for: Life-threatening bullous, blistering, or exfoliating skin lesions; confirmed interstitial lung disease (ILD); severe drug-induced hepatic impairment; gastrointestinal perforation; persistent ulcerative keratitis; symptomatic left ventricular dysfunction; and severe or intolerable AR occurring at a dose of 20 mg per day.[1]

https://www.gilotrifhcp.com/dosing-and-administration

AEs and Efficacy after Dose Modification of the Afatinib

EGFR-TKI : 2nd G

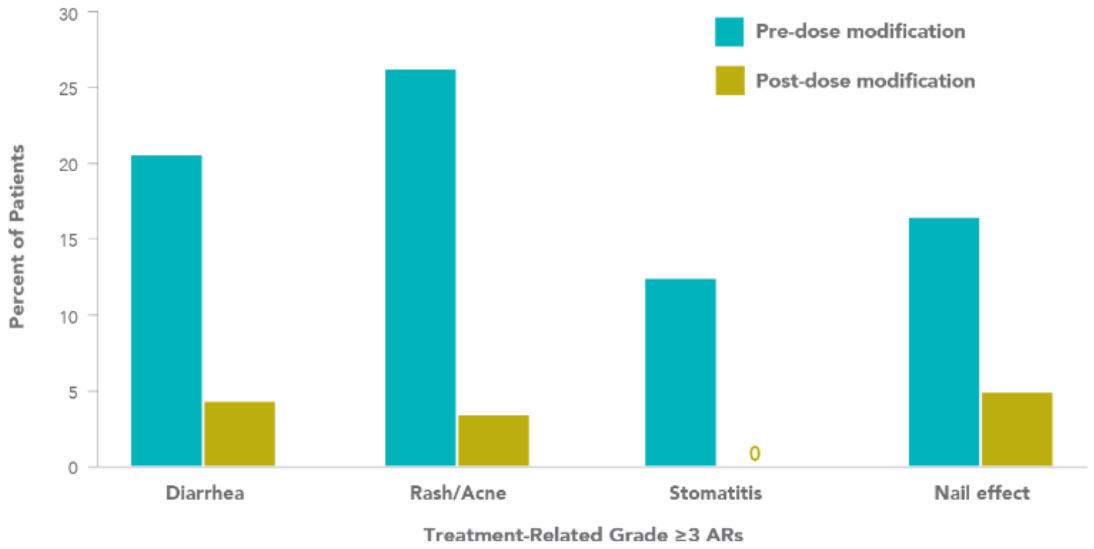
Rash,acne,diarrhea,paronychia,stomatitis

Reduced starting dose[1]

LUX-Lung 3: Over half of patients reduced their dose[1,5]

The most common Grade 3 ARs that led to dose reduction with GILOTRIF in the analysis were rash/acne (26.2%), diarrhea, (20.5%), paronychia (16.4%), and stomatitis (12.3%)[5]

Grade ≥3 ARs with dose adjustment[5,a,b]

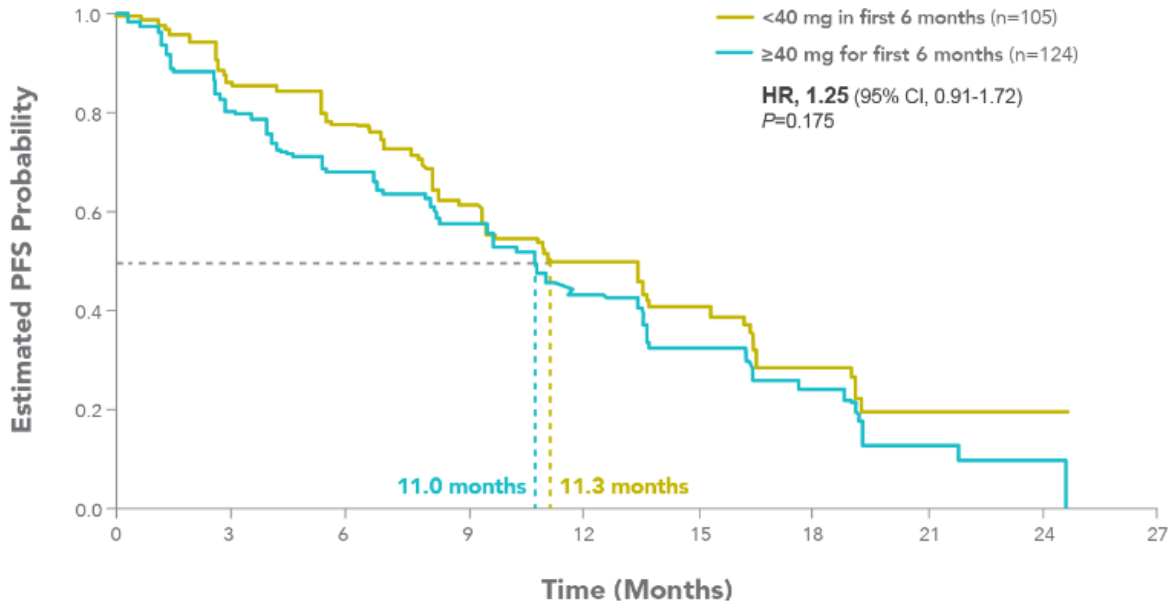


ARs=adverse reactions.

[a]Selected based on the 4 most common treatment-related adverse reactions pre- and post-dose reduction in LUX-Lung 3.

[b]Post-hoc analysis included all of GILOTRIF-treated patients in LUX-Lung 3.

PFS in patients with or without dose reductions within the first 6 months[5,c]



[c]Data from intention-to-treat population, which includes both patients with common and uncommon EGFR mutations.

https://www.gilotrifhcp.com/dosing-and-administration

Therapeutic Approach to diarrhea in adult cancer patients

Uncomplicated diarrhoea[a]

Oral hydration
Dietary modification
Loperamide (4 mg initially, 2 mg after every loose stool to maximum of 16 mg/day)
Avoid skin irritation
Notify treating physician

Grading Diarrhea Severity: CTCAE v 5.0

Grade	Diarrhea Severity		
1	Increase of <4 stools/day	Mild increase in ostomy output	
2	Increase of 4 - 6 stools/day	Moderate increase in ostomy output	Limiting instrumental ADL
3	Increase of ≥7 stools/day Hospitalization indicated	Severe increase in ostomy output	Limiting self care ADL
4	Life-threatening consequences Urgent intervention		
5	Death		

Administer:
Loperamide (4 mg initially, 2 mg after every loose stool to maximum of 16 mg/day)
i.v. fluids and electrolytes

Daily evaluation:
CBC
Electrolytes
Urinary output

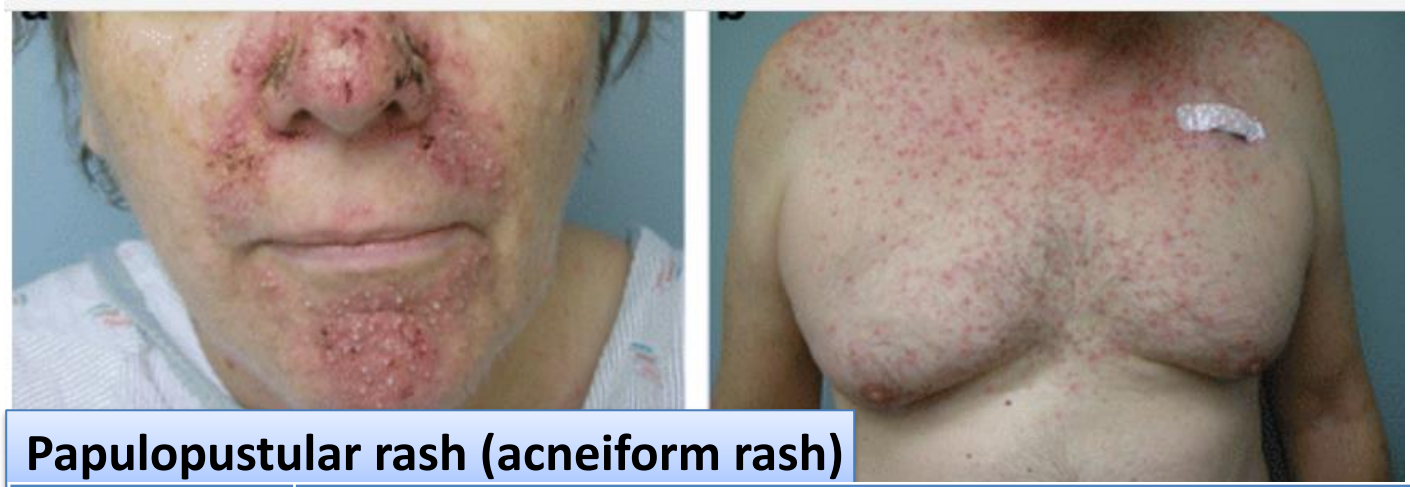
s.c.100–150 µg tid
or
i.v. 25–50 µg tid
Escalation up to 500 µg tid

Fluoroquinolones
Metronidazole
Broad sprectrum

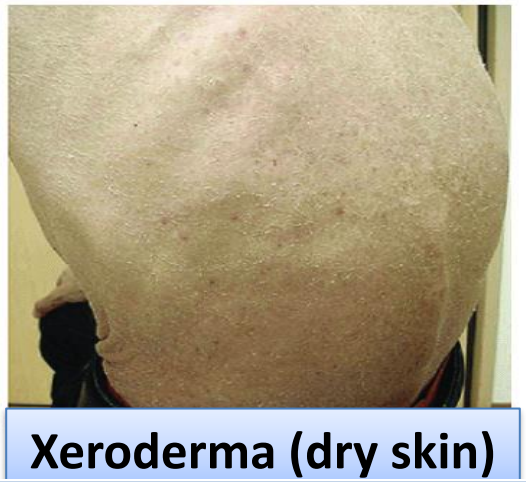
Blood and stool microbiology testing[c]

Ann Oncol (2018) 29 (Suppl 4): iv126–iv142

Common EGFR-Related Cutaneous Adverse Events



Papulopustular rash (acneiform rash)



Xeroderma (dry skin)

	CTCAE Version 5.0 Grading system for acneiform rash
Grade 1	Papules and/or pustules covering <10% of body surface area (BSA) with/ without symptoms of pruritus or tenderness.
Grade 2	Papules and/or pustules covering 10-30% of BSA with/without symptoms of pruritus or tenderness; associated with psychosocial impact and limitations on instrumental activities of daily life (ADL).
Grade 3	Papules/pustules covering > 30% of BSA with/without symptoms of pruritus or tenderness; limitations on self-care ADL and associated with local superinfection with oral antibiotics indicated.
Grade 4	Papules and/or pustules covering any percent of BSA with/without symptoms of pruritus or tenderness; associated with extensive superinfection with intravenous antibiotics indicated; life-threatening consequences.

https://www.researchgate.net/figure/The-EGFR-inhibitor-induced-papulopustular-eruption-Erythematous-sterile-papules-and_fig1_301669100 Asia-Pac J Clin Oncol. 2018;14:23–31.

