Drug-induced Interstitial Lung Disease -Best Clinical Approaches

ILD school 2019
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박종선

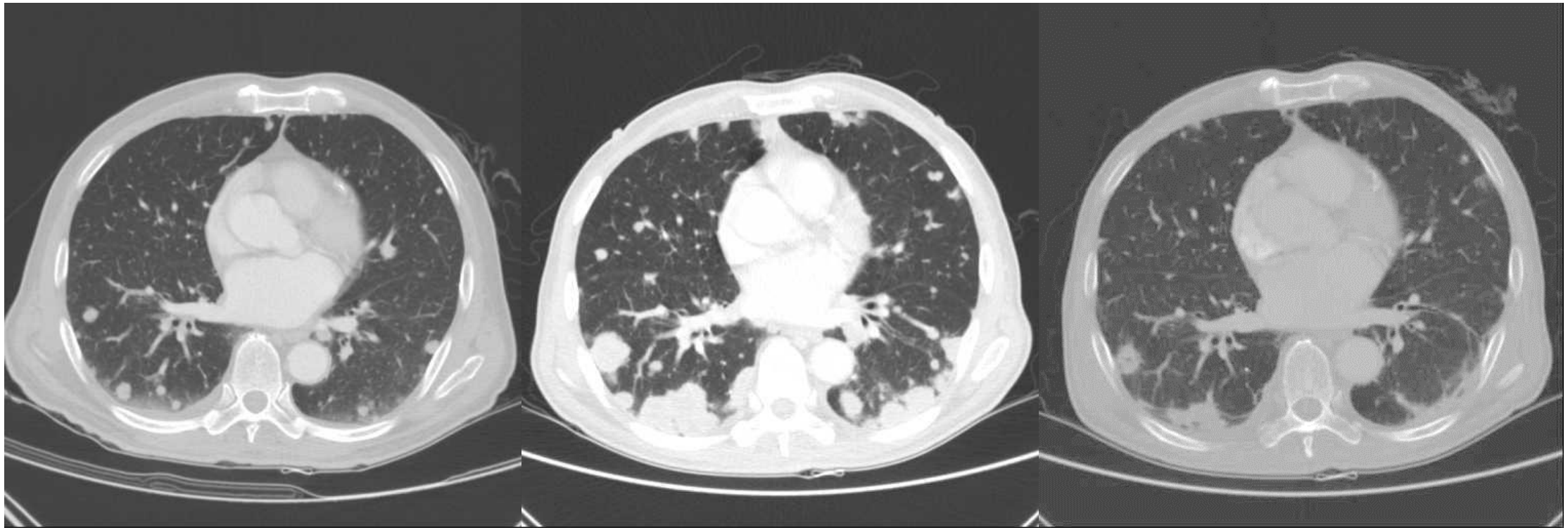
Contents

- Incidence
- Potential mechanisms
- Risk factors
- Diagnosis
- Radiologic patterns
- Treatment
- Prognosis

M/74, AGC, lung metastasis

Progression after cytotoxic chemotherapy

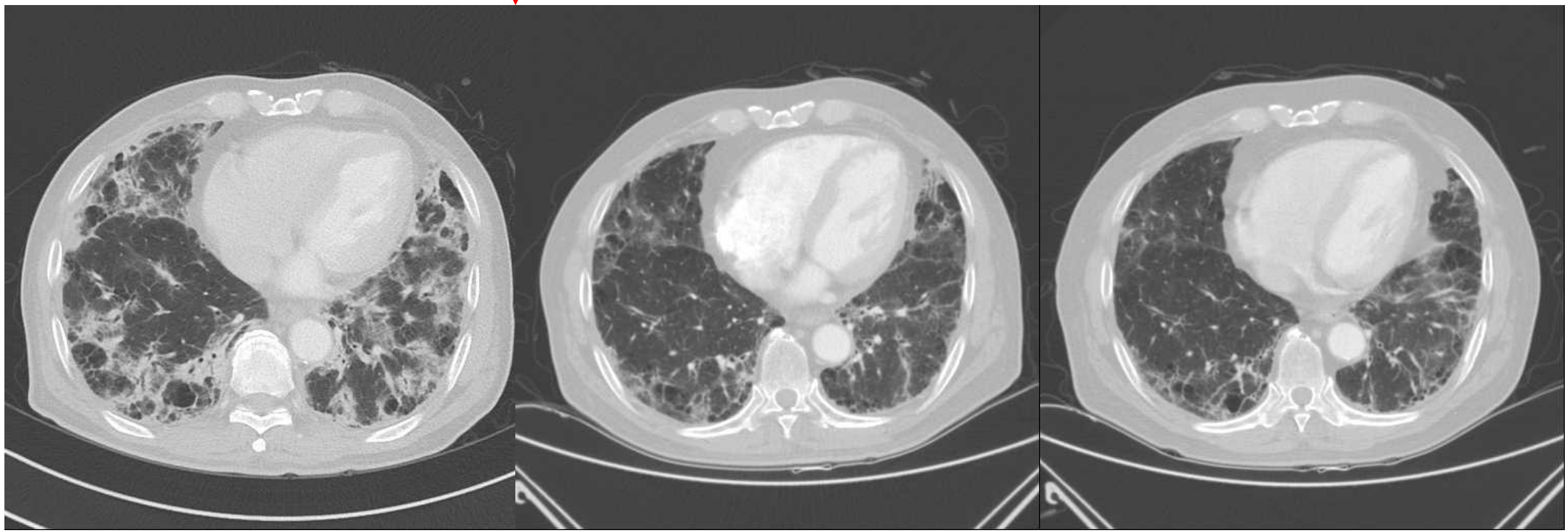
Margetuximab+Pembrolizumab started



2016.12.27 2017.10.20 2018.2.22

M/74, AGC, lung metastasis

Margetuximab+Pembrolizumab 2017.10.2-2018.6.27
Stopped d/t Gr2 pneumonitis, treated with prednisolone 40mg, taper~2019.1.18



2018.7.18 2018.10.20 2019.2.22

Drug-induced interstitial lung diseases (DILD)

- Lung injury that results from the specific use of a drug

- Main lesions of drug-induced lung injury
  1. Alveolar and interstitial regions
  2. Airway
  3. Blood vessels
  4. Pleura

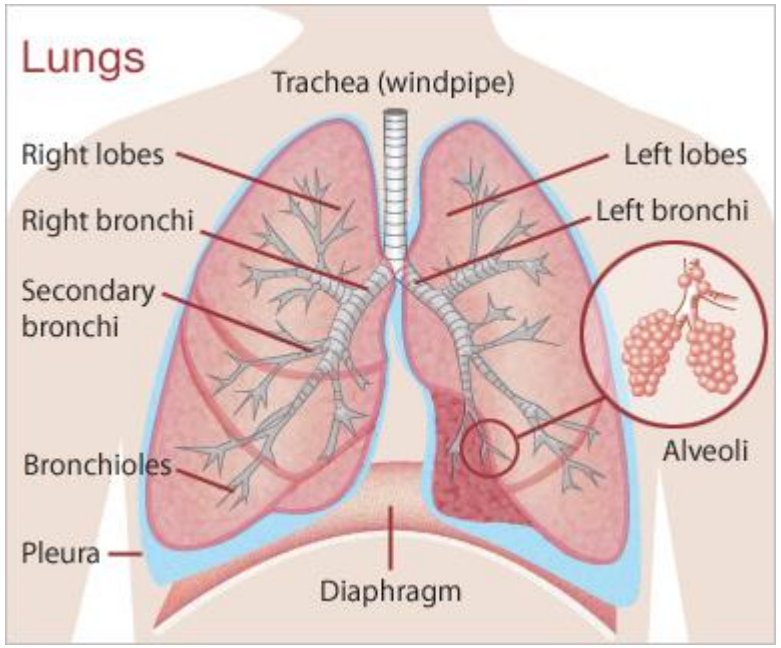


Table 1 – Main clinical types and histological diagnoses of DLIs (in contrast to common diffuse pulmonary diseases).

Main lesion site	Clinical disease type[a]	Histological diagnosis[b]
1. Alveolar and interstitial regions		
	Acute respiratory distress syndrome/acute lung injury (ARDS/ALI)	Diffuse alveolar damage (DAD) (clinically severe)
	Idiopathic interstitial pneumonias (IIPs) (collective term)	
	Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD) (clinically severe)
	Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP) (clinically severe)
	Non-specific interstitial pneumonia (NSIP)	Non-specific interstitial pneumonia (NSIP)
	Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
	Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
	Lymphocytic interstitial pneumonia (LIP)	Lymphocytic interstitial pneumonia (LIP)
	Eosinophilic pneumonia (EP)	Eosinophilic pneumonia (EP)
	Hypersensitivity pneumonia (HP)	Hypersensitivity pneumonia (HP)
	Granulomatous interstitial lung diseases	Granulomatous interstitial pneumonia
	Pulmonary edema	Pulmonary edema
	Capillary leak syndrome	Pulmonary edema
	Pulmonary alveolar proteinosis	Alveolar proteinosis
	Diffuse alveolar hemorrhage	Alveolar hemorrhage
2. Airway		
	Bronchial asthma	Bronchial asthma
	Bronchiolitis obliterans syndrome (BOS)	Bronchiolitis obliterans (BO)
	Bronchiolitis obliterans syndrome (BOS)	Constrictive bronchiolitis obliterans (CBO) (clinically severe)
3. Blood vessels		
	Vasculitis	Vasculitis
	Pulmonary hypertension	Pulmonary hypertension
	Pulmonary veno-occlusive disease	Pulmonary veno-occlusive disease
4. Pleura		
	Pleuritis	Pleuritis

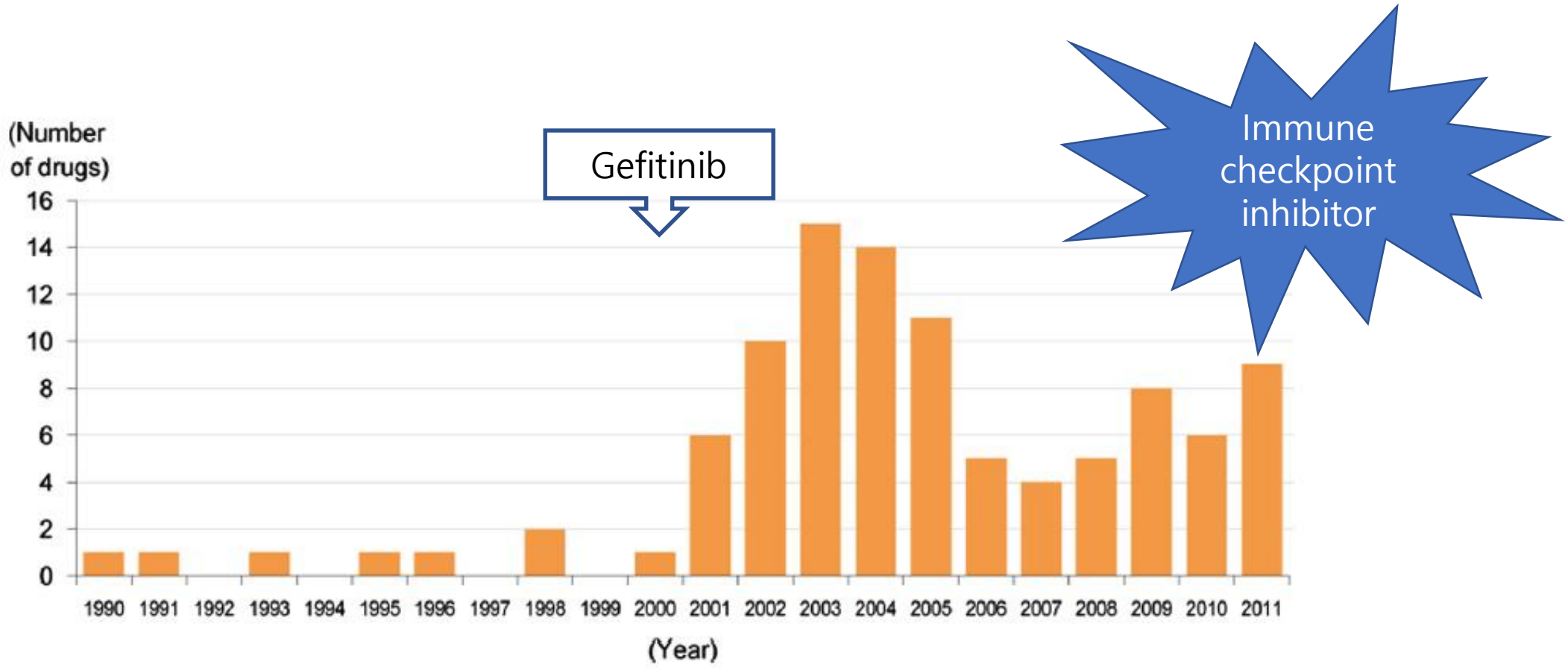
Kubo K et al, Respir Investig 2013;51:260–77.

Clinical disease type of DILD

- Acute
  - Hypersensitivity pneumonia (HP)
  - Acute eosinophilic pneumonia (AEP)
  - Diffuse alveolar damage (DAD)
  - DDx. non-cardiogenic pulmonary edema

- Chronic
  - Nonspecific interstitial pneumonia (NSIP)
  - Organizing pneumonia (OP)

Number of drugs reported to cause DILD, Japan



Kubo K et al, Respir Investig 2013;51:260–77

Incidence of drug-induced lung injury

Table 3 – Incidence of DLIs in Japan and abroad.

Drug	Japan	Abroad[a]
Gefitinib	3.98% (n=1482)	0.3% (United States: n=23,000)
Leflunomide	1.81% (n=3867)	0.017% (Abroad: n=861,860)
Bleomycin	0.66% (n=3772)	0.01% (Abroad: n=295,800)
Bortezomib	2.33% (n=3556)	0.16% (Abroad: n=106,832)
Erlotinib	4.52% (n=3488)	0.7% (Abroad: n=4900)

Kubo K et al, Respir Investig 2013;51:260–77.