Management of Skin AEs related to EGFR-TKIs

Condition	Grade	TKI administration decision	Treatments and interventions
Paronychia	1	Continue TKI at current dose	• Topical potent corticosteroids[e] • Vinegar soaks (soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 min every day) may be useful.
	2	Continue TKI at current dose	• Potent topical corticosteroids with/or without antimicrobials[f] • Silver nitrate applications to treat exuberant granulation tissue. • Refer to podiatrist/dermatologist for physical treatments. • Consider long-term prophylactic anti-inflammatory antibiotic eg doxycycline
	3	1. Interrupt TKI treatment 2. Refer to a dermatologist 3. Resume TKI at reduced dose if patient improves	As above
	4	1. Interrupt TKI treatment 2. Refer to a dermatologist (may need admission to dedicated skin/burn care unit)	

Asia-Pac J Clin Oncol. 2018;14:23–31.

AEs of Osimertinib in 1st line setting (FLAURA) vs 1st G

EGFR-TKI : 3rd G

ADVERSE REACTIONS OCCURRING IN ≥10% OF PATIENTS ON TAGRISSO[1]*

Advers	TAGRISSO (n=279)	erlotinib/gefitinib (n=277)
		3 r (%)
Skin (		
Rash		
Dry s		
Nail t		
Pruri		
Cardi		
Prolo		

QTc prolongation grade	Definition
1	QTc >450 but ≤470 ms
2	QTc >470 but ≤500 ms and/or an increase of ≥60 ms from baseline QTc
3	QTc >500 ms
4	QTc >500 ms with life-threatening signs or symptoms (i.e., arrhythmia, CHF, hypotension, shock, syncope, TdP)
5	Death

CHF, congestive heart failure; QTc, rate-corrected QT interval; TdP, torsade de pointes.

Data from the National Cancer Institute Cancer Therapy Evaluation Program, 9 August 2006 <http://ctep.cancer.gov/protocoldevelopment/>.

QTc interval-related toxicity grading

- QTc prolongation
  - Check concomitant medication
  - Heart rate, BP, EKG, electro

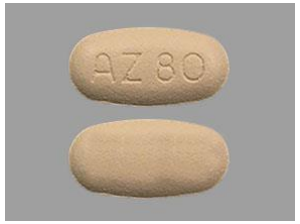
- Permanent DC rate : 13%
- Dose reduction : 2.9%

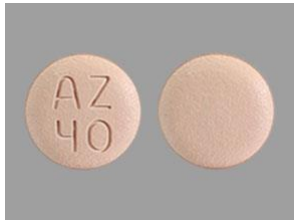
https://www.tagrissohcp.com/metastatic-egfrm-nsclc/safety.html

Dose Modification : Osimertinib (Tagrisso®)

EGFR-TKI : 3rd G

Target Organ	Adverse Reaction*	Dosage Modification
Cutaneous [see Warnings and Precautions (5.5)]	Erythema Multiforme Major (EMM), Stevens-Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)	Withhold TAGRISSO if suspected and permanently discontinue if confirmed.
Blood and bone marrow [see Warnings and Precautions (5.7)]	Aplastic anemia	Withhold TAGRISSO if aplastic anemia is suspected and permanently discontinue if confirmed.
Other [see Adverse Reactions (6.1)]	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.





AEs of Lasertinib (LECLAZA®) in 1st line setting (LASER 301)

EGFR-TKI : 3rd G

[Overall population]

Preferred term, n(%)	Lazertinib (N=196)			Gefitinib (N=197)		
	Any grade	Grade 3	> Grade 4	Any grade	Grade 3	> Grade 4
Median duration of exposure	15.1 months (range 0.2 to 29.0)			11 months (range 0.1 to 27.7)		
Rash	71 (36)	2 (1)	0	72 (37)	5 (3)	0
Diarrhoea	51 (26)	5 (3)	0	77 (39)	1 (1)	0
Paraesthesia	77 (39)	5 (3)	0	13 (7)	0	0
ALT increased	30 (15)	2 (1)	0	59 (30)	18 (9)	0
Pruritus	52 (27)	1 (1)	0	36 (18)	0	0
AST increased	22 (11)	1 (1)	0	52 (26)	13 (7)	0
Paronychia	35 (18)	1 (1)	0	34 (17)	1 (1)	0
Decreased appetite	33 (17)	3 (2)	0	31 (16)	1 (1)	0
Anaemia	36 (18)	7 (4)	0	23 (12)	7 (4)	0
Dry skin	29 (15)	0	0	23 (12)	0	0
Constipation	28 (14)	0	0	20 (10)	0	0
Nausea	30 (15)	0	0	18 (9)	0	0
Dermatitis acneiform	21 (11)	2 (1)	0	27 (14)	1 (1)	0
Stomatitis	31 (16)	0	0	16 (8)	1 (1)	0
Interstitial lung disease*	5 (3)	2 (1)	1 (1)	3 (2)	2 (1)	0
Electrocardiogram QT prolonged	7 (4)	2 (1)	0	3 (2)	2 (1)	0

[Korean Subset]

Preferred term, n(%)	Lazertinib (N=87)			Gefitinib (N=85)		
	Any grade	Grade 3	Grade >4	Any grade	Grade 3	Grade > 4
Rash	40 (46)	1 (1)	0	43 (51)	5 (6)	0
Pruritus	38 (44)	0	0	30 (35)	0	0
Diarrhoea	25 (29)	2 (2)	0	41 (48)	0	0
Paraesthesia	46 (53)	2 (2)	0	7 (8)	0	0
Decreased appetite	23 (26)	1 (1)	0	20 (24)	0	0
Alanine aminotransferase increased	11 (13)	1 (1)	0	29 (34)	9 (11)	0
Paronychia	15 (17)	0	0	21 (25)	1 (1)	0
Stomatitis	25 (29)	0	0	10 (12)	0	0
Aspartate aminotransferase increased	9 (10)	0	0	25 (29)	8 (9)	0
Constipation	17 (20)	0	0	14 (16)	0	0
Anaemia	12 (14)	3 (3)	0	7 (8)	5 (6)	0
Back pain	13 (15)	0	0	6 (7)	0	0
Nausea	13 (15)	0	0	6 (7)	0	0
Muscle spasms	15 (17)	0	0	3 (4)	0	0
Interstitial lung disease*	2 (2)	2 (2)	0	3 (4)	2 (2)	0
Electrocardiogram QT prolonged	2 (2)	0	0	2 (2)	2 (2)	0

BC Cho et al. ESMO Asia 2022 Oral presentation, JH Kang et al. CRT 2023

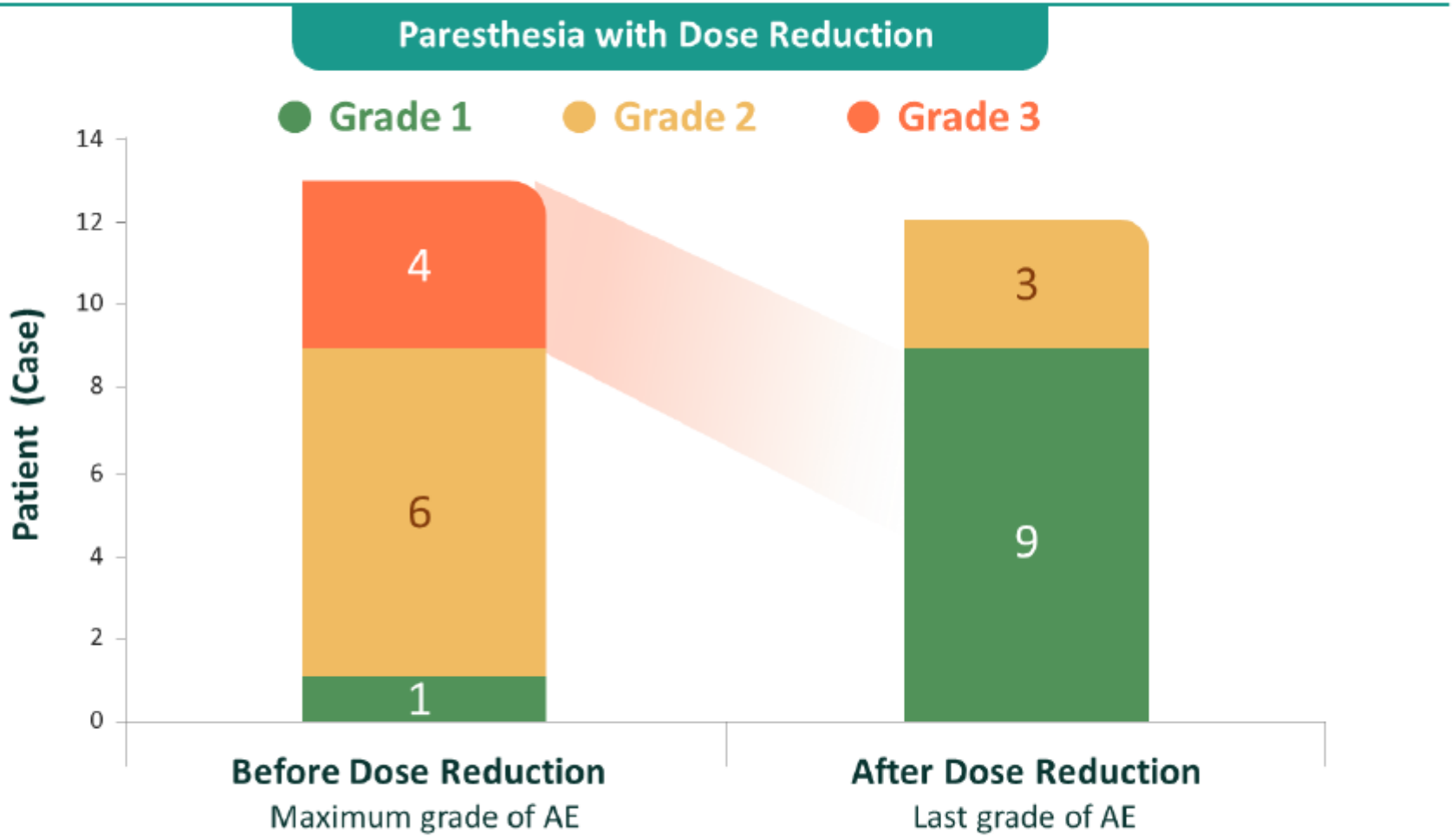
Paresthesia with Dose Reduction: *Lasertinib (LECLAZA®) LASER-301*

EGFR-TKI : 3rd G

- The severity of paresthesia was relieved following dose reduction

240mg (3T once daily)

-> 160mg once



Paresthesia is a preferred term.
Before dose reduction: maximum grade of AE.
After dose reduction: last grade of AE

Data on File (Yuhan)

Adverse Events of ALK inhibitors : Alectinib vs Crizotinib

Adverse Reaction	ALECENSA (n=152)		crizotinib (n=151)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Constipation	34%	0%	33%	0%
Nausea			48%	3.3%
Diarrhea			45%	2%
Vomiting			38%	3.3%
Fatigue[a]	26%	1.3%	23%	0.7%
Edema[b]	22%	0.7%	34%	0.7%
Myalgia[c]	23%	0%	4%	0%
Rash[d]	15%	0.7%	13%	0%
Dysgeusia[e]	3.3%	0.7%	19%	0%
Vision disorders[f]	4.6%	0%	23%	0%
Bradycardia[g]	11%	0%	15%	0%
Renal impairment[h]	12%	3.9%[i]	0%	0%

- Nausea/vomiting
  - metoclopropamide, dimenhydrinate

https://www.alecensa.com/hcp/alk-mnsclc-clinical-overview/1l-safety-profile.html

Dose Modification : Crizotinib (Xalkori®)

ALK, ROS1 - inhibitors : 1st G

XALKORI® (crizotinib) 250 mg taken orally twice daily, with or without food, for patients with either ROS1+ or ALK+ metastatic NSCLC

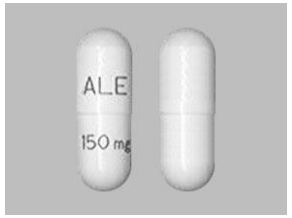
- **Severe renal / hepatic impairment : 250mg once**
- **Permanent D/C**
  - G2-4 AST/ALT elevation with G2-4 bilirubin elevation
  - ILD any grade
  - G4 QTc prolongation / bradycardia

https://xalkori.pfizerpro.com/dosing

Dose Modification Guideline : Alectinib (Alecensa®)

ALK-inhibitors : 2nd G

Dose Reduction Schedule	Dose Level
Starting dose	ALECENSA 600 mg taken orally twice daily
First dose reduction	ALECENSA 450 mg taken orally twice daily
Second dose reduction	ALECENSA 300 mg taken orally twice daily
Discontinue if patients are unable to tolerate the 300 mg twice daily dose.	



Adverse Event	Baseline Testing	Regular Monitoring
Musculoskeletal toxicity	None Serum CK or CPK ??	Serum CK or CPK should be tested every 2 weeks for the first month of treatment in patients reporting muscle symptoms

Criteria	Dose Modification
CK (CPK) elevation > 5x ULN	Temporarily withhold until recovery to baseline or to 2.5x ULN, then resume at same dose
CK (CPK) elevation > 10x ULN or second occurrence of CK (CPK) elevation > 5x ULN	Temporarily withhold until recovery to baseline or to 2.5x ULN, then resume at same dose

https://www.alecensa.com/hcp/alk-mnsclc-clinical-overview/1l-safety-profile.html

ALK-inhibitors : 2nd G

Adverse Reactions in ≥10% (All Grades[a]) or ≥2% (Grades 3-4) of Patients by Arm in ALTA 1L (N=273)[1]

Vascular Disorders				
Hypertension[g]	32	13	8	2.9
General Disorders and Administration Site Conditions				
Fatigue[h]	32	1.5	40	2.2
Edema[i]	18	0.7	48	0.7
Pyrexia	15	0.7	15	0
Musculoskeletal and Connective Tissue Disorders				
Myalgia[j]	28	0	23	0
Back pain	21	0.7	17	1.5
Arthralgia	14	0	12	0
Pain in extremity	5.1	0	15	0.7
Nervous System Disorders				
Headache[k]	22	2.2	17	0
Dizziness	15	0.7	20	0.7
Peripheral neuropathy[l]	11	0.7	18	0
Dysgeusia	2.9	0	14	0
Investigations				
Increased blood cholesterol[m]	13	0	0.7	0
Cardiac Disorders				
Bradycardia[n]	12	0.7	23	0

Dose Modification : Brigatinib (ALUNBRIG®)

ALK-inhibitors
2nd G

180-mg tablets: oval, white to off-white film-coated tablet

90-mg tablets: oval, white to off-white film-coated tablet

30-mg tablets: round, white to off-white film-coated tablet

Dose		First		Second
90 mg once daily	*intolerable* →	60 mg once daily	*intolerable* →	Permanently discontinue

Dose		First		Second		Third
180 mg once daily	*intolerable* →	120 mg once daily	*intolerable* →	90 mg once daily	*intolerable* →	60 mg once daily

- Dose interruption and/or reduction may be required based on individual safety and tolerability
- ALUNBRIG® should be permanently discontinued if patient is unable to tolerate the 60-mg once-daily dose

Reference 알룬브릭® 국내허가사항, 식약처 의약품안전나라, available at https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=201804848, Accessed on 9th Sep 2020.

Brigatinib-Associated Early-Onset Pulmonary Events (EOPEs): *Case Definition*

ALK-inhibitors : 2nd G

- Brigatinib is well tolerated in most patients. Early studies reported a rare pulmonary AE within the first 7 days after brigatinib initiation in a small subset of patients, prompting creation of a distinct identifier for these AEs: EOPEs[1]

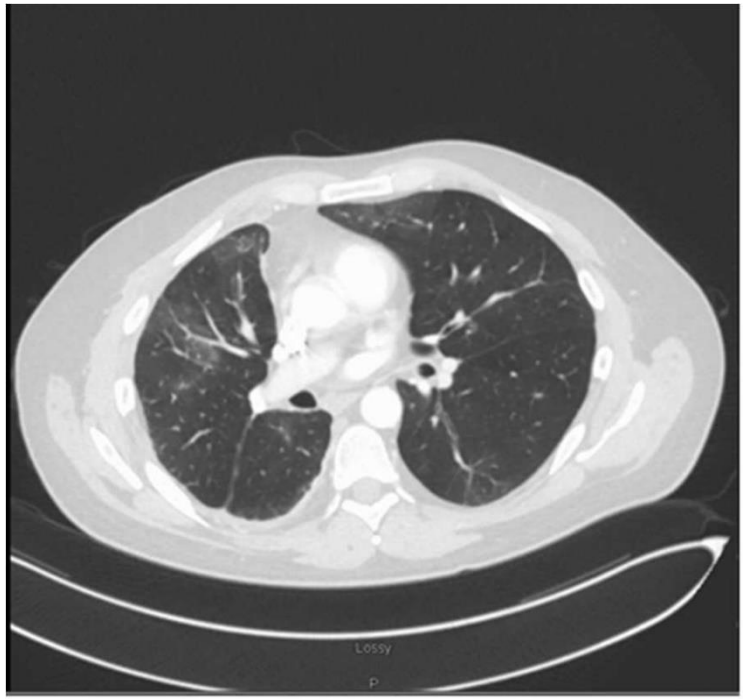
Case Definition for Brigatinib-Associated EOPE[1,a]

Brigatinib-associated EOPE was deemed *possible* when criteria 1 and 2 were met or *definite* when all 3 criteria were met:

1. Presence of a temporal relationship (defined as signs or symptoms beginning **within the first 7 days after initiation** [median, 2 days], **retreatment after ≥ 7 days' interruption**, or **dose escalation of brigatinib**)
2. Evidence of a pneumonitis-like process (eg, hypoxia or dyspnea along with supportive imaging or pathologic findings[b])
3. Determination that other etiologies are unlikely (eg, infectious, tumor progression)

Unequivocal evidence of resolution on dose interruption or recurrence of the event on brigatinib rechallenge was considered as supportive information.

Example of Grade 3 EOPE[2]



Day 2 after starting brigatinib at 180 mg. CTPA showed new ground-glass opacities bilaterally.

AE, adverse event; CTPA; computed tomographic pulmonary angiography.
[a] Case definition for brigatinib-associated EOPE was applied to the phase 1/2 and ALTA data sets. In ALTA-1L, all such events, whether observed as symptoms, or through radiographic imaging, were considered EOPEs; [b] Such as ground-glass opacities on computed tomography or x-ray or diffuse alveolar damage on histopathology.
1. Ng TL, et al. *J Thorac Oncol.* 2020;15:1190-1199; 2. Camidge DR, et al. *J Thorac Oncol.* 2019;14:1547-1555.

Pulmonary Toxicity : *Monitoring & Dose Modification*

Adverse Event	Baseline Testing	Regular Monitoring
ILD/Pneumonitis	None	Chest CT, Pulmonary function test if indicated by symptoms

Criteria	Dose Modification
Any grade	Permanently discontinue > Continue with steroids or Resume at reduced dose after recovery

Table 4. Pneumonitis severity classification according to NCI-CTCAE version 5.0 and American Society of Clinical Oncology (ASCO) 2018 guidelines.