Drug-induced Interstitial Lung Diseases: Nationwide Spontaneous Reports in Korea over ten years (2005-2015)

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

Gun Woo Koo, Tai Sun Park, Dong Won Park, Ji-Yong Moon, Sang-Heon Kim, Tae-Hyung Kim, Jang Won Sohn, Dong Ho Shin and Ho Joo Yoon

Purpose: Many drugs can cause interstitial lung diseases by various mechanisms. However, the epidemiology and causes of the drugs-induced interstitial lung diseases (DILD) have not been well described yet. This study aimed to assess the characteristics of the subjects with DILD and the causative drugs of DILD cases, which has been reported spontaneously in Korea.

Methods: Cases of DILD were recruited from the spontaneously reported pharmacovigilance data which has been recorded in the Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System database (KIDS-KAERS database) over recent 10 years (from Jul 2005 to Jun 2015). DILD was defined using WHO-Adverse Reaction Terminology indicative of interstitial lung diseases.

Results: From 767,960 cases of spontaneously reported adverse drug event cases, 445 cases (0.06%) were identified as DILD. Of the subjects with DILD, males were more common than females (70.8% vs.29.2%). Regarding severity, 315 cases (70.8%) were classified as serious based on WHO criteria. The most common causative drugs were antineoplastic and immunomodulating agents (70.65%), followed by antiinfectives and cardiovascular drugs.

Conclusions: The prevalence of DILD among the spontaneously reported adverse drug event cases in Korea was low. Males were more frequently affected and the majority of cases were induced by antineoplastic immunomodulating agents.

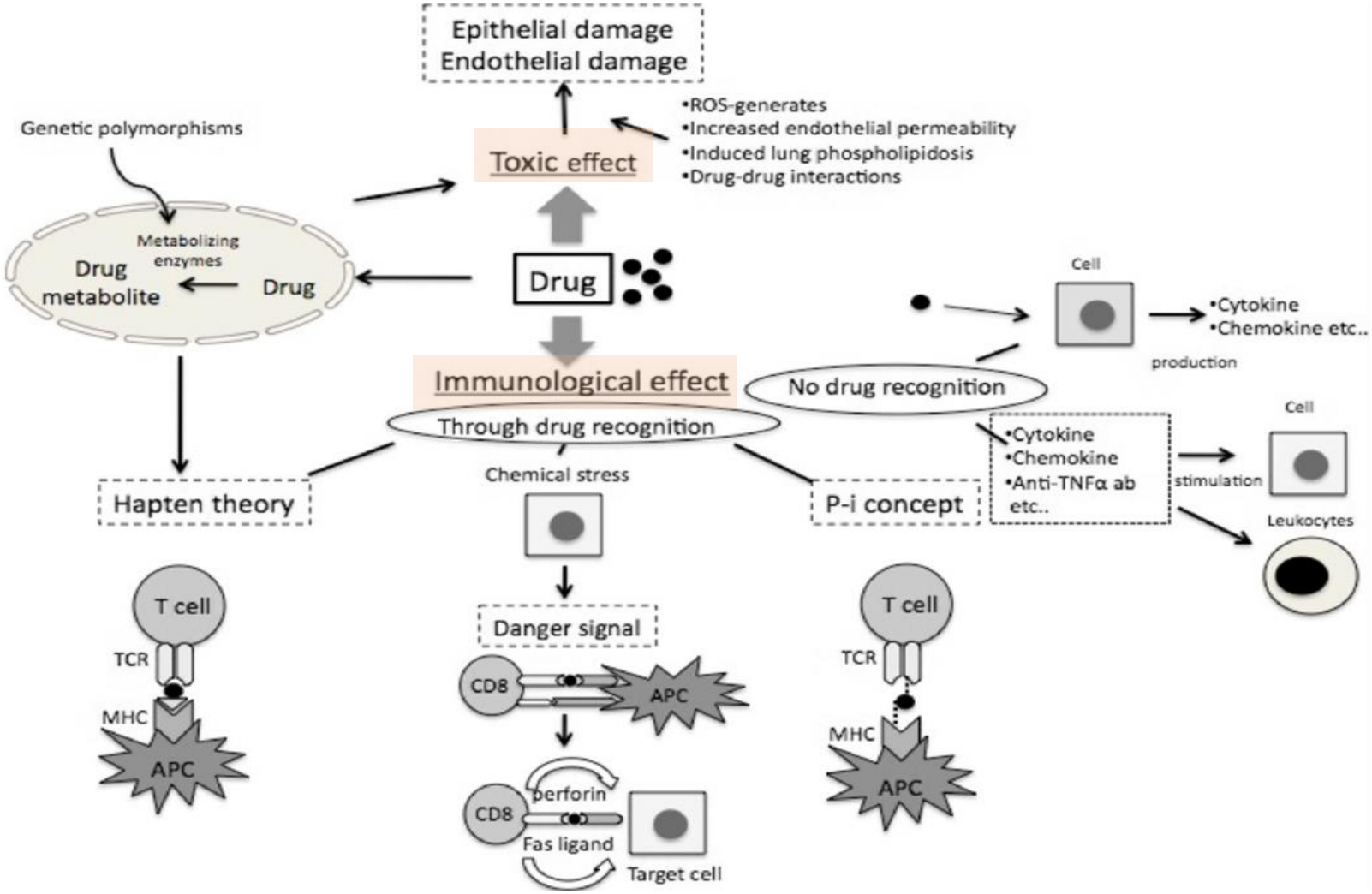
제 122 차 대한결핵 및 호흡기학회 추계학술대회 2016

Drug/Class	Number of Studies	Quality	Study Design	Patient Population	Sample Size (Range)	Case Definition of DIILD	Estimated Incidence (Range)	Estimated Mortality in Those with DIILD (Range)
Cancer Therapies								
Bleomycin [18–24]	7	Moderate = 3 Low = 3 Very low = 1	Meta-analysis = 2 Observational studies = 5	Various cancers (1 meta-analysis in ovarian sex cord stromal tumours and 1 in all cancer RCT data)	22–1147	variable	Meta-analyses: 6.8–15% Other studies: 6.8–21%	Meta-analyses: 8.1–23% Other studies: 0–48%
Gemcitabine [13,25–32]	9	Moderate = 2 Low = 6 Very low = 1	Meta-analysis = 2 Clinical trial = 3 Observational = 4	Cancer (predominantly pancreatic and non-small cell lung cancer but also others)	Meta-analysis: 1308–1742 Others: 26–2440	variable	1.1–3.9%	0–22%
Epidermal growth factor receptor-targeted therapies (EGFR)								
Erlotinib [34–36,89,9		Moderate = 2	Meta-analysis = 2 Post marketing					5%
Gefitinib [34–37]	4	Low = 2	Post marketing surveillance = 2	colorectal cancer	70–5468	variable	1.9–3.5%	18–44%
Panitumumab [33,39]	2 (but reporting from same cohort)	Moderate = 2	Post marketing surveillance	Colorectal cancer	3085	Expert case review	1.3%	51.3%
Cetuximab [38]	1	Moderate = 3	Post marketing surveillance	Colorectal cancer	2006	Physician reported	1.2%	41.6%
Mechanistic target of rapamycin protein (MTOR) inhibitors								
Everolimus [40–43,45,46,48,49]	8	Moderate = 3 Low = 3 Very low = 2	Meta-analysis = 1 Clinical trial = 2 (same trial 2 separate published analyses) Observational = 5	Neuroendocrine cancer Renal cell cancer Renal transplant	40–2261	Variable, including radiographic signs of DIILD	2.8–58%	5.4–20%
Temsirolimus [44,47]	2	Low = 2	Meta-analysis = 1 Clinical trial = 1 Observational study = 1	Neuroendocrine cancer Endometrial cancer Renal cell cancer	22–408	Variable	29–36%	n/a
Sirolimus [48]	1	Very low = 1	Observational	Renal/pancreas transplant	115	Physician reported	9.5%	0%
Check point inhibitors (CPI)								
All CPIs [51–53]	3	High = 2 Moderate = 1	Meta-analysis = 2 Observational = 1	Non-small cell lung cancer	1826–3232	variable	1.1–3.6%	8–9.4%

DILD accounts for 3–5% of prevalent cases of ILD.

Skeoch et al, J. Clin. Med. 2018, 7, 356; doi:10.3390

Potential mechanisms of DILD



Matsuno et al. Respiratory Research 2012, 13:39

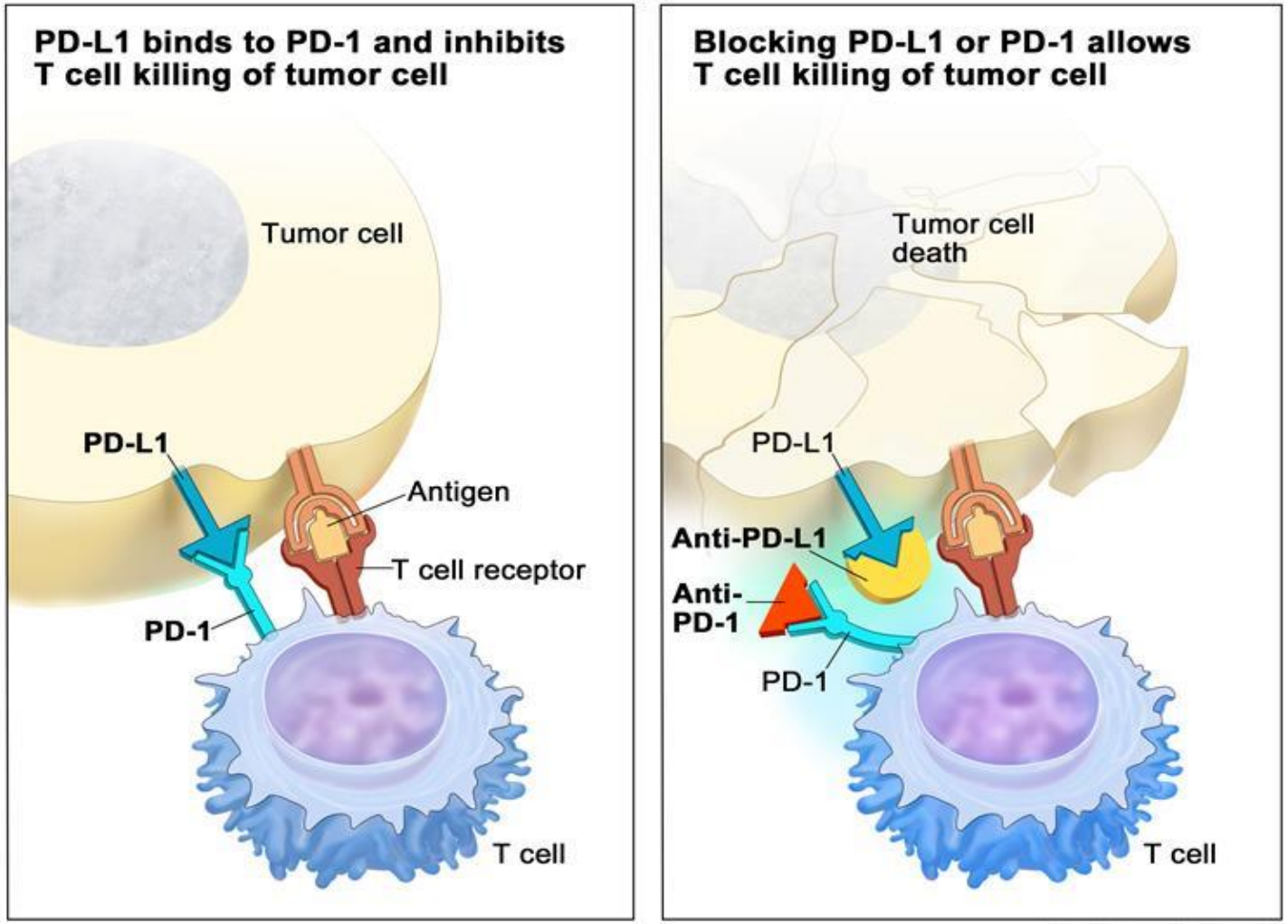
Potential mechanisms of DILD

- Cytotoxic pulmonary injury
  - chemotherapeutic agents (e.g. gemcitabine)
  - bleomycin, MTX, cyclophosphamide
  - Possible by non-cytotoxic drugs (sulfasalazine, amiodarone..)
  - Causes diffuse alveolar damage

- Immune-mediated pulmonary injuries
  - Activate immune cells by acting as a hapten or mimicking an antigen

Kubo K et al, Respir Investig 2013;51:260–77

Immune checkpoint inhibitor (ICI)



From NCI dictionary, U.S Government

ICI-related pneumonitis

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer

Jun Yeun Cho[a], Junghoon Kim[b], Jong Seok Lee[c], Yu Jung Kim[c], Se Hyun Kim[c], Yeon Joo Lee[a], Young-Jae Cho[a], Ho Il Yoon[a], Jae Ho Lee[a], Choon-Taek Lee[a], Jong Sun Park[a,*]

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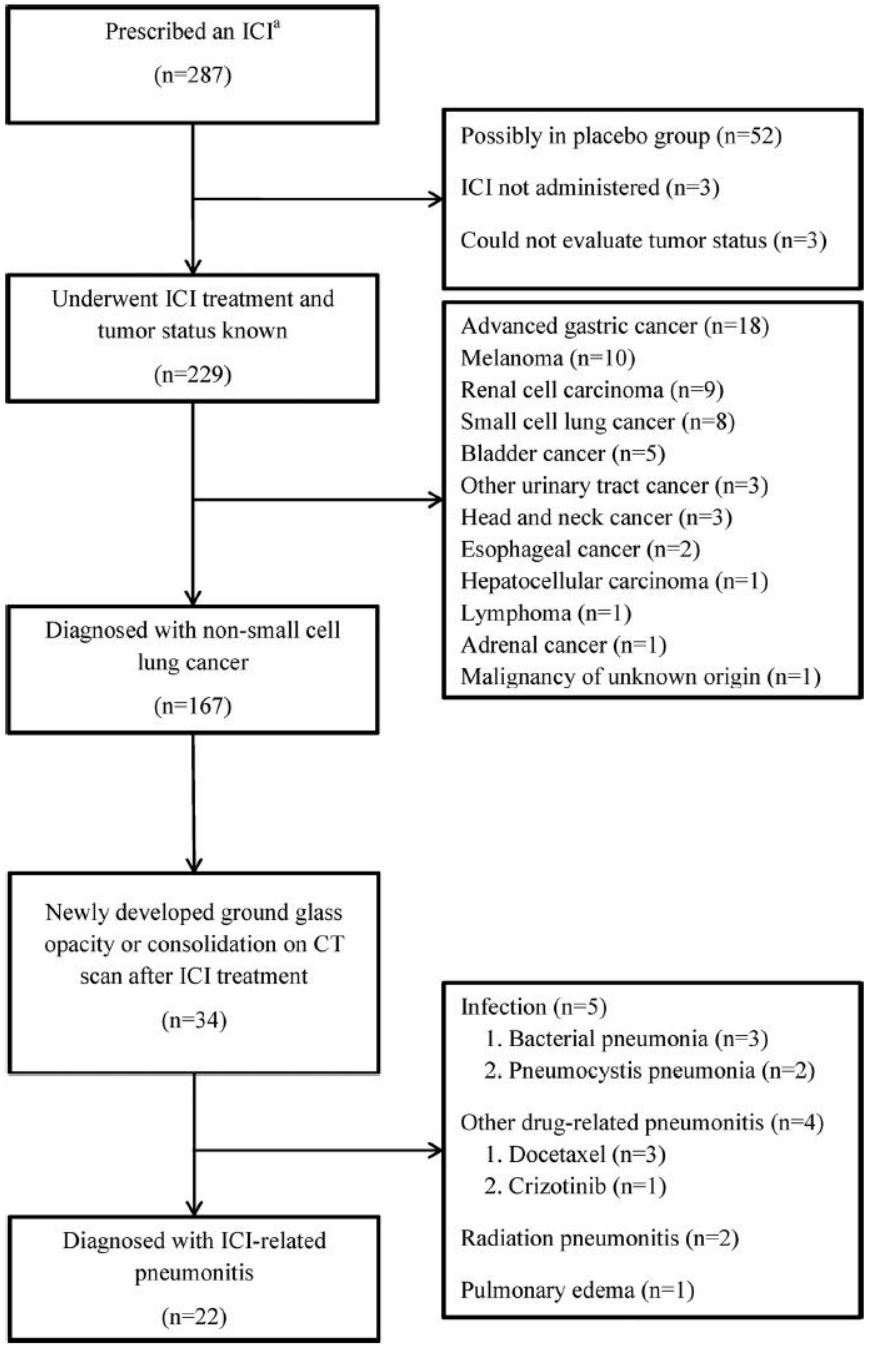
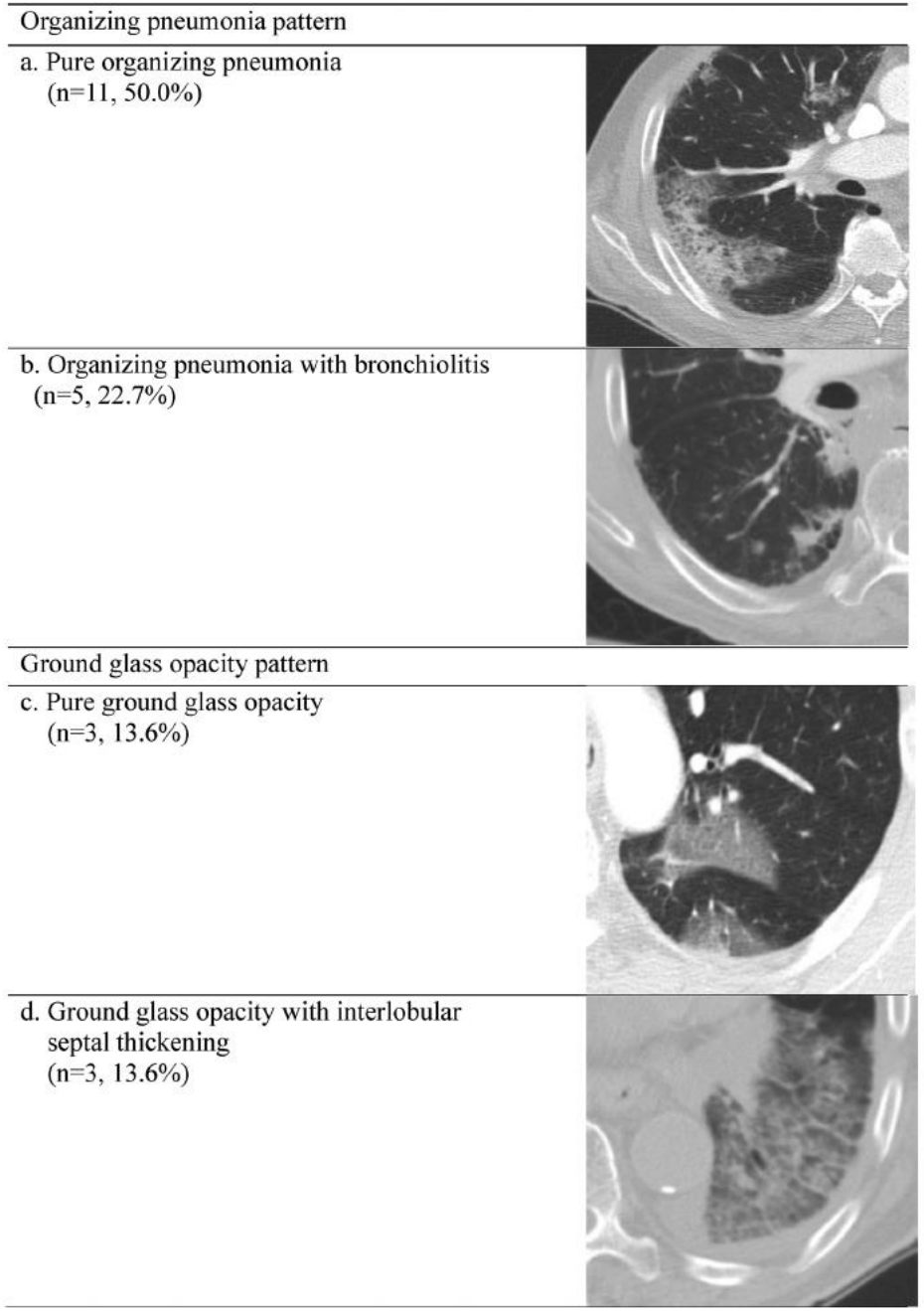
Cho et al, Lung Cancer 125 (2018) 150–156


Prescribed an ICI[a]
(n=287)
Possibly in placebo group (n=52)
ICI not administered (n=3)
Could not evaluate tumor status (n=3)
Underwent ICI treatment and tumor status known
(n=229)
Advanced gastric cancer (n=18)
Melanoma (n=10)
Renal cell carcinoma (n=9)
Small cell lung cancer (n=8)
Bladder cancer (n=5)
Other urinary tract cancer (n=3)
Head and neck cancer (n=3)
Esophageal cancer (n=2)
Hepatocellular carcinoma (n=1)
Lymphoma (n=1)
Adrenal cancer (n=1)
Malignancy of unknown origin (n=1)
Diagnosed with non-small cell lung cancer
(n=167)
Newly developed ground glass opacity or consolidation on CT scan after ICI treatment
(n=34)
Infection (n=5)
1. Bacterial pneumonia (n=3)
2. Pneumocystis pneumonia (n=2)
Other drug-related pneumonitis (n=4)
1. Docetaxel (n=3)
2. Crizotinib (n=1)
Radiation pneumonitis (n=2)
Pulmonary edema (n=1)
Diagnosed with ICI-related pneumonitis
(n=22)

13.2%


Organizing pneumonia pattern
a. Pure organizing pneumonia
(n=11, 50.0%)
b. Organizing pneumonia with bronchiolitis
(n=5, 22.7%)
Ground glass opacity pattern
c. Pure ground glass opacity
(n=3, 13.6%)
d. Ground glass opacity with interlobular septal thickening
(n=3, 13.6%)

Characteristics and risk factors of ICI-pneumonitis

Variable	Without pneumonitis (n = 145)	With pneumonitis (n = 22)	P
Age ≥ 70 years	44 (30.3)	12 (54.5)	0.025
Male sex	110 (75.9)	18 (81.8)	0.538
Former/Current smoker	102 (70.3)	18 (81.8)	0.265
ECOG ≥ 2	16 (11.0)	4 (18.2)	0.336
COPD	19 (13.1)	6 (27.3)	0.083
Bronchiectasis	7 (4.8)	1 (4.5)	0.954
Interstitial lung disease[a]	4 (2.8)	4 (18.2)	0.002
Postoperative recurrence	31 (21.4)	6 (27.3)	0.535
Pathology			0.060
Adenocarcinoma	96 (66.2)	10 (45.5)	
Non-adenocarcinoma	49 (33.8)	12 (54.5)	
Treatment line			0.732
1st	41 (28.3)	7 (31.8)	
≥ 2nd	104 (71.7)	15 (68.2)	
PD-L1 expression > 0%, pharmDx[b]	35/46 (76.1)	5/6 (83.3)	1.000
PD-L1 expression > 0%, SP263[c]	17/22 (77.3)	5/6 (83.3)	1.000
Previous cytotoxic chemotherapy	106 (73.1)	16 (72.7)	0.970
Previous EGFR-TKI	22 (15.2)	1 (4.5)	0.178
Previous thoracic radiotherapy	21 (14.5)	6 (27.3)	0.129
Extrathoracic metastasis	85 (58.6)	7 (31.8)	0.019
Observation period[d], day	140.0 (3–1511)	145.5 (40–1379)	0.533
ICI exposures, n	5 (1–63)	5 (1–68)	0.627

Incidence: 19%

Risk factors of ICI-related pneumonitis.

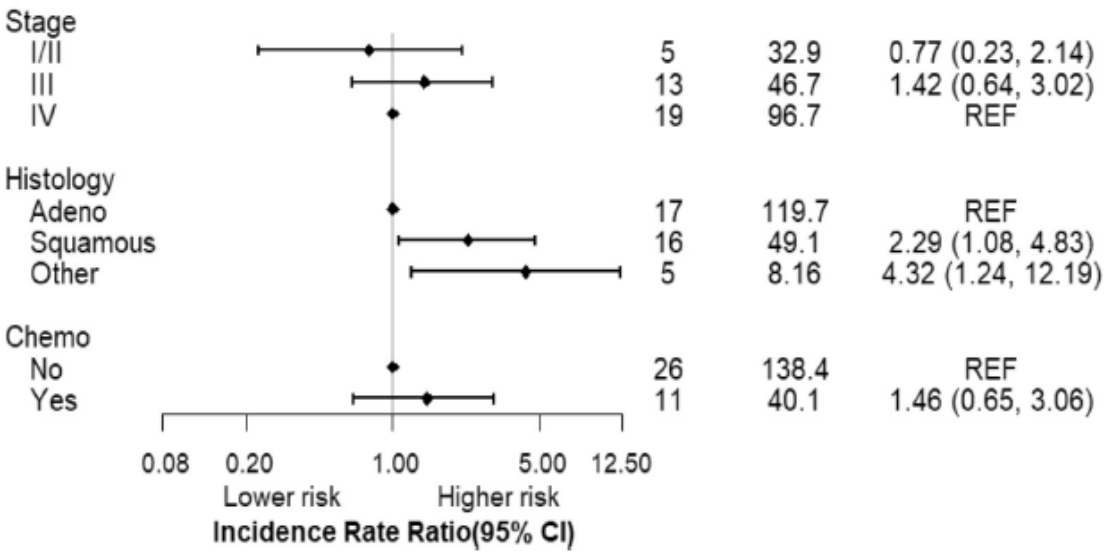
Variable	Univariate		Multivariate		
	OR	95% CI	OR	95% CI	P
Age ≥ 70 years	2.76	1.11–6.85	1.87	0.69–5.05	0.218
Interstitial lung disease	7.83	1.80–34.08	6.03	1.19–30.45	0.030
Extrathoracic metastasis	0.33	0.13–0.86	0.34	0.13–0.92	0.034

Cho et al, Lung Cancer 125 (2018) 150–156

Risk factors of ICI-pneumonitis in lung cancer

Table 2. Risk Factors for Development of CIP at 1 Year

Risk Factor	OR	CI	*p* Value
Univariate analysis			
Demographics			
Female Sex	1.12	(0.53-2.35)	0.75
Smoking	0.86	(0.41-1.82)	0.70
Age	1	(0.96-1.04)	0.69
Race (vs. white)			
Black	1.08	(0.37-2.72)	0.87
Asian/other	2.09	(0.28-10.2)	0.39
Tumor characteristics			
Adenocarcinoma	0.42	(0.19-0.89)	0.02
Initial stage (vs. stage IV)			
I	0.33	(0.01-1.83)	0.30
II	1.24	(0.26-4.39)	0.74
III	1.44	(0.62-3.26)	0.38
Therapy-related factors			
Chemotherapy	0.86	(0.38- 2.0)	0.72
Surgery	0.53	(0.17-1.37)	0.22
ICI therapy (vs. nivolumab therapy)			
Pembrolizumab	0.39	(0.06-1.44)	0.22
Other	0.19	(0.01-1.00)	0.11
Combination ICI	1.72	(0.80-3.67)	0.16
Multivariate analysis[a]			
Adenocarcinoma	0.38	(0.17-0.82)	0.01



Suresh K et al, J Thorac Oncol 2018;13(12):1930-1939

Table 2. Risk Factors for DILD Development in Lung Cancer Patients.