Guidelines	G1	G2	G3	G4
CTCAE Version 5.0	Asymptomatic, clinical or diagnostic observations only, intervention not indicated	Symptomatic, medical intervention indicated, limiting instrumental ADL	Severe symptoms, limiting self-care ADL, oxygen indicated	Life-threatening respiratory Compromise, urgent intervention indicated (e.g., tracheotomy or intubation)
ASCO guidelines	Asymptomatic, confined to one lobe of the lung or <25% of lung parenchyma, clinical or diagnostic observations only	Symptomatic, involves more than one lobe of the lung or 25–50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, limiting self-care ADL, oxygen indicated	Life-threatening respiratory compromise, urgent Intervention indicated (intubation)

Curr Oncol 2014;21:19-26
Cancers (Basel) 2021;13(5):1052

Pulmonary Toxicity : *Dose Modification*

ALK-inhibitors : 2nd G

I 간질성폐질환(ILD, interstitial lung disease)/폐렴

중증도	치료 후 처음 7일 동안 새로운 폐 증상이 발생한 경우		처음 7일 이후 새로운 폐 증상이 발생한 경우	
	알룬브릭® 투여 보류 기간	알룬브릭® 재개 시 용량	알룬브릭® 투여 보류 기간	알룬브릭® 재개 시 용량
1등급	기저상태로 회복될 때까지	동일한 용량	기저상태로 회복될 때까지	동일한 용량
2등급	기저상태로 회복될 때까지	한 단계 낮은 용량	기저상태로 회복될 때까지	• ILD/폐렴으로 의심되는 경우 한 단계 낮은 용량으로 • 그렇지 않은 경우 동일한 용량으로
	치료 후 처음 7일 동안 ILD/폐렴이 의심되는 경우 알룬브릭®을 180 mg으로 증량해서는 안됩니다.			
3등급/4등급	알룬브릭®의 투여를 영구 중단합니다.			

주의: 모든 등급에서 알룬브릭®의 용량 조절 및 재개 이후에 ILD/폐렴이 재발한 경우 알룬브릭®의 투여를 영구 중단합니다.

Hepatic Toxicity : *Brigatinib vs Alectinib vs Loratinib*

Table 3. Adverse Events of Any Grade That Differed by More Than 5 Percentage Points in Fr

Brigatinib (ALTA-1)

Event	Brigatinib (N=136)	
	Any Grade	Grade ≥3
		number of pa
Any adverse event	132 (97)	83 (61)
Diarrhea	67 (49)	2 (1)
Increased blood creatine kinase level*	53 (39)	22 (16)
Nausea	36 (26)	2 (1)
Cough	34 (25)	0
Hypertension	31 (23)	13 (10)
Increased alanine aminotransferase level	26 (19)	2 (1)
Increased lipase level†	26 (19)	18 (13)
Vomiting	25 (18)	1 (1)
Constipation	20 (15)	0
Increased amylase level†	19 (14)	7 (5)
Pruritus	18 (13)	1 (1)
Rash	14 (10)	0
Decreased appetite	10 (7)	1 (1)
Dermatitis acneiform	9 (7)	0
Dyspepsia	8 (6)	0
Epistaxis	8 (6)	0
Bradycardia	7 (5)	1 (1)
Peripheral edema	6 (4)	1 (1)
Dysgeusia	6 (4)	0
Upper abdominal pain	6 (4)	1 (1)
Pain in extremity	6 (4)	0
Increased blood creatinine level	3 (2)	0
Neutropenia	2 (1)	0
Pleural effusion	2 (1)	1 (1)
Photopsia	1 (1)	0
Gastroesophageal reflux disease	1 (1)	0
Visual impairment	0	0
Deep-vein thrombosis	0	0

Table 3. Safety Overview and Adverse Events of Any G e Points or More in Frequency between Groups.*

Alectinib (ALEX)

	Alectinib (N=152)	
	Any Grade	Grade 3–5
	nts (percent)	
Adverse events that differed by ≥5 percentage points in frequency between groups		
Nausea	21 (14)	1 (1)
Diarrhea	18 (12)	0
Vomiting	11 (7)	0
ALT increased	23 (15)	7 (5)
AST increased	21 (14)	8 (5)
Blood bilirubin increased	23 (15)	3 (2)
Weight increased	15 (10)	1 (1)
γ-Glutamyltransferase increased	1 (1)	1 (1)
Peripheral edema	26 (17)	0
Dizziness	12 (8)	0
Dysgeusia	4 (3)	0
Visual impairment	2 (1)	0
Vision blurred	3 (2)	0
Photopsia	0	0
Myalgia	24 (16)	0
Musculoskeletal pain	11 (7)	0
Anemia	30 (20)	7 (5)
Alopecia	1 (1)	0
Photosensitivity reaction	8 (5)	1 (1)

Table 3. Adverse Events in the Safety Population.*

Lorlatinib (CROWN)

Event	Lorlatinib (N=149)				
	Grade	Grade 1	Grade 2	Grade 3	Grade 4
					number of pat
Any adverse event	149 (100)	6 (4)	28 (19)	87 (58)	21 (14)
Hypercholesterolemia†	105 (70)	24 (16)	57 (38)	23 (15)	1 (1)
Hypertriglyceridemia†	95 (64)	28 (19)	37 (25)	19 (13)	11 (7)
Edema†	82 (55)	54 (36)	22 (15)	6 (4)	0
Increased weight	57 (38)	11 (7)	21 (14)	25 (17)	0
Peripheral neuropathy†	50 (34)	36 (24)	11 (7)	3 (2)	0
Cognitive effects†‡	32 (21)	20 (13)	9 (6)	3 (2)	0
Diarrhea	32 (21)	21 (14)	9 (6)	2 (1)	0
Anemia	29 (19)	16 (11)	9 (6)	4 (3)	0
Fatigue†	29 (19)	25 (17)	2 (1)	2 (1)	0
Hypertension	27 (18)	1 (1)	11 (7)	15 (10)	0
Vision disorder†	27 (18)	25 (17)	2 (1)	0	0
Increased ALT level	26 (17)	22 (15)	0	4 (3)	0
Constipation	26 (17)	24 (16)	2 (1)	0	0
Mood effects†§	24 (16)	14 (9)	8 (5)	2 (1)	0
Nausea	22 (15)	21 (14)	0	1 (1)	0
Increased AST level	21 (14)	18 (12)	0	3 (2)	0
Vomiting	19 (13)	16 (11)	2 (1)	1 (1)	0
Hyperlipidemia	16 (11)	6 (4)	7 (5)	2 (1)	1 (1)
Dysgeusia	8 (5)	8 (5)	0	0	0
Decreased appetite	5 (3)	3 (2)	2 (1)	0	0
Bradycardia	2 (1)	2 (1)	0	0	0

N Engl J Med 2017;377:829-838 ;N Engl J Med 2018;379:2027-2039 ; N Engl J Med 2020;383:2018-2029

Hepatic Toxicity : Monitoring & Dose Modification

Adverse Event	Baseline Testing	Regular Monitoring
Hepatotoxicity	AST, ALT, ALP, bilirubin	Every 2 weeks during the first 2 (3) months, then monthly and as clinically indicated. More frequent testing for grade 2, 3 or 4 elevation.
Moderate CYP3A inducers (if com-med is unavoidable)	AST, ALT, and bilirubin	48 hours after initiating lorlatinib and at least 3 times during the first week of lorlatinib treatment

Criteria	Dose Modification
AST/ALT elevation >5x ULN with total bilirubin ≤2 x UNL	Temporarily withhold until recovery to baseline or to ≤3x UNL, then resume at reduced dose.
ALT or AST elevation >3x with total bilirubin elevation >2x UNL in the absence of cholestasis or hemolysis	**Permanently discontinue**
Total bilirubin elevation of > 3× ULN	Temporarily hold until recovery to baseline or to ≤ 1.5 × ULN, then resume at reduced dose

Curr Oncol 2014;21:19-26

Oncologist 2019;24(8):1103-1110

Adverse Events : Lorlatinib (LORVIQUA®)

ALK-inhibitors : 3rd G

Table 1. Adverse reactions in ≥10% of all patients or Grade ≥3 adverse reactions in any patient treated with lorlatinib 100 mg once daily

Adverse drug reactions, *n* (%)	Pooled lorlatinib 100 mg once daily (*N* = 295) §		
	All grades	Grade 3	Grade 4
Hypercholesterolemia[a]	243 (82.4)	41 (13.9)	5 (1.7)
Hypertriglyceridemia[a]	179 (60.7)	39 (13.2)	7 (2.4)
Edema[a]	151 (51.2)	7 (2.4)	0 (0.0)
Peripheral neuropathy[a]	129 (43.7)	7 (2.4)	0 (0.0)
Cognitive effects[a]	68 (23.1)	5 (1.7)	0 (0.0)
Fatigue[a]	68 (23.1)	1 (0.3)	0 (0.0)
Mood effects[a]	62 (21.0)	4 (1.4)	0 (0.0)
Weight increase	61 (20.7)	7 (2.4)	0 (0.0)
Arthralgia	58 (19.7)	0 (0.0)	0 (0.0)
Diarrhea	52 (17.6)	2 (0.7)	0 (0.0)
Constipation	42 (14.2)	0 (0.0)	0 (0.0)
Vision disorder[a]	39 (13.2)	1 (0.3)	0 (0.0)
Speech effects[a]	28 (9.5)	1 (0.3)	0 (0.0)

[a]Clustered term comprising adverse events that represent similar clinical symptoms/syndromes.
Based on Common Terminology Criteria for Adverse Events (v4.03).

- Temporary dose interruptions and reduction : 21.7% and 19.7%
  - Most common cause: Edema 5.8%, 6.1%
- Permanent discontinuation
  - Cognitive disorder (n=2), mood disorder (n=2), edema (n=1), fatigue (n=1)

§: patients who had received lorlatinib 100 mg QD, in the phase I/II study (NCT01970865).

Oncologist 2019;24(8):1103-1110

Hyperlipidemia : Lorlatinib (LORVIQUA®)

ALK-inhibitors : 3rd G

- Time of onset: Usually occurred within the first few weeks of treatment (Median 15days [range, 1-219])

- Incidence

	All grade	Grade 3&4	Dose delay	Dose reduction	Permanent discontinuation
Hypercholesterolemia	82.4%	15.6%	3.4%	0.7%	-
Hypertriglyceridemia	60.7%	15.6%	4.7%	1.7%	-

- Lipid lowering agent prescription rate
  - 81% of patients received at least one lipid lowering agents (Median time to start: 20days [range, 1-190])
  - 22.1%(50/226) and 30.8%(61/198) of patient required the additional medication

- Selection of lipid lowering agent

Table S1. Pharmacokinetic properties of statins

Generic name (or equivalent)	Pitavastatin	Pravastatin	Rosuvastatin	Atorvastatin	Simvastatin	Lovastatin	Fluvastatin
Metabolism[a]	++	+	+	+++	+++	+++	+++
Metabolizing CYP enzymes (of lactone or acid form)	(2C9)	(3A4)	2C9 (2C19)	3A4 (2C8)	3A4, 2C8	3A4, 2C8?	2C9

- HyperTG : fenofibrate, fish oil, nicotinic acid, ezetimibe > gemfibrozil

Oncologist 2019;24(8):1103-1110

Hyperlipidemia : Lorlatinib (LORVIQUA®)

ALK-inhibitors : 3rd G

Table 2. Dose modification guidelines for lorlatinib-related hyperlipidemias by severity

Severity	Guidance
Mild: Cholesterol ULN–300 mg/dL OR Triglycerides 150–300 mg/dL Moderate: Cholesterol >300–400 mg/dL OR Triglycerides >300–500 mg/dL	• Introduce or modify lipid-lowering therapy • Continue at the same lorlatinib dose
Severe: Cholesterol >400–500 mg/dL OR Triglycerides >500–1,000 mg/dL	• Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy • Continue at the same lorlatinib dose without interruption
Life threatening: **Gr4 by CTCAE Ver4.0** Cholesterol >500 mg/dL OR Triglycerides >1000 mg/dL	• Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy • Withhold lorlatinib dose until hyperlipidemia is moderate or mild before rechallenging at same dose while maximizing lipid-lowering therapy • If severe hyperlipidemia recurs despite maximal lipid-lowering therapy, reduce lorlatinib dose by one dose level (by 25 mg)

Table S2. Recommended monitoring for patients on lorlatinib

Toxicity	Baseline testing	Ongoing monitoring
Hyperlipidemia	Serum cholesterol and triglycerides	1 and 2 months after initiating lorlatinib, and periodically thereafter

Oncologist 2019;24(8):1103-1110

Neurologic Toxicities : Lorlatinib (LORVIQUA®)

ALK-inhibitors : 3rd G

- Cognitive dysfunction, mood disturbance, speech disturbance, peripheral neuropathy
- Generally mild, transient, and fully reversible with holding treatment / dose-dependent

Table 4. Mood disorder adverse events with lorlatinib

	Pooled lorlatinib 100 mg once daily (*N* = 295)		
Preferred term, *n* (%)	**All grades**	**Grade 3**	**Grade 4**
Any adverse event	62 (21.0)	4 (1.4)	0 (0.0)
Irritability	18 (6.1)	2 (0.7)	0 (0.0)
Anxiety	15 (5.1)	1 (0.3)	0 (0.0)
Depression	12 (4.1)	1 (0.3)	0 (0.0)
Affect lability	7 (2.4)	0 (0.0)	0 (0.0)
Personality change	5 (1.7)	0 (0.0)	0 (0.0)
Mood swings	3 (1.0)	0 (0.0)	0 (0.0)
Affective disorder	2 (0.7)	0 (0.0)	0 (0.0)
Aggression	2 (0.7)	0 (0.0)	0 (0.0)
Agitation	2 (0.7)	1 (0.3)	0 (0.0)
Mood altered	2 (0.7)	0 (0.0)	0 (0.0)
Depressed mood	1 (0.3)	0 (0.0)	0 (0.0)
Euphoric mood	1 (0.3)	0 (0.0)	0 (0.0)
Mania	1 (0.3)	0 (0.0)	0 (0.0)

Based on Common Terminology Criteria for Adverse Events (v4.03).

Table 5. Cognitive disorder adverse events with lorlatinib

	Pooled lorlatinib 100 mg once daily (*N* = 295)		
Preferred term, *n* (%)	**All grades**	**Grade 3**	**Grade 4**
Any adverse event	68 (23.1)	5 (1.7)	0 (0.0)
Memory impairment	26 (8.8)	0 (0.0)	0 (0.0)
Cognitive disorder	18 (6.1)	2 (0.7)	0 (0.0)
Amnesia	16 (5.4)	0 (0.0)	0 (0.0)
Confusional state	11 (3.7)	2 (0.7)	0 (0.0)
Disturbance in attention	7 (2.4)	0 (0.0)	0 (0.0)
Delirium	2 (0.7)	1 (0.3)	0 (0.0)
Mental impairment	2 (0.7)	0 (0.0)	0 (0.0)
Attention deficit/hyperactivity	1 (0.3)	0 (0.0)	0 (0.0)

Table S3. Speech disorder adverse events with lorlatinib

	Pooled lorlatinib 100 mg once daily (*N* = 295)		
Preferred term, *n* (%)	**All grades**	**Grade 3**	**Grade 4**
Any adverse event	28 (9.5)	1 (0.3)	0 (0.0)
Dysarthria	11 (3.7)	0 (0.0)	0 (0.0)
Slow speech	10 (3.4)	1 (0.3)	0 (0.0)
Speech disorder	7 (2.4)	0 (0.0)	0 (0.0)

N Engl J Med 2020;383:2018-2029

Dose modification for Neurologic Toxicities : Lorlatinib (LORVIQUA®)

ALK-inhibitors : 3rd G

Table 3. Dose modification guidelines for lorlatinib-related central nervous system effects by CTCAE grade[a]

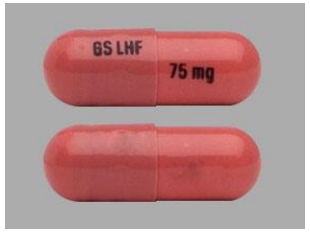
CTCAE grade	Guidance
Grade 1: Mild	• Continue at the same dose or withhold dose until recovery to baseline • Rechallenge at the same dose or reduce dose by one dose level (by 25 mg)
Grade 2: Moderate OR Grade 3: Severe	• Withhold dose until adverse event is grade ≤1 • Rechallenge at one reduced dose level (by 25 mg)
Grade 4: Life-threatening/ urgent intervention indicated	• Permanently discontinue lorlatinib

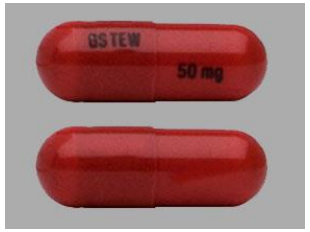
[a]Based on CTCAE (v4.03).
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

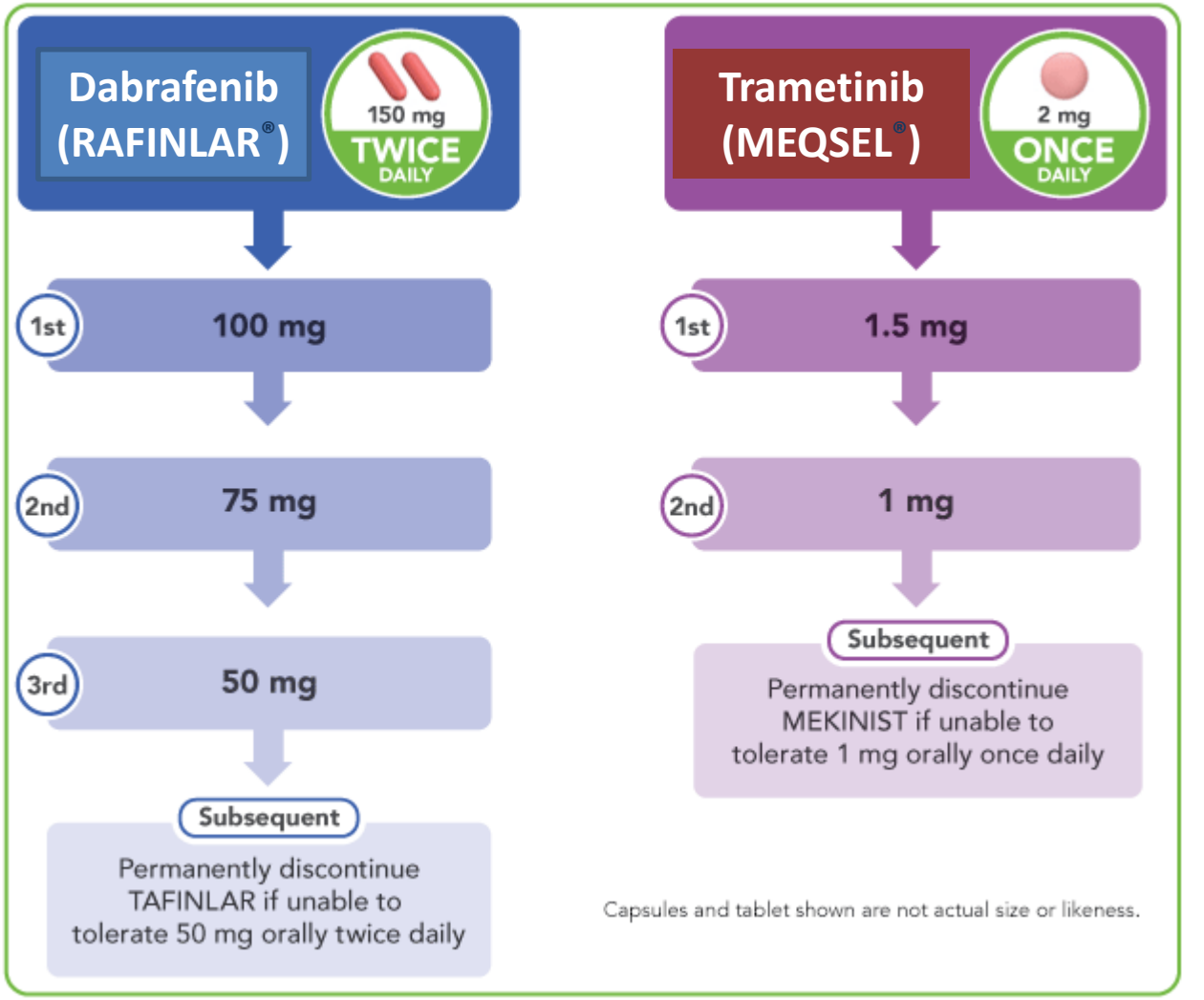
Oncologist 2019;24(8):1103-1110

Dose Modification Guideline : Dabrafenib/Trametinib

BRAF inhibitors







https://www.hcp.novartis.com/products/tafinlar-mekinist/metastatic-nsclc/dosing-and-administration/