Variables	Univariate Analysis			Multivariate Analysis		
	Odds Ratio (95% CI)		*P*	Odds Ratio (95% CI)		*P*
Age ≥75 years (vs <75 years)	0.80	(0.32, 1.98)	0.621	—		—
ECOG PS[a] ≥2 (vs 0/1)	0.62	(0.18, 2.10)	0.445	—		—
Smoking status, ex/current (vs never)	1.83	(0.63, 5.36)	0.268	—		—
Histology						
Adenocarcinoma (vs nonadenocarcinoma)	0.52	(0.23, 1.17)	0.114	—		—
Squamous cell carcinoma (vs nonsquamous cell carcinoma)	2.19	(1.04, 4.63)	0.039	1.72	(0.78, 3.83)	0.181
SCLC (vs NSCLC)	0.68	(0.27, 1.69)	0.406	—		—
Stage IV (vs <IV)	1.05	(0.49, 2.09)	0.890	—		—
Prior thoracic radiotherapy (vs none)	1.17	(0.58, 2.33)	0.665	—		—
Preexisting ILD (vs non-ILD)	5.39	(2.49, 11.70)	<0.001	5.38	(2.47, 11.73)	<0.001

Sakurada et al, Annals of Pharmacotherapy 2015:49(4);398–404

Other risk factors for DILD

- Age, >60years
- Pre-existing lung disease
- History of pulmonary surgery
- Radiation exposure to the lung
- Decreased renal function ?

Kubo K et al, Respir Investig 2013;51:260–77

Diagnosis of DILD

- Identification of the causative drug
- Temporal relationship
- Diagnosis of exclusion !
- Exclusion of other causes or infection
  - Bronchoalveolar lavage
  - Blood tests

Diagnosis of DILD

Table 4 – Diagnostic criteria for DLIs.

1.	History of ingestion of a drug that is known to induce lung injury	Specifically inquire about the following when taking the patient's history: over-the-counter (OTC) drugs, health foods, and illegal narcotic drugs/antihypnotic drugs.
2.	The clinical manifestations have been reported to be induced by a drug.	The clinical manifestations include clinical findings, imaging findings, and pathological features.
3.	Other causes of the clinical manifestations could be ruled out.	Differentiation from infection, cardiogenic pulmonary edema, exacerbation of an underlying disease, etc.
4.	Improvement of the clinical manifestations after drug discontinuation.	Spontaneous remission or remission in response to an adrenocorticosteroid.
5.	Exacerbation of the clinical manifestations after resuming drug administration.	Resuming drug administration to identify the causative drug is not generally recommended, but is acceptable if the patient requires the drug and safety is assured.

Kubo K et al, Respir Investig 2013;51:260–77

Role of bronchoalveolar lavage in DILD

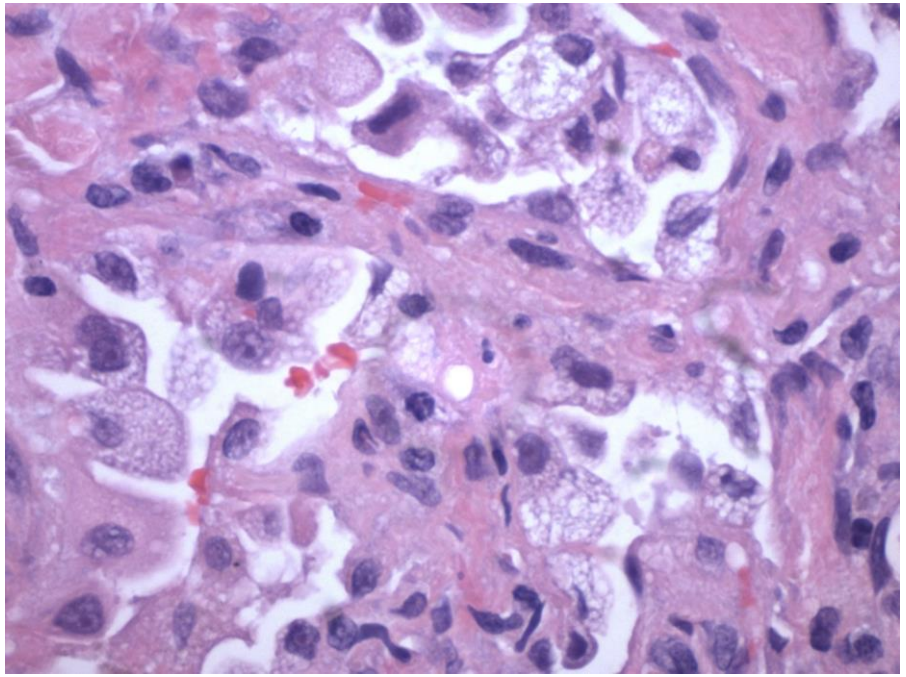
- Rule out other diseases, such as infection
- Provide clues to disease pathology and help predict histopathological findings.

- Cellular pneumonia: lymphocyte >50%
- Eosinophilic pneumonia : eosinophil >25%
- Cytotoxic reactions
  - neutrophils ↑, aggregates of atypical alveolar type II epithelial cells

Bronchoalveolar lavage fluid in DILD

- Diffuse alveolar hemorrhage
  - Hemosiderin-containing macrophage

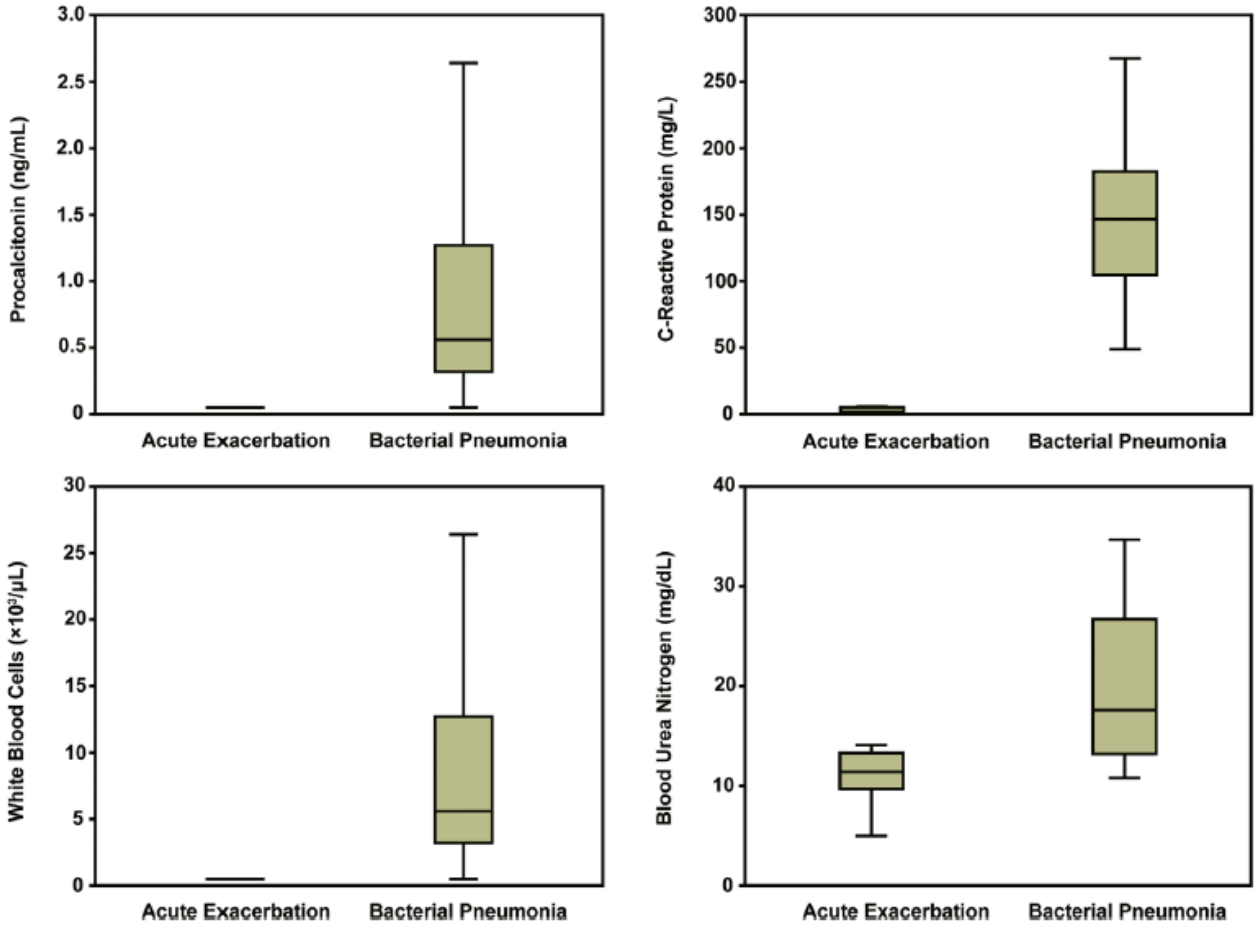
- Amiodarone-induced alveolar damage
  - Alveolar macrophages containing foamy cytoplasm
  - Attributable to the accumulation of phospholipids (surfactant-like substances)



Blood tests for DILD

- Tests for non-specific inflammatory response, tissue damage & allergic reaction
  - ESR, CRP, LDH, eosinophil count, procalcitonin
- Markers associated with interstitial pneumonia
  - Krebs von der Lungen-6 (KL-6)
  - Pulmonary surfactant protein-A (SP-A)
  - Pulmonary surfactant protein-D (SP-D)
- Drug lymphocyte stimulation test (DLST)
  - Sensitized lymphocytes are collected from patients
  - Mixed with the offending drug
  - Measure 3H–thymidine uptake by the lymphocytes

Procalcitonin in ILD



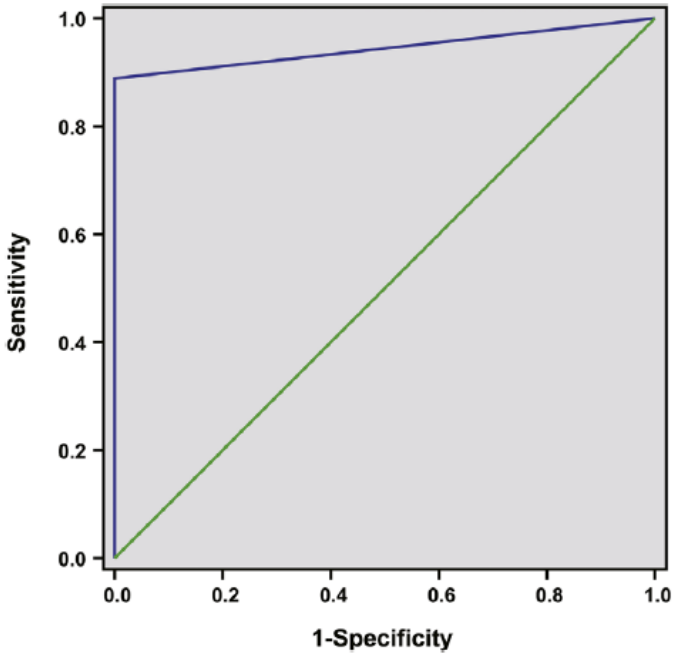


FIGURE 3. Receiver operating characteristics curve of the procalcitonin level for a differential diagnosis of bacterial pneumonia and acute exacerbation of interstitial lung disease.

cutoff 0.1ng/mL

AM J Med Sci 2016;351(5):499– 505

Procalcitonin을 이용한 Bacterial Pneumonia와 Radiotherapy Pneumonitis 및 Chemotherapy Induced Pneumonitis의 감별

국립암센터 폐암센터 호흡기내과

강효재, 황보빈, 이희석

목적: Procalcitonin은 세균감염 혹은 패혈증이 있을 때 상승하며 특히 폐렴의 경우 바이러스 감염이나 비감염성 염증반응에서는 올라가지 않아 bacterial pneumonia (BP)의 조기진단 및 질병 경과의 추적에 도움이 된다고 알려져 있다. 그러나 이 검사법이 BP를 Radiotherapy pneumonitis (RTP)나 chemotherapy induced pneumonitis (CIP)와 감별하는데 도움이 되는지에 대해서는 알려진 바가 없어, 이 연구를 통해 이들 질환의 감별에 대한 Procalcitonin 검사의 유용성을 확인하고자 하였다.

방법: 2011년 5월부터 2013년 5월까지 국립암센터에서 호흡기증상 및 영상학적 소견으로 폐렴 의심 하에 procalcitonin 검사를 시행 받은 환자들을 대상으로, 세균학적 검사 결과 및 폐렴 발생 6개월 이내의 방사선 치료나 항암치료 여부 및 치료 후 질병 경과를 분석하여 BP, RTP, CIP 세 군으로 나누어 procalcitonin 검사 결과를 분석하였다.

성적: Procalcitonin 검사를 시행한 환자 220명 중에 BP는 84명(38.2%), RTP는 29명(13.2%), CIP는 9명(4.1%), 기타 98명(44.5%)이었다. BP, RTP, CIP 세군 간의 나이 및 성별에는 큰 차이가 없었다[남자 63명 (75%): 19명 (65.5%): 7명 (77.8%), P=0.58; 평균 나이 65.2±11.46세: 67.1±8.59세: 70.3±7.25세, P=0.36)]. BP군의 평균 procalcitonin level은 5.64±18.97였고 RTP 환자는 0.08±0.05, CIP 환자는 0.14±0.12으로 BP 군의 평균 procalcitonin level은 RTP, CIP 와 각각 통계적으로 유의한 차이를 보였다($p<0.001$, $p=0.008$, MW test). 그러나 RTP와 CIP 두군 사이에는 유의한 차이는 없었다($p=0.08$, MW test).

결론: 임상에서 BP와 RTP 및 CIP 의 감별이 필요할 때 procalcitonin은 매우 유용한 검사이다.

제116차 대한결핵 및 호흡기학회 추계학술대회 2013

Krebs von der Lungen-6 (KL-6) in ILD

- KL-6 is a MUC1 mucin with a sialylated carbohydrate chain that is recognized by anti-KL-6 antibody.
- Mainly produced by alveolar type II epithelial cells.