Adverse Events : Dabrafenib/Trametinib

Adverse Reactions	RAFINLAR + MEQSEL (N=206) All grades, %	RAFINLAR + MEQSEL (N=206) Grade 3 or 4, %
General		
Pyrexia	55	4.9
Fatigue[b]	50	5
Chills	30	0.5
Edema peripheral[c]	22	0
Gastrointestinal		
Nausea	40	1.5
Constipation	27	0
Vomiting	27	1.5
Diarrhea	26	2.9
Skin		
Rash[d]	40	2.4
Nervous system		
Headache	30	1.5
Vascular disorders		
Hemorrhage[e]	29	4.4
Respiratory		
Cough[f]	29	0
Musculoskeletal and connective tissue		
Myalgia[g]	24	0.5
Arthralgia	23	0.5

https://www.hcp.novartis.com/products/tafinlar-mekinist/advanced-melanoma/dosing-and-administration/

Management of Pyrexia by *Dabrafenib/Trametinib*

BRAF inhibitors

PYREXIA

≥ 38°C

1 Interrupt

TAFINLAR+ MEKINIST at the onset of pyrexia (≥100.4°F) OR first symptom in case of recurrence.

2 Manage

- until pyrexia (100.4°F-104°F) resolves
- until febrile reactions resolve for at least 24 hours for pyrexia >104°F or fever complicated by rigors, hypotension, dehydration, or renal failure, OR discontinue permanently

3 Restart

- at same or lower dose for pyrexia (100.4°F-104°F)
- at a lower dose for pyrexia >104°F or fever complicated by rigors, hypotension, dehydration, or renal failure

Manage pyrexia with antipyretics or corticosteroids depending on episode and severity

Antipyretics can be used to help manage pyrexia, including as secondary prophylaxis when resuming TAFINLAR + MEKINIST if patient had a prior episode of severe febrile reaction or fever associated with complications.

Corticosteroids can be considered and administered for at least 5 days for second or subsequent pyrexia if temperature doesn't return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications, such as dehydration, hypotension, renal failure, or severe chills/rigors, and there is no evidence of active infection.

Monitor renal function and serum creatinine during and following severe pyrexia.

https://www.hcp.novartis.com/products/tafinlar-mekinist/advanced-melanoma/dosing-and-administration/

Safety Profile of Capmatinib (TABRECTA® : GEOMETRY-MONO1)

METex14skipping mutation inhibitor

Most common TRAEs (≥ 10% in safety population)

	All patients N = 373		Patients with METex4 and brain metastasis n = 29	
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)
Number of patients with at least 1 TRAE	324 (86.9)	147 (39.4)	26 (89.7)	14 (48.3)
Peripheral edema[a]	178 (47.7)	34 (9.1)	14 (48.3)	4 (13.8)
Nausea	128 (34.3)	6 (1.6)	15 (51.7)	1 (3.4)
Increased blood creatinine	74 (19.8)	0	2 (6.9)	0
Vomiting	71 (19.0)	7 (1.9)	8 (27.6)	0
Fatigue	51 (13.7)	10 (2.7)	4 (13.8)	2 (6.9)
Decreased appetite	47 (12.6)	3 (0.8)	4 (13.8)	0
Diarrhea	40 (10.7)	1 (0.3)	0	0

- **Dose reduction : 31%**
- **Discontinue : 16%**

*Very common adverse event refers that events occur ≥1/10 patients.
[a]Peripheral edema includes peripheral swelling, peripheral edema, and fluid overload.
[b]Fatigue includes fatigue and asthenia.
[c]Noncardiac chest pain includes chest discomfort, musculoskeletal chest pain, noncardiac chest pain, and chest pain.
[d]Pyrexia includes pyrexia and body temperature increased.

References 1. [타브렉타정150mg, 200mg (카프마티닙염산염일수화물)] 식품의약품안전처 의약품통합정보시스템(nedrug.mfds.go.kr) **2.** Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957.

Safety Profile of Tepotinib (TEPMEKO®: Vision)

METex14skipping mutation inhibitor

Most common TRAEs (≥10% in the safety population)

Characteristic	VISION Cohort A+C (N=255)		GEOMETRY Mono-1 All patients (N=373)
	All grades, n (%)	Grade 3/4, n (%)	Grade 3/4, n (%)
Number of patients with at least 1 TRAE	220 (86.3)	62 (24.3)	151 (40.5)
Peripheral edema[a]	138 (54.1)	19 (7.5)	34 (9.1)
Nausea	51 (20.0)	1 (0.4)	6 (1.6)
Increased blood creatinine	45 (17.6)	1 (0.4)	1 (0.3)
Vomiting	14 (5.5)	1 (0.4)	7 (1.9)
Fatigue	18 (7.1)	1 (0.4)	10 (2.7)
Decreased appetite	21 (8.2)	1 (0.4)	3 (0.8)
Diarrhea	50 (19.6)	1 (0.4)	1 (0.3)
Hypoalbuminemia	37 (14.5)	6 (2.4)	
Amylase increased	19 (7.5)	5 (2.0)	

[a]Peripheral edema includes peripheral swelling, peripheral edema and fluid overload.
BM, brain metastasis; *MET*ex14, *MET* exon 14 skipping mutation; TRAE, treatment-related adverse event

P.K. Paik, et al. NEJM 2020;383:931-43.

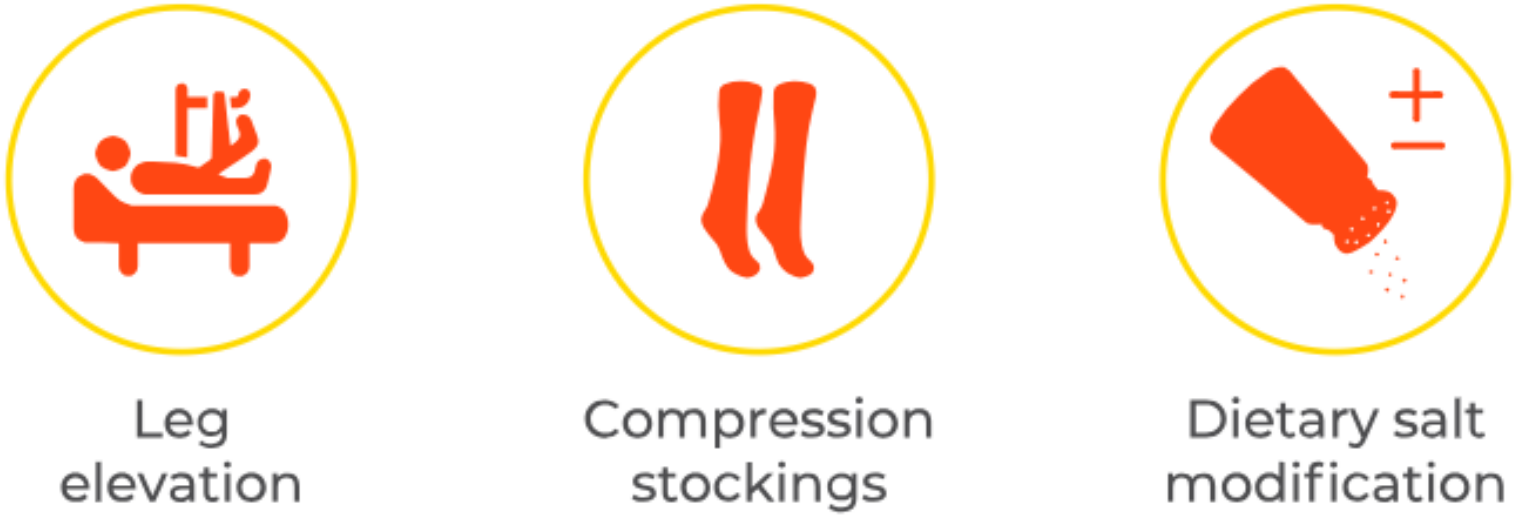
Management of edema

METex14skipping mutation inhibitor

In the GEOMETRY mono-1 clinical trial, edema occurred in 59% of patients and was managed based on severity[2,4]:

- **Grade ≤2 peripheral edema:** Consider measures such as leg elevation, compression stockings, or dietary salt modification

Role of diuretics : Not clear



- **Grade ≥3 peripheral edema:** Initiate or intensify the above measures

https://www.hcp.novartis.com/products/tabrecta/met-exon-14-skipping-mutation-nsclc/safety-profile/

Dose Modification : Capmatinib (TABRECTA®)

METex14skipping mutation inhibitor

권고 용량: 400 mg 1일 2회	오전: 200 mg 2정	오후: 200 mg 2정
		

※정제 이미지는 실제 사이즈가 아닙니다.

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- 약의 투여를 잊거나 구토가 발생하는 경우, 환자는 해당 투여분을 보충투여하지 않도록 하고, 예정된 시간에 다음 투여분을 복용해야 합니다.

이상반응의 조절을 위해 용량 조절이 가능합니다.

1차 감량 300 mg 1일 2회	오전: 150 mg 2정	오후: 150 mg 2정
두번째 용량 조절 200 mg 1일 2회	오전: 200 mg 1정	오후: 200 mg 1정

- 1일 2회 200 mg 경구 투여에 대하여 내약성을 나타내지 못하는 환자는 타브렉타® 투여를 중단하여야 합니다.
- 경증-중등증의 신장애 환자에 대한 용량 조절은 필요하지 않습니다.

타브렉타®는 두가지 용량의 정제가 사용가능합니다.

 200 mg

 150 mg

처방법

타브렉타 200 mg x 2정
30일간 1일 2회
경구 투여

References 1. [타브렉타정150mg, 200mg (카프마티닙염산염일수화물)] 식품의약품안전처 의약품통합정보시스템(nedrug.mfds.go.kr)

Dose Modification : Tepotinib (TEPMETKO®)

METex14skipping mutation inhibitor

TEPMETKO® is the only MET inhibitor with a once-daily oral dosing regimen, which can help to improve patient satisfaction, adherence, and QoL

TEPMETKO® allows for once-daily dosing due to:[1–3]

- good bioavailability
- a long half-life of 32 hours: Once daily dosing of TEPMETKO® maintains optimal concentrations (>95% inhibition in 90% of the population)
- a manageable tablet size

In the VISION study, patients received a standard dose of 450 mg[a] PO QD TEPMETKO®[4]

Dose reduction

450 mg daily dose
2 x 225 mg tablets[a]

If patient's require dose modification, TEPMETKO® is the only MET inhibitor that offers a prescription-free drop from two tablets to one[1,5,6]

225 mg daily dose
1 x 225 mg tablet[a]

https://www.tepmetko.com/en/line-agnostic.html#

Adverse Events: Pralsetinib (GAVRETO®)

RET Fusion inhibitor

Adverse Event, %	*RET* Fusion-Positive NSCLC (n = 233)		All Patients (n = 471)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Neutropenia	42	20	40	19
AST increased	39	3	39	3
Anemia	38	13	35	13
WBC count decreased	30	7	32	8
Lymphopenia	16	9	18	11
Diarrhoea	16	1	16	1
Blood creatinine increased	15	0	15	0
Dysgeusia	15	0	14	0
Thrombocytopenia	15	4	15	4

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions.

2
12
3
1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell.
Curigliano G, et al. J Clin Oncol. 2021;39(15 suppl):9089.

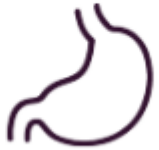
Dose Modification: Pralsetinib (GAVRETO®)

RET Fusion inhibitor

Recommended starting dose: 400 mg once daily

Capsules are not actual size.

Four 100-mg Capsules



Patients should take GAVRETO on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO).

Table 1: Recommended Dose Reductions for GAVRETO for Adverse Reactions

Dose Reduction	Recommended Dosage
First	300 mg once daily
Second	200 mg once daily
Third	100 mg once daily

https://www.gavreto-hcp.com/mnsclc/dosing-and-administration/dosing.html

Adverse Events: Mobocertinib (EXKIVITY®)

Exon 20 INS

Adverse Reaction[1]	Oral EXKIVITY 160 mg Once Daily (N=114) All Grades†	Grade 3 or 4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain**	34%	2.6%§
General Disorders and Administration Site Conditions		
Fatigue††	29%	3.5%§
Respiratory, Thoracic, and Mediastinal Disorders		
Cough‡‡		
Upper respiratory tract infection§§		
Dyspnea‖‖		
Rhinorrhea		
Eye Disorders		
Ocular toxicity¶¶	11%	0
Cardiac Disorders		
QTc interval prolongation##	10%	3.5%
Hypertension***	10%	4.4%§
Nervous System Disorders		
Headache	10%	0

Dose reductions[1]

STARTING DOSE	FIRST REDUCTION	SECOND REDUCTION
160 mg ONCE DAILY	120 mg ONCE DAILY	80 mg ONCE DAILY

Adverse Events: Amivantamab (RYBREVANT®)

Exon 20 INS

Infusion-related reactions (IRRs)

IRRs occurred in 66% of patients treated with RYBREVANT®[1]

- The incidence of infusion modifications due to IRR was 62%, and 1.3% of patients permanently

Of the patien
subsequent i

Body Weight at Baseline	Initial Dose	1st Dose Modification	2nd Dose Modification	3rd Dose Modification
Less than 80 kg	1050 mg	700 mg	350 mg	Discontinue RYBREVANT®
Greater than or equal to 80 kg	1400 mg	1050 mg	700 mg	

Dermatologic adverse reactions

RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis.

Keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®.

Interstitial lung disease (ILD/pneumonitis)

ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®.

- Grade 3 ILD/pneumonitis occurred in 0.7% of patients
- ILD/pneumonitis led to discontinuation of RYBREVANT® in 1% of patients

https://www.rybrevanthcp.com/safety

Adverse Events: Sotorasib (LUMAKRAS®)

KRAS G12C mutation

Adverse reaction (≥ 10%) of patients in CodeBreak 100 (N=204)

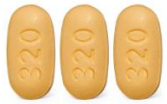
	All Grades (%)	Grades 3 to 4 (%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[††]	35	8
Arthralgia	12	1
General disorders and administration site conditions		
Fatigue[‡‡]	26	2
Edema[§§]	15	0
Metabolism and nutrition disorders		
Decreased appetite	13	1
Infections and infestations		
Pneumonia***	12	7
Skin and subcutaneous tissue disorders		
Rash[†††]	12	0

https://www.lumakrashcp.com/sotorasib-safety

Dose Modification: Sotorasib (LUMAKRAS®)

KRAS G12C mutation

Starting dose options



3× 320 mg tablets once daily[1]

or

8× 120 mg tablets once daily[1]

First Dose Reduction[1] (480 mg)

4× 120 mg tablets once daily[1]

Second Dose Reduction[1] (240 mg)

2× 120 mg tablets once daily[1]

BE CAUTIOUS !!

- **PPI, H2 blocker**
- **Rosuvastatin**

Hepatotoxicity	ILD/pneumonitis		Diarrhea	Other adverse reactions
AST or ALT > 3 × ULN with total bilirubin > 2 × ULN and no alternative causes	Any Grade suspected	AST or ALT	Despite appropriate supportive care: Grade 3–4	Grade 3–4
Permanently discontinue LUMAKRAS[1]	Withhold LUMAKRAS and permanently discontinue if confirmed[1]	Withhold LUMAKRAS until recovered to ≤ Grade 1 or baseline. After recovery, resume LUMAKRAS at the next lower dose level[1]		

https://www.lumakrashcp.com/sotorasib-safety

Drug-Induced ILD during cancer therapies : Incidence

Class	Estimated DIILD incidence (range)[a]
Bleomycin[1]	7%-21%
EGFR inhibitors[1,2]	0.3%-6%
HER2 inhibitors (including ADCs)[3-5]	2.4% (up to 15.8% with T-DXd)
BRC/ABL tyrosine kinase inhibitors[6-8]	Unknown (imatinib and dasatinib); ≥1/1,000 to <1/100 (nilotinib)
ALK inhibitors[9]	2.5% (95% CI: 1.7%-3.6%)
BRAF inhibitors[10]	2.4% (trametinib); data not shown
TRK/ROS1 inhibitors[13]	Data not shown
VEGFR inhibitors[14]	0.37% (bevacizumab in combination with FOLFOX and FOLFIRI)
Immune checkpoint inhibitors[1]	1.1%-3.6%
CDK4/6 inhibitors[15]	0.3%-2.1%
mTOR inhibitors[16]	11%

Conte P, et al. https://doi.org/10.1016/j.esmoop.2022.100404

Treatment Algorithm for the Treatment of DILD : Grade 2

B

Definition of grade 2 (moderate) DIILD: mild respiratory symptoms that do not deteriorate the patient's quality of life

TREATMENT[e]

RECOMMENDED

- Immediate **discontinuation of the anticancer drug**[f]
- **Steroid therapy**: 1-2 mg/kg/day prednisone or equivalent
- Consider antibiotic therapy when an overlapping infection cannot be excluded (fever, increased CRP and/or neutrophil counts)
- Consider TMP-SMX prophylaxis for opportunistic infections with high-dose steroids

[f]Definitive discontinuation of the anticancer drug should be recommended whenever possible. Rechallenge with immunotherapy is acceptable but caution should be exercised

FOLLOW-UP[g]

- Monitoring of dyspnoea on exertion (with SpO_2)
- Specialist lung assessment with repeated spirometry and DLCO
- HRCT of the chest
- Chest X-ray at the patient's bed only in case of worsening of the patient's condition

[g]Generally every 3-5 days for clinical monitoring and after 2 weeks for imagining and respiratory function test

RESPONSE

REDUCTION to GRADE 1 or COMPLETE RESOLUTION of DIILD

- **Tapering** of steroid therapy **after 4-6 weeks**
- Oncological assessment of the risks and benefits and discussion with the patient on whether to resume the **anticancer drug**[h]

[h]Depending on the anticancer drug administered

In case of REFRACTORY or PERSISTENT grade 2 DIILD (after 3-5 days from the start of steroid therapy)

Use the algorithm suggested for grade 3 DIILD (Figure 4B)

MULTIDISCIPLINARY EVALUATION SHOULD CONTINUE AT EVERY STAGE OF THERAPEUTIC PROCESS

[e]The completion of all diagnostic procedures (3A) is not necessary to start treatment, especially in the case of clinical deterioration

Conte P, et al. https://doi.org/10.1016/j.esmoop.2022.100404

Treatment Algorithm for the Treatment of DILD : Grade 3

B Definition of grade 3 (severe) DIILD: Symptoms that lead to a worsening of the quality of life and limit the activities of daily living of the patient, possibly needing oxygen therapy, regardless of the severity of the radiologic findings

PATIENT WITH GRADE 3 DIILD SHOULD BE HOSPITALIZED

TREATMENT[e]

RECOMMENDED IN REFRACTORY GRADE 2 AND IN GRADE 3 DIILD

- **Consider hospitalisation** and **oxygen therapy** until resolution of respiratory failure
- Timely and definitive **discontinuation of the anticancer drug**
- **Steroid therapy**: 1-2 mg/kg/day methylprednisolone or equivalent
- Consider antibiotic therapy when an overlapping infection cannot be excluded
- Consider TMP-SMX prophylaxis for opportunistic infections with high-dose steroids