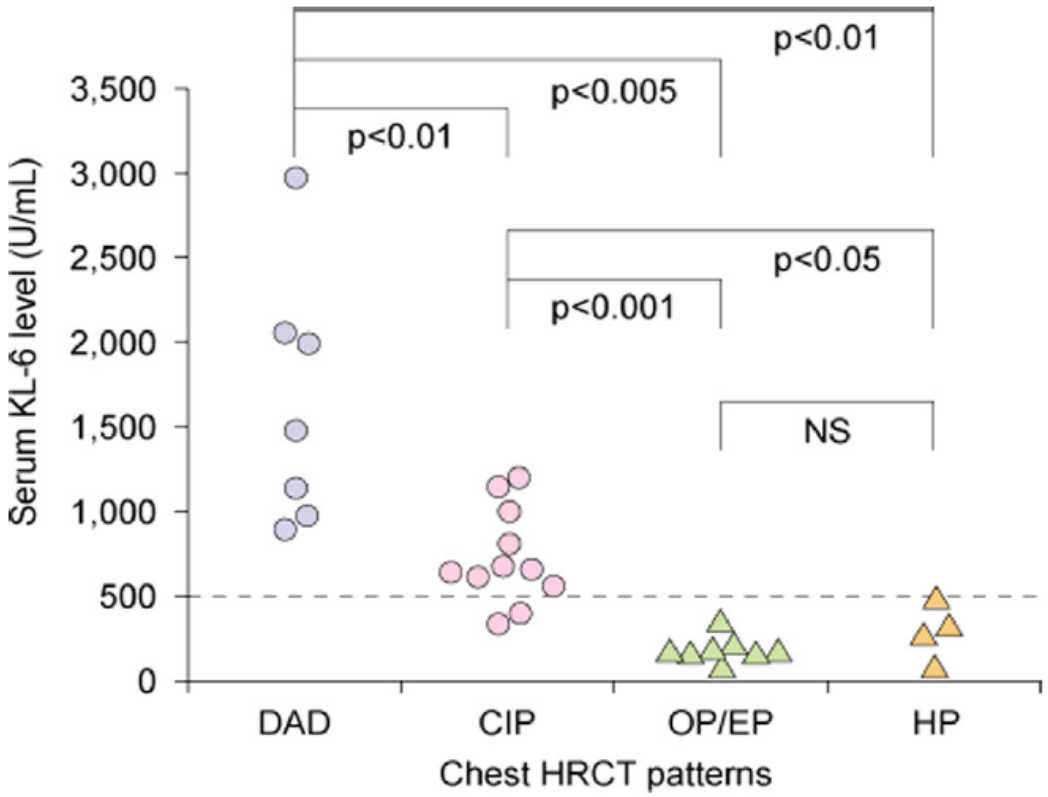
Table 1. KL-6 concentrations in interstitial lung disease patients, disease controls, and healthy controls

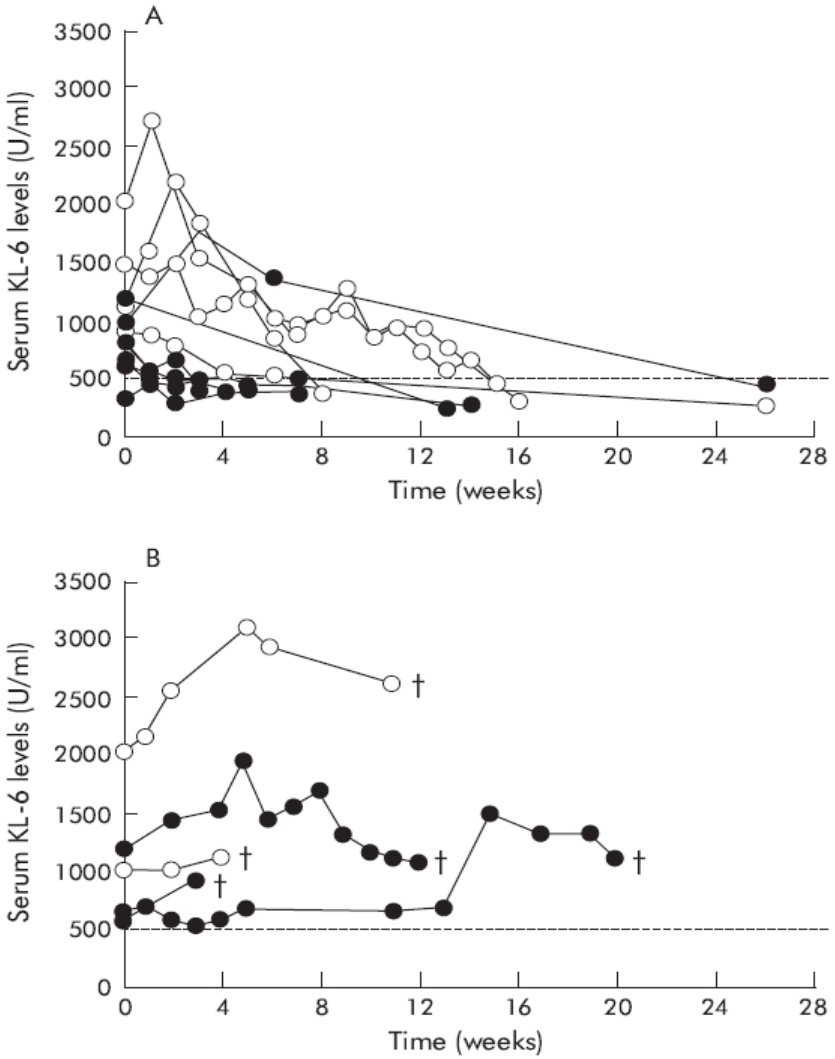
Group		N	Mean	SD	*P*	*P* (vs control group)
ILD patients	IPF	52	912.2	557.8	0.050	<0.001 (vs disease control group)
	NSIP	14	818.0	620.5		<0.001 (vs healthy control group)
	COP	19	670.5	527.3		
	Unclassifiable	68	514.8	494.8		
	CTD-ILD	44	685.3	566.3		
	HP	10	749.3	275.8		
	Others	23	743.0	1,108.2		
Disease control group	Infectious diseases	60	188.6	132.1	0.215	0.027 (vs healthy control group)
	Airway disease	27	249.0	140.7		
	RIPF	29	215.4	159.8		
Healthy control group	Healthy control	200	168.4	62.4	-	-