FOLLOW-UP[f]

- Specialist lung assessment with spirometry and DLCO (to be carried out after the improvement of the patient's condition)
- HRCT of the chest

[f]Generally after 2 weeks from hospital discharge and, in any case, in relation to the clinical course of disease

RESPONSE

REDUCTION TO GRADE 1

Tapering of steroid therapy **after 8-12 weeks** of treatment

REFRACTORY DISEASE (after 48-72 h of treatment)

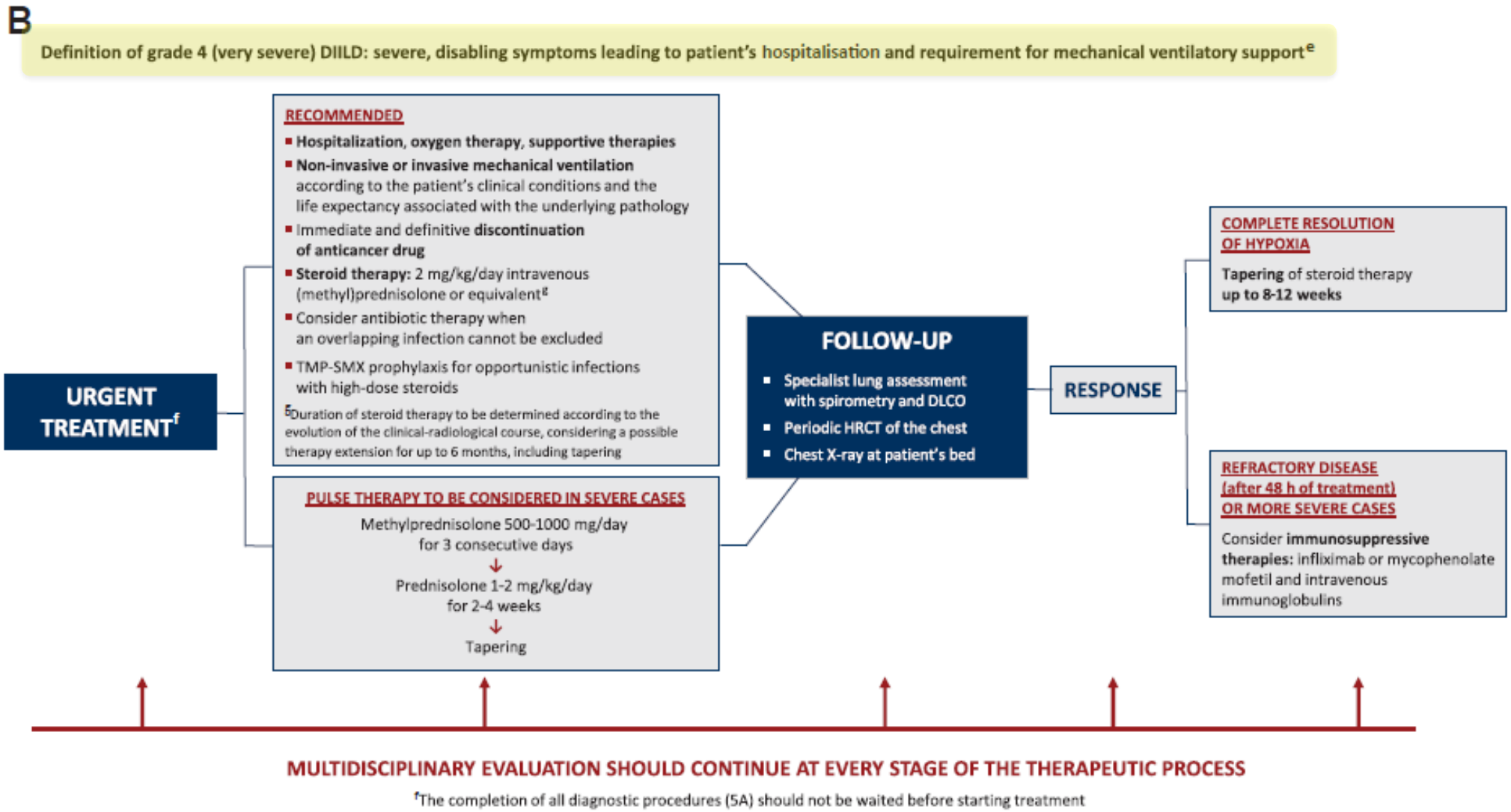
Consider **immunosuppressive therapies:** infliximab, tocilizumab or mycophenolate mofetil and intravenous immunoglobulins

MULTIDISCIPLINARY EVALUATION SHOULD CONTINUE AT EVERY STAGE OF THERAPEUTIC PROCESS

[e]The completion of all diagnostic procedures (4A) is not necessary to start treatment

Conte P, et al. https://doi.org/10.1016/j.esmoop.2022.100404

Treatment Algorithm for the Treatment of DILD : Grade 4



Conte P, et al. https://doi.org/10.1016/j.esmoop.2022.100404

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Takeaway Messages

- As pharmacologic treatment options for lung caner are increasing, and indications of systemic treatment are expanding, treatment-related toxicities cannot be avoided.
- The clinical characteristics of adverse events of each treatment are so diverse, care givers should be familiar with the AEs and recommended managements.
- Adverse events might be fatal, so risk stratification and prediction, early detection and early management to minimize the risk and maximize the benefit should be done.
- If necessary, multidisciplinary interactions are essential to improve outcomes.

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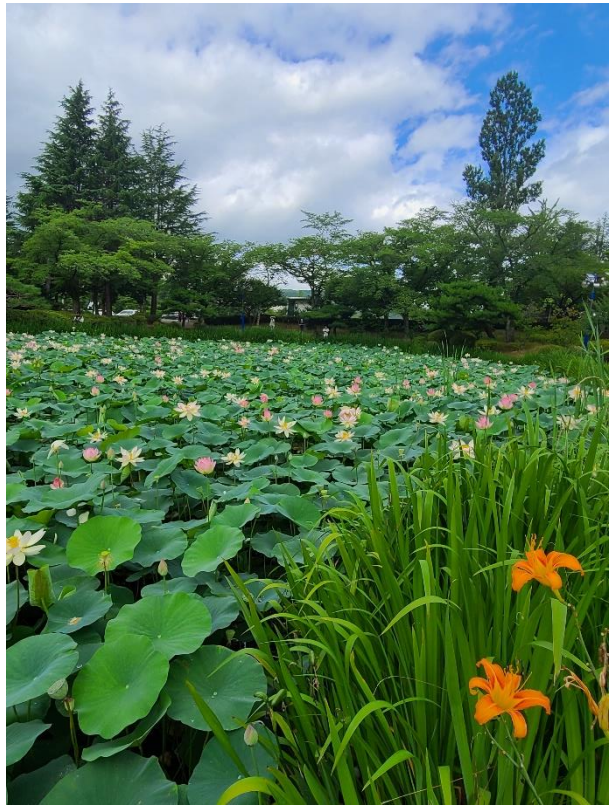
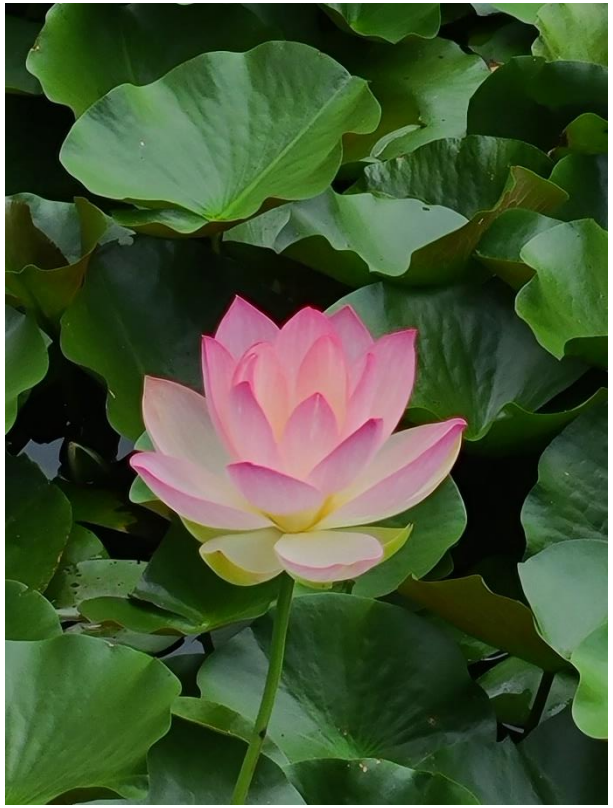
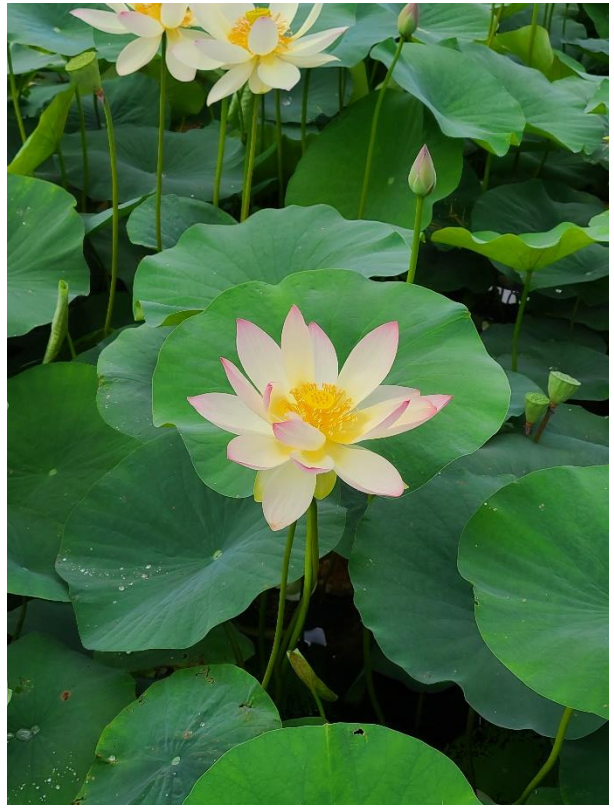


Thank you for your kind attention.