Cho EJ et al, Ann Lab Med 2019;39:245-251

KL-6 in DILD

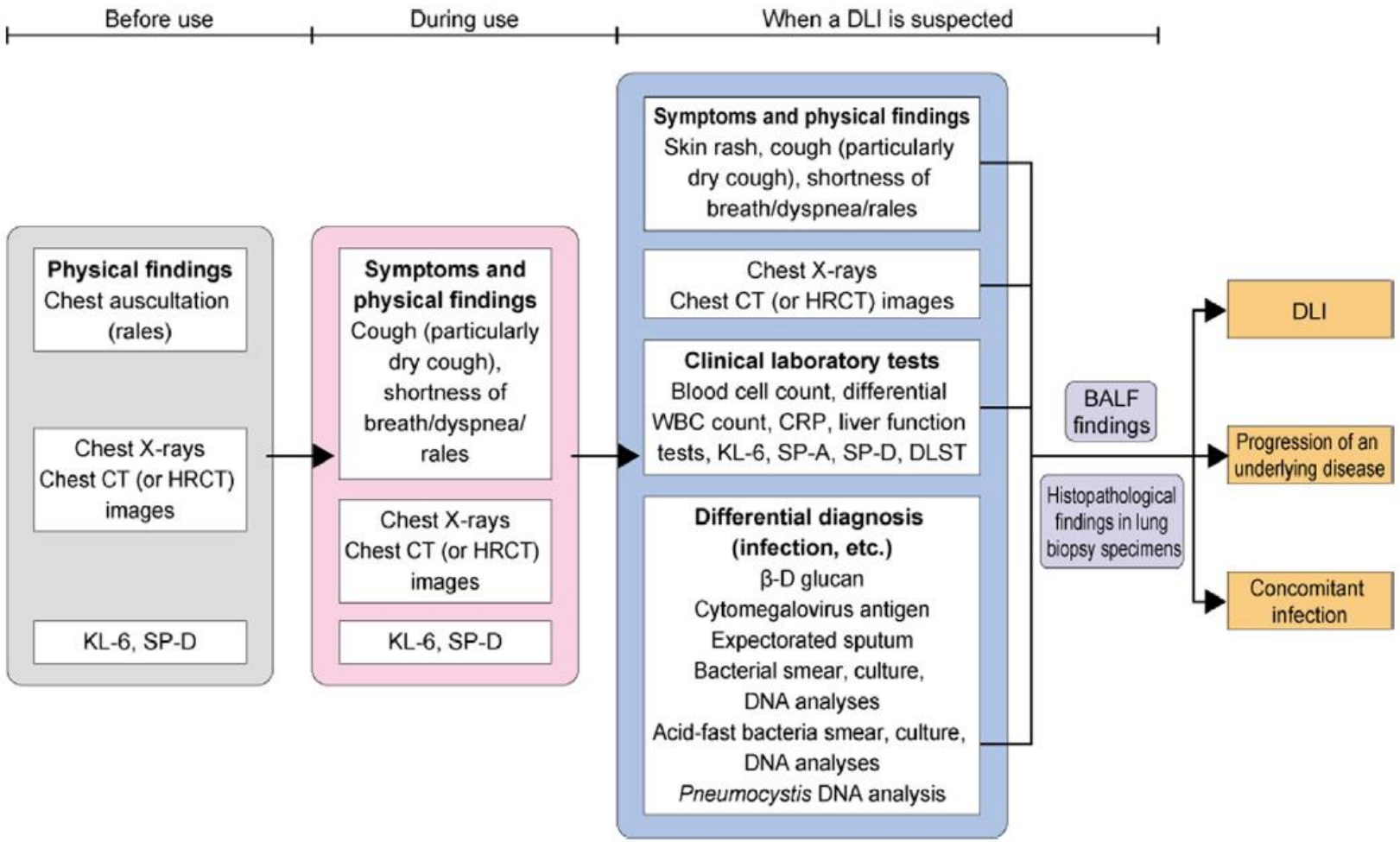
Drug induced pneumonitis, N=30





Ohnishi H et al, Thorax 2003;58 (10): 872-5

Flow of diagnosing DILD



Kubo K et al, Respir Investig 2013;51:260–77

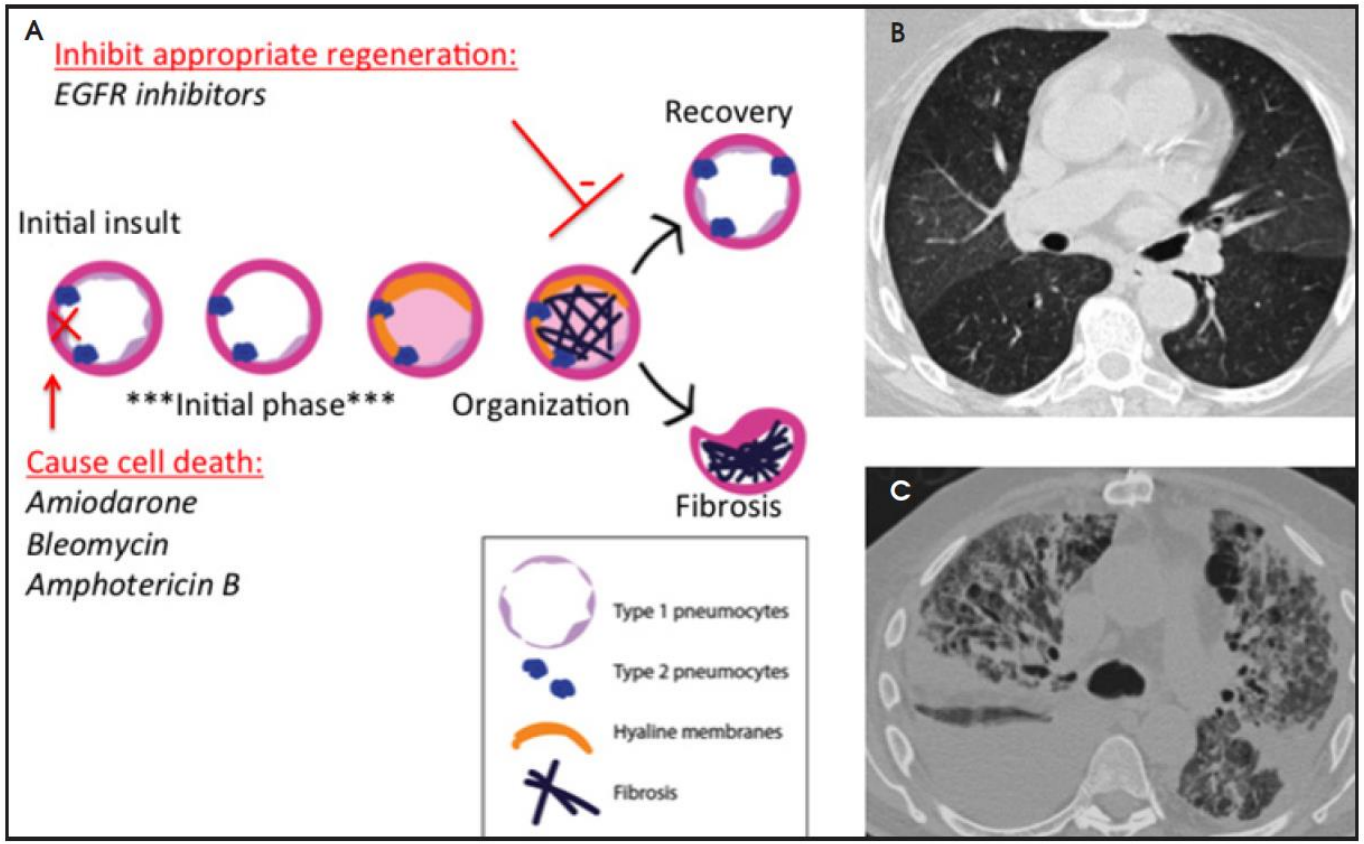
Radiologic patterns of DILD

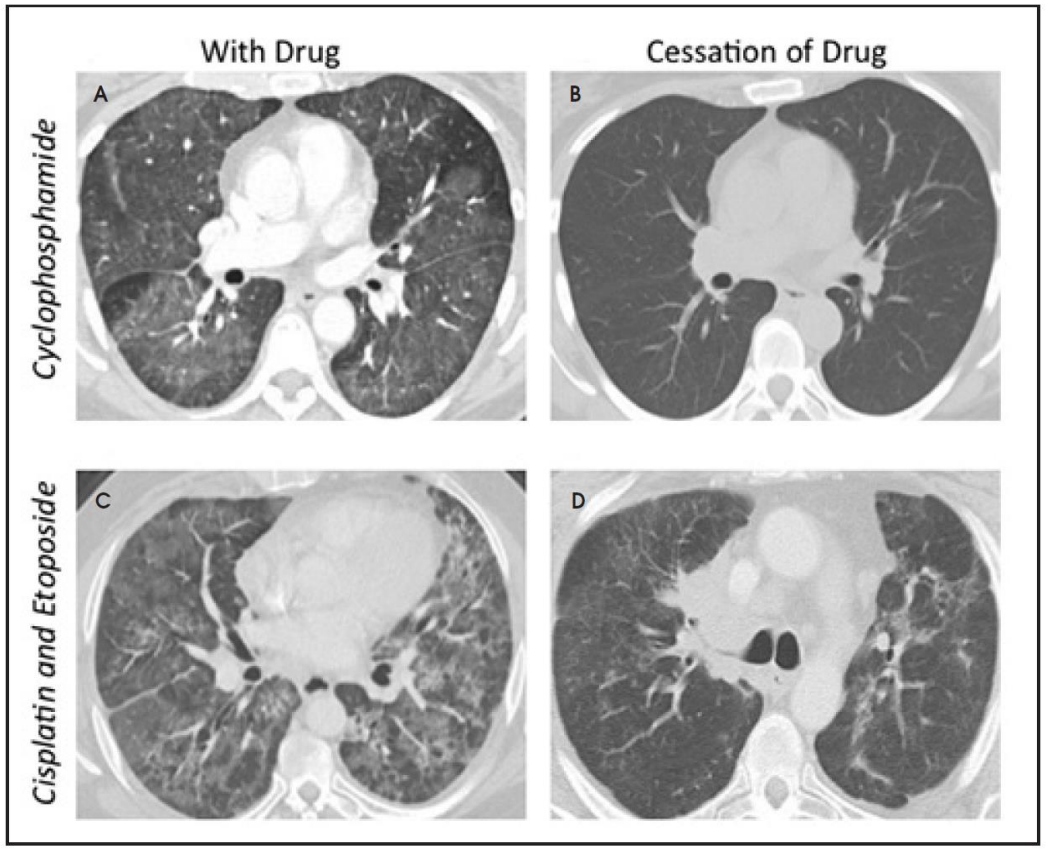
Table 7 – Imaging findings for DLIs manifesting as diffuse pulmonary disease.

	Diffuse alveolar damage (DAD)	Chronic interstitial pneumonia (CIP)	Eosinophilic pneumonia (EP)	Organizing pneumonia (OP)	Hypersensitivity pneumonia (HP)
Chest X-ray Images	Patchy infiltrative shadows and ground glass opacities in both lung fields	Ground glass opacities and patchy infiltrative shadows predominantly in the lower lung fields bilaterally	Diffuse infiltrative shadows or ground glass opacities predominantly in the periphery	Multiple, nonsegmental infiltrates in both lung fields	Decreased lung volume and ill-defined interstitial shadows in the basal segment of both lungs
Chest CT images	Bilateral patchy ground glass opacities and infiltrative shadows (predominantly in the posterior portion of the lung) Structural changes of traction bronchiectasis,etc., (after organizing stages)	Ground glass opacities, infiltrative shadows, linear shadows, thickening of broncho-vascular bundles, and evidence of traction bronchiectasis predominantly in the periphery of both lung fields	Ground glass opacities, infiltrative shadows, nodule-like shadows, mediastinal lymphadenopathy, pleural effusion, interlobular septum, and thickening of broncho-vascular bundles	Nodular shadows, patchy shadows, ground glass opacities, and reversed halo sign in the subpleura or along the broncho-vascular bundles	Diffuse ground glass opacities in both lung fields

Kubo K et al, Respir Investig 2013;51:260–77

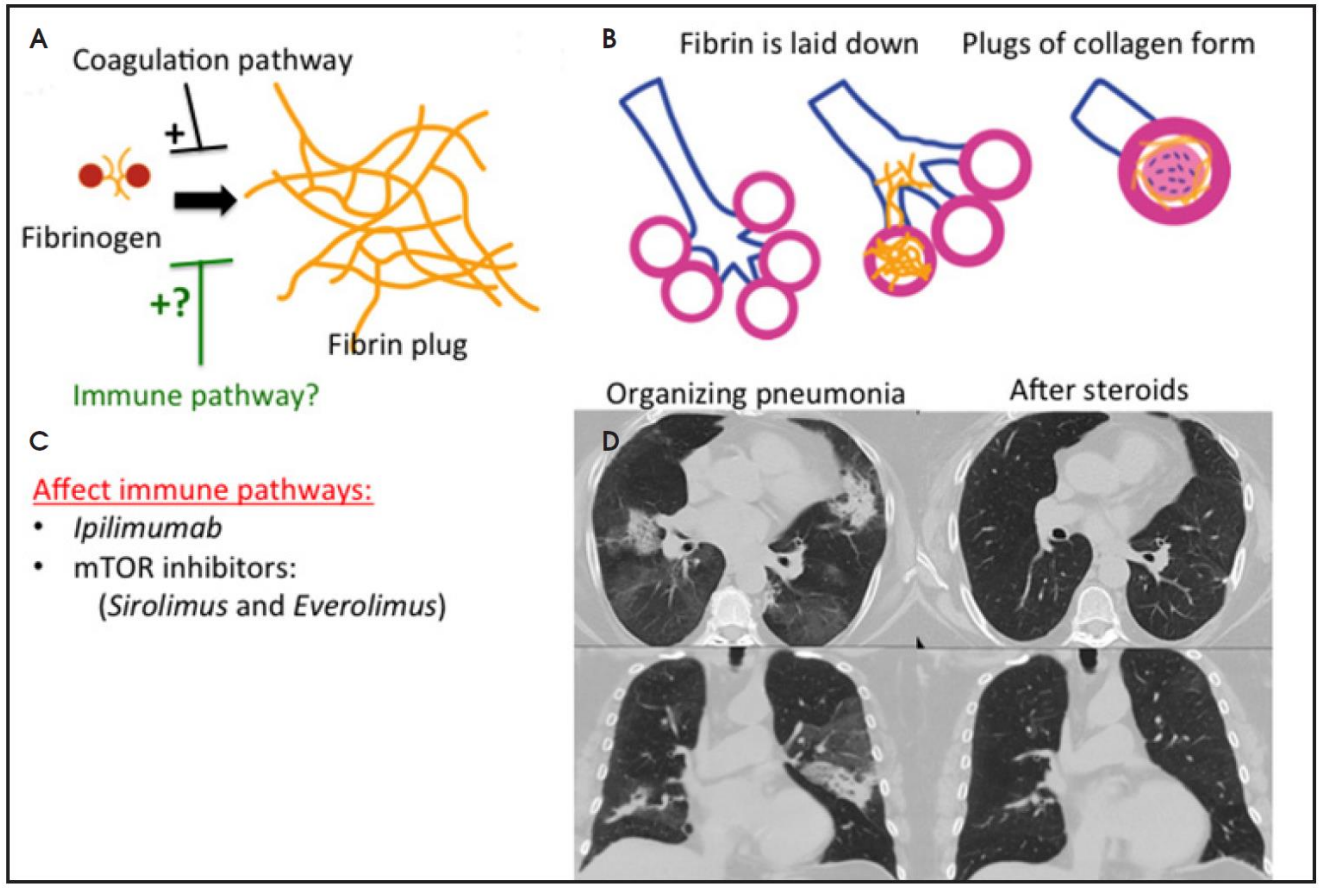
Diffuse alveolar damage

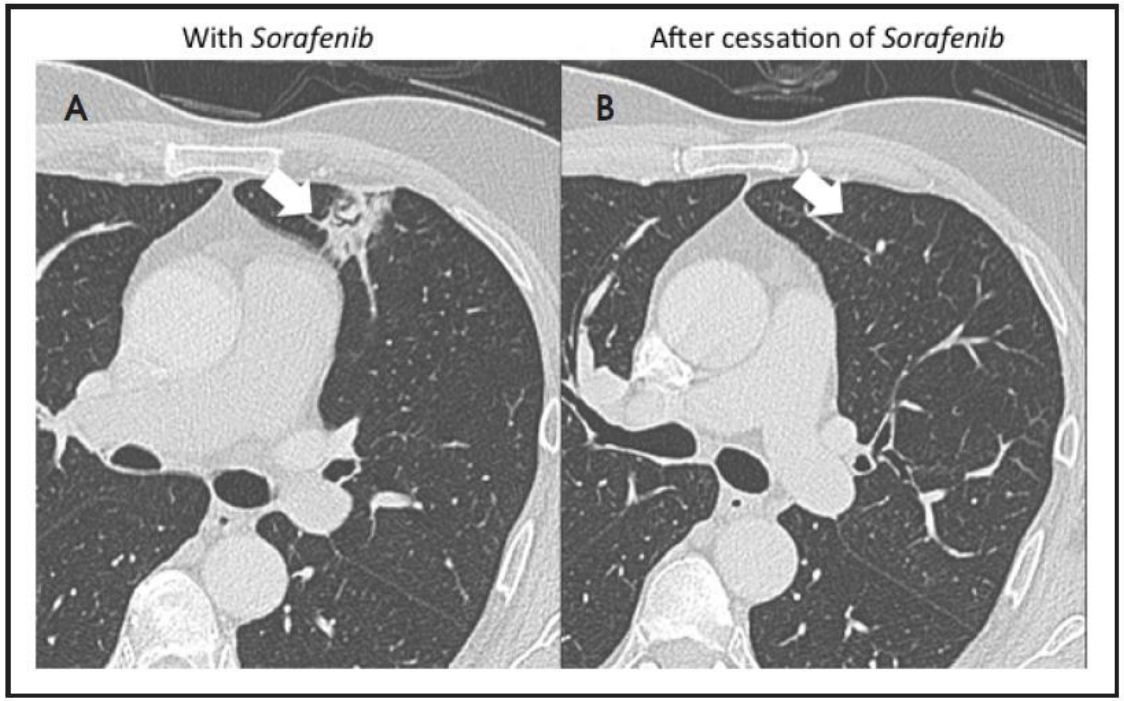




Ripley BA et al. Appl Radiol. 2016;45(4):9-18

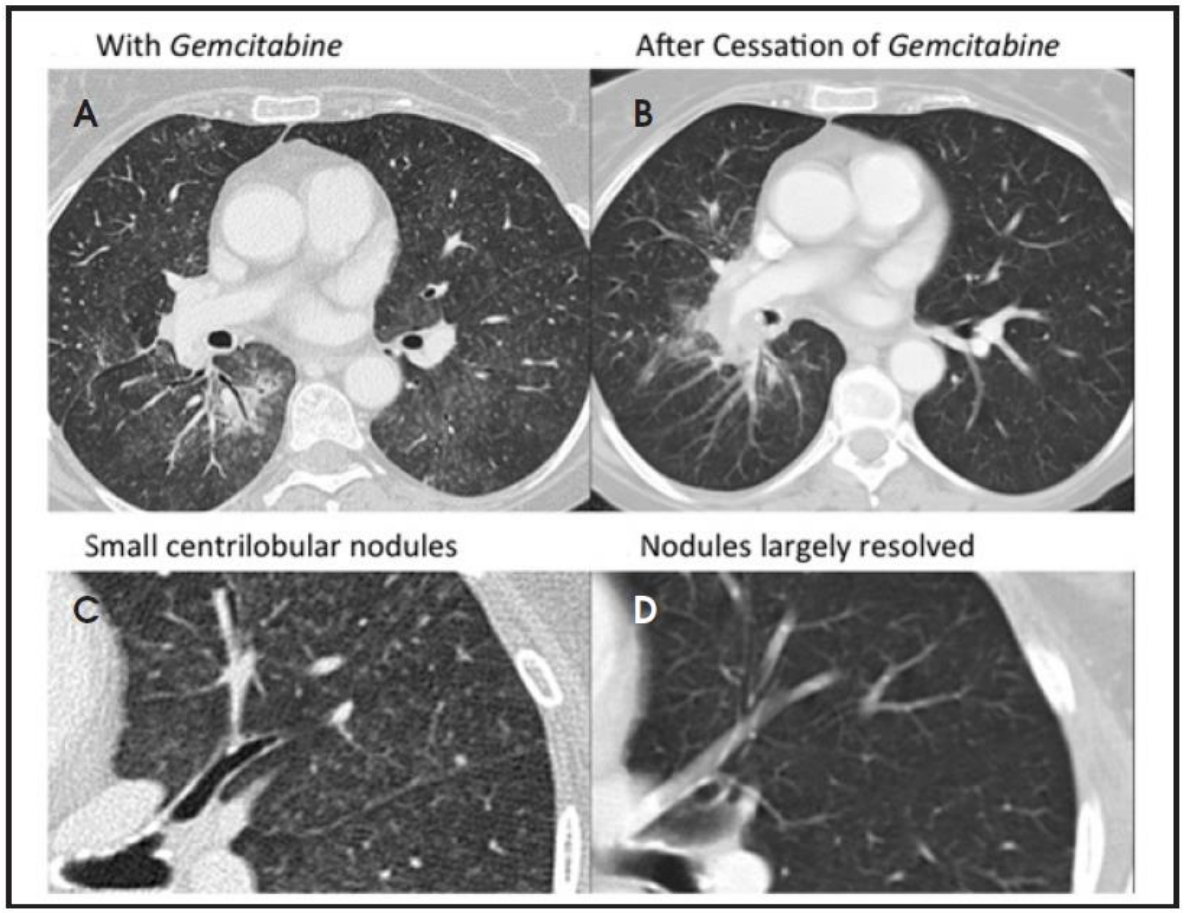
Organizing pneumonia

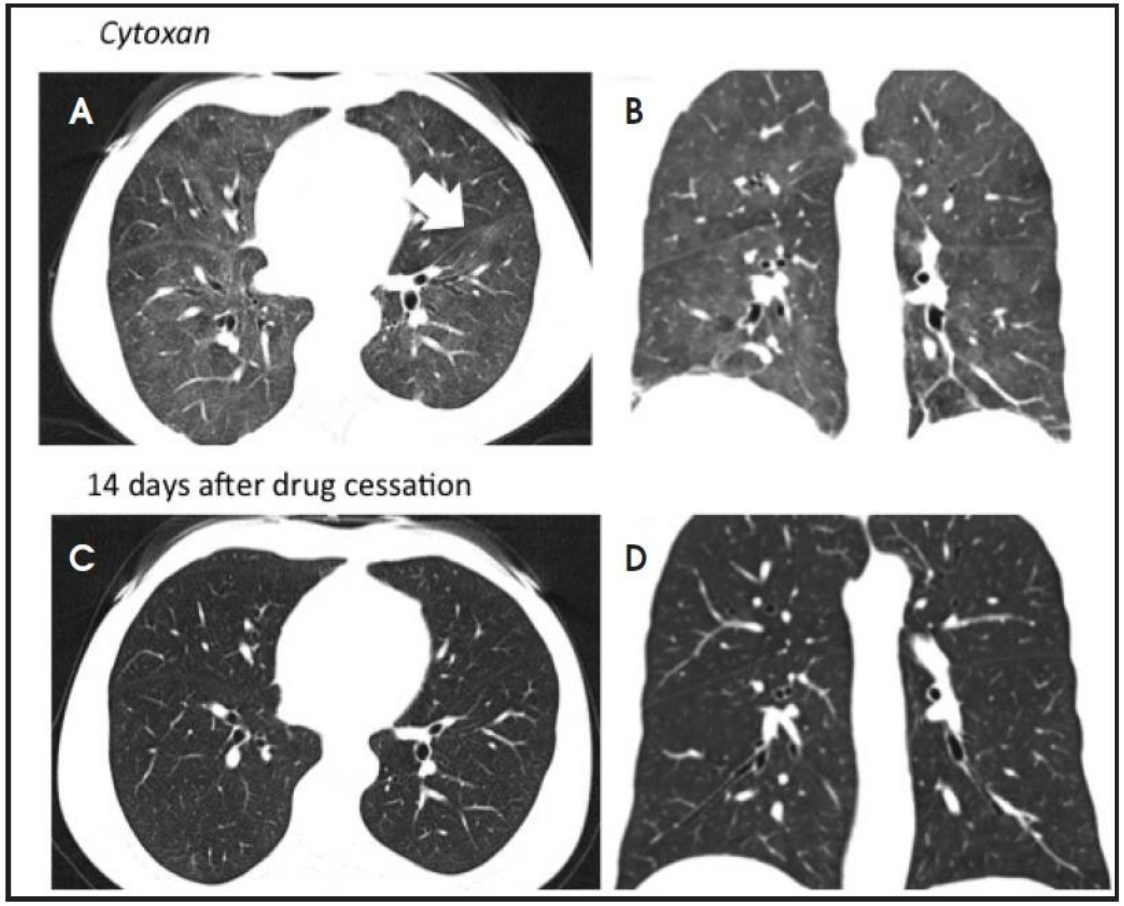




Ripley BA et al. Appl Radiol. 2016;45(4):9-18

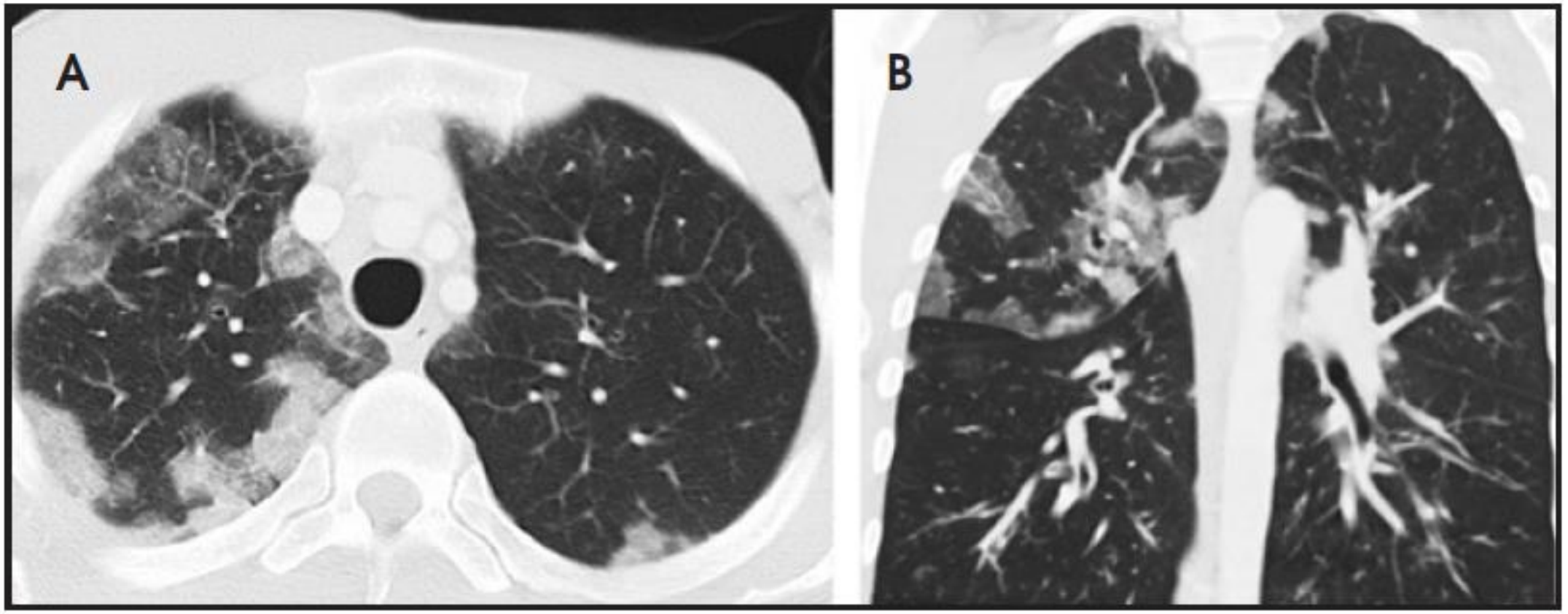
Hypersensitivity pneumonitis





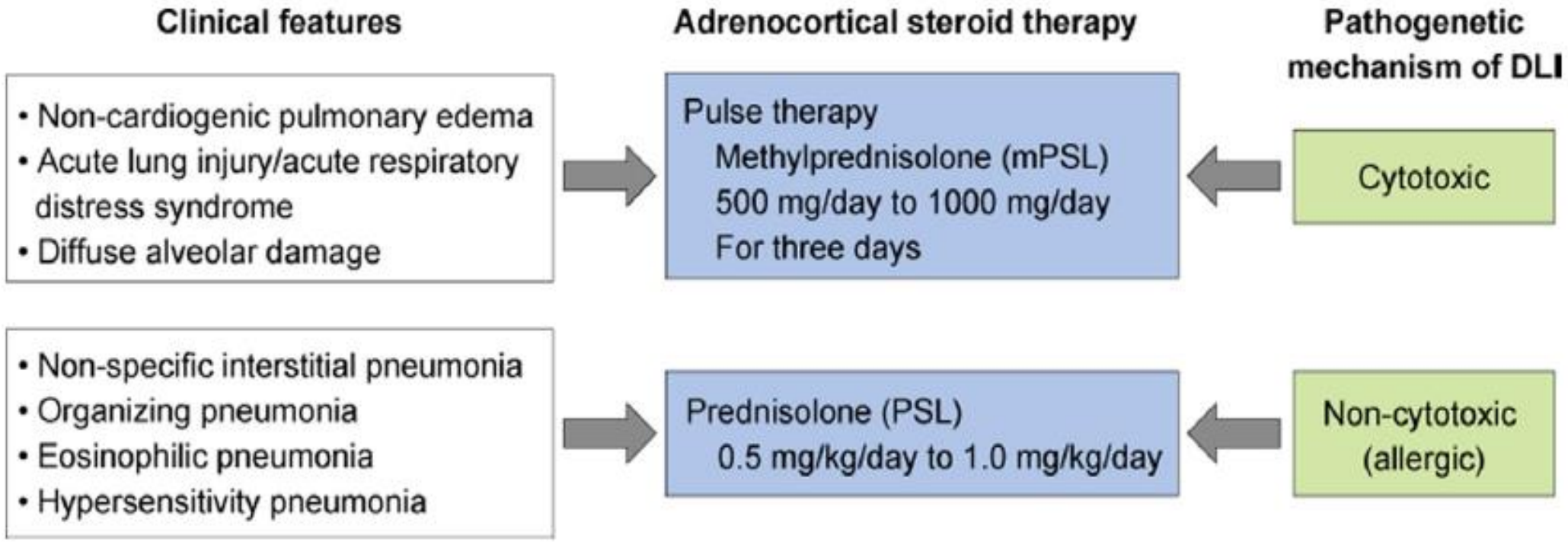
Ripley BA et al. Appl Radiol. 2016;45(4):9-18

Eosinophilic pneumonia



Ripley BA et al. Appl Radiol. 2016;45(4):9-18

Treatment of DILD



Kubo K et al, Respir Investig 2013;51:260–77

Corticosteroid in DILD

- No comparative studies evaluating the adjunctive role of GC therapy alongside withdrawal of the causative drug

- Only low-quality evidence to support the efficacy and dosing of corticosteroids by grade of severity and radio-pathological subtype of DIILD

- What dose and duration of corticosteroid is optimal in treatment of DILD?

Treatment of ICI-related pneumonitis

- Corticosteroids
  - grade 2 : prednisone 1 mg/kg/d
  - grade 3-4: 4 mg/kg/d
  - No improvement after 48 to 72hours
    → considered steroid refractory

- Infliximab (TNFa inhibitor)
- IV Immunoglobulin
- Tocilizumab (IL-6 inhibitor)

Suresh K et al, CHEST 2018; 154(6):1416-1423

Weber JS et al, Am Soc Clin Oncol Educ Book. 2012:174–177

Corticosteroid in DILD

Author	Drug	Patient Population	Sample Size	Glucocorticoids Dose (Oral or IV)	Response
Chap et al. [116]	Cyclophosphamide, cisplatin and BCNU	Breast cancer patients treated with prior mentioned	64 (37 cases of DIILD)	37/37 treated with prednisolone 60 mg oral twice daily × 10 days, then 30 mg/day × 1 week, 20 mg/day × 1 week, 15 mg/day × 1 week, followed by 5 mg taper on daily dose each week. Initiation of prednisolone based on scoring system; crackles on lung auscultation = 2, drop in D_{LCO} by >10% from baseline = 3, drop in O_2 saturation ≥4% with 2 min walk = 3, interstitial infiltrates on CXR = 3. Patients with a score ≥6 received prednisolone as above.	Glucocorticoid therapy associated with rapid clinical improvement in "most patients" (absolute numbers not available). 11 patients required prolonged prednisolone therapy (4–8 months), having experienced exacerbation of symptoms when prednisolone reduced to 15–20 mg/day
Hamada et al. [30]	Gemcitabine	pancreatic, lung, urothelial, breast, ovarian	25,924 (428 cases of ILD not verified as DIILD)	363/428 (84%) patients with ILD received either oral or intravenous glucocorticoids	20% of hospitalised DIILD patients with severe disease died, no data on glucocorticoid-treated group outcome versus non-glucocorticoid-treated patients

- Coticosteroids 0.5-1.0 mg/kg/day for 2-4weeks, then tapered
- If the lung injury and hypoxemia resolve immediately, corticosteroids can be completed in 1-2 months.

Skeoch et al, J. Clin. Med. 2018, 7, 356; doi:10.3390

Corticosteroid therapy against treatment-related pulmonary toxicities in lung cancer

Table 2 The response of corticosteroid for the treatment-related pulmonary toxicities

	Drug-induced ILD (n=88)		Radiation pneumonitis (n=189)		AE COPD (n=47)		Others (n=74)		P[a]
	No.	%	No.	%	No.	%	No.	%	
Steroid regimen[b]									<0.001
Pulse	22	25	5	3	0	0	7	10	
High-dose	42	48	33	17	19	40	21	28	
Low-dose	24	27	151	80	28	60	46	62	
Corticosteroid response									<0.001
Fatal	31	35	24	13	9	19	28	38	
Recovered	57	65	165	87	38	81	46	62	

Kim S et al. J Thorac Dis 2014;6(9):1209-1217

Clinical characteristics and mortality of patients with drug-induced interstitial lung disease

Table 4 Clinical characteristics and mortality of patients with drug-induced interstitial lung disease

	All cases (n=88)		One month mortality[a] (n=32)		P[b]	Two months mortality[a] (n=51)		P[b]
	No.	%	No.	%		No.	%	
The number of involved pulmonary lobes					0.872			0.090
1-3	43	49	16	37		21	49	
4-5	45	51	16	36		30	67	
CT finding					0.132			0.032
NSIP pattern	45	51	15	33		28	62	
BOOP pattern	33	38	10	30		14	42	
DAD pattern	7	8	5	71		7	100	
Mixed pattern[c]	3	3	2	67		2	67	
Steroid regimen[d]					0.001			0.001
Pulse	22	25	13	59		18	82	
High-dose	42	48	17	41		26	62	
Low-dose	24	27	2	8		7	29	

Kim S et al. J Thorac Dis 2014;6(9):1209-1217

Outcomes of ICI-pneumonitis

Clinical features, treatment, and outcome of ICI-related pneumonitis.

Variable	ICI-related pneumonitis (n = 22)
Drug exposures, n	3 (1–68)
Time to pneumonitis, days	54.5 (20–972)
Tumor response at time of pneumonitis	
Partial response	5 (22.7)
Stable disease	10 (45.5)
Progression of disease	7 (31.8)
Initial manifestation	
Asymptomatic	5 (22.7)
Dyspnea	9 (40.9)
Cough	5 (22.7)
Fever	2 (9.1)
General weakness	1 (4.5)
Laboratory values	
Peripheral white blood cells > 11,000/mm^3	12 (54.5)
Neutrophil > 75%	13 (56.5)
C-reactive protein, mg/dL[a]	10.7 (1.3–25.6)
Bronchoalveolar lavage lymphocyte, %[b]	14.0 (4.0–90.0)
Drug discontinuation	21 (95.5)
Treatment	
Steroid	17 (77.3)
Total steroid days	27 (2–269)
Antibiotics	13 (59.1)
Glucocorticoid dosage, mg/kg[c]	0.8 (0.4–11.7)
Outcome	
Complete recovery	5 (22.7)
Improved	6 (27.3)
Stable	1 (4.5)
Death	4 (18.2)
Unknown	6 (27.3)
Drug re-challenge[d]	7 (31.8)

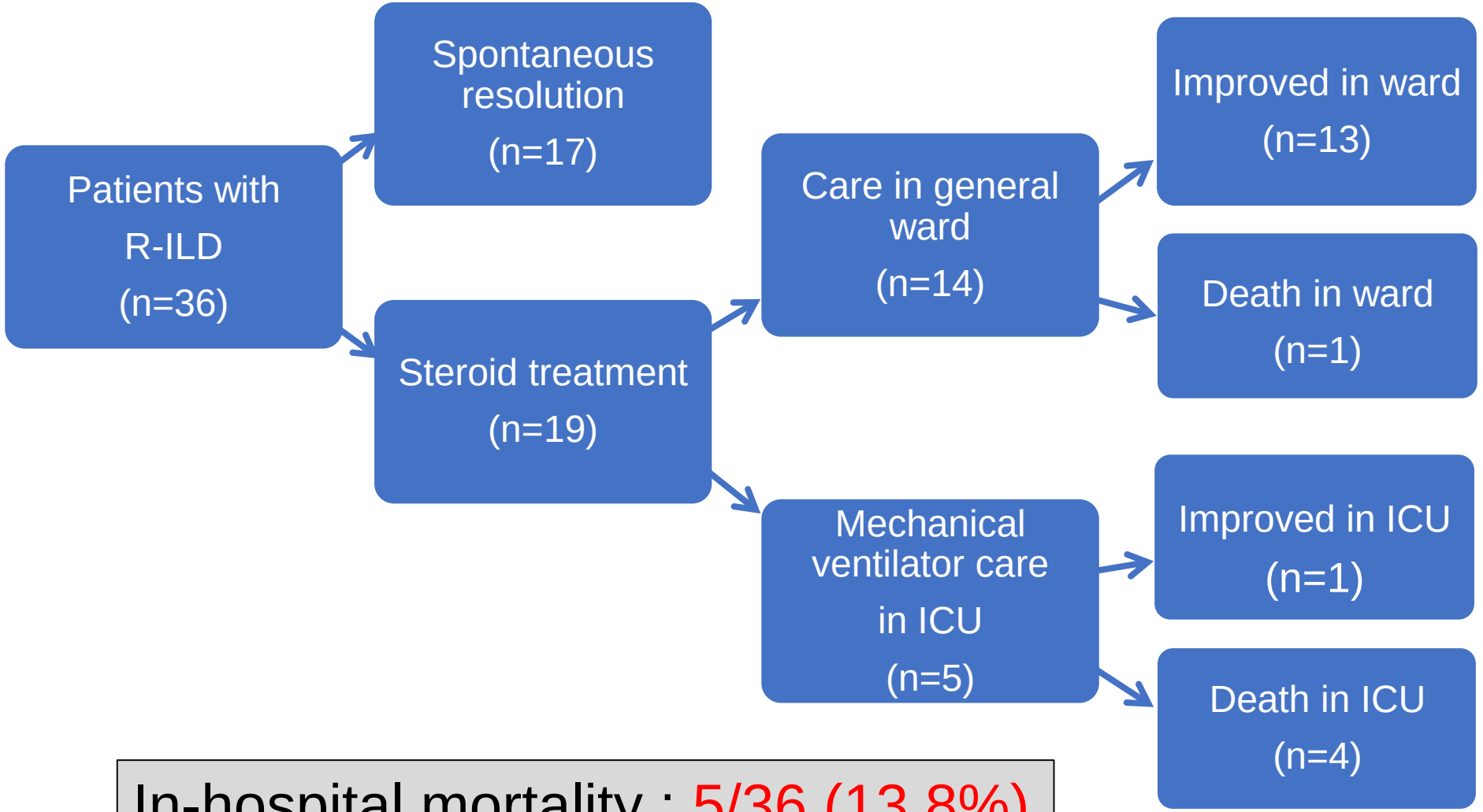
Table 3. CIP Grade and Outcomes

Outcome	n (%)
All pneumonitis	39 of 205 (19)
Grade	
2	14 (35.8)
3	17 (43.5)
4	2 (5.1)
5	5 (12.8)
Unknown	1 (2.5)
Clinical outcome	
Completely resolved	2 (5.1)
Improved	20 (51.2)
Stable/unchanged	5 (12.8)
Worsened	9 (17.9)
Unknown	3 (10.2)

Cho et al, Lung Cancer 125 (2018) 150–156

Suresh K et al, J Thorac Oncol 2018;13(12):1930-1939

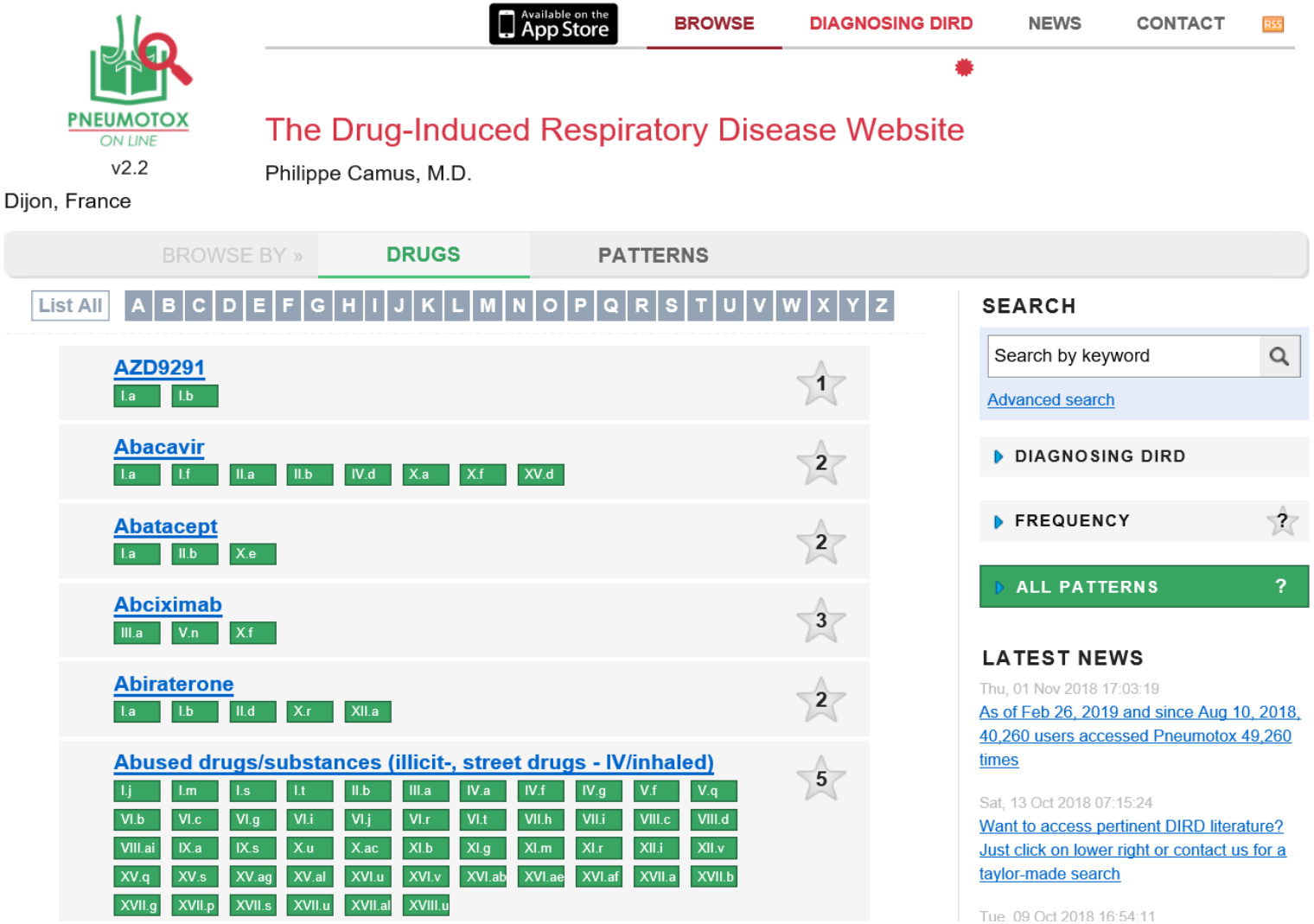
Clinical course of Rituximab-associated ILD



In-hospital mortality : 5/36 (13.8%)

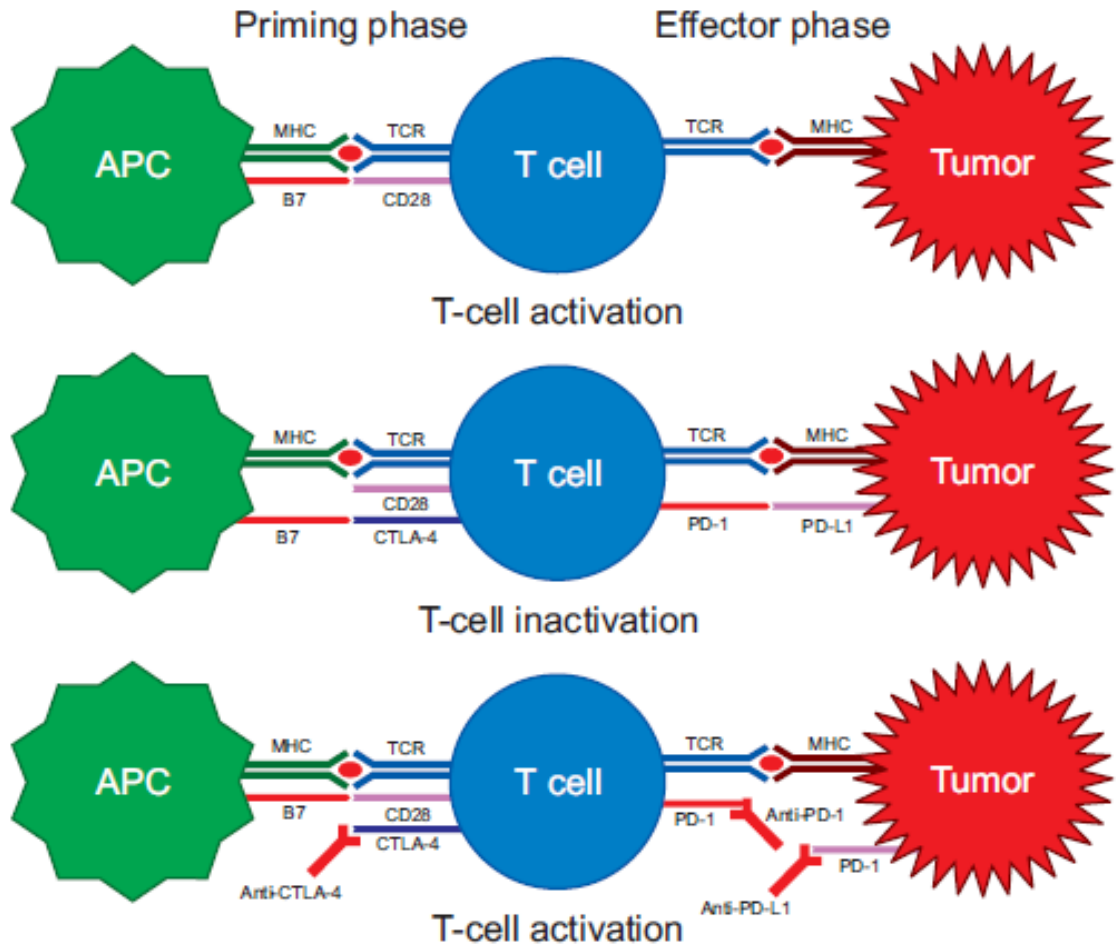
SNUBH data

https://www.pneumotox.com



Summary

- DILD is not uncommon and shows various clinical course.
- Careful examination of drug history is mandatory.
- Radiologic and BALF findings are helpful in the diagnosis of DILD.
- Further studies are needed.


Priming phase
Effector phase
APC
MHC
TCR
B7
CD28
T cell
TCR
MHC
Tumor
T-cell activation
APC
MHC
TCR
CD28
B7
CTLA-4
T cell
TCR
MHC
PD-1
PD-L1
Tumor
T-cell inactivation
APC
MHC
TCR
B7
CD28
CTLA-4
Anti-CTLA-4
T cell
TCR
MHC
PD-1
Anti-PD-1
PD-1
Anti-PD-L1
Tumor
T-cell activation