

Drug-induced pneumonitis : A Common Clinical Challenge

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One of several kinds of ILD

- Drug-induced pneumonitis
 - one of exposure-related ILD
 - usually acute to subacute course
 - but can cause chronic ILD

	Acute	Subacute	Chronic
Idiopathic	Acute interstitial pneumonia	Cryptogenic organising pneumonia	Idiopathic pulmonary fibrosis Idiopathic non-specific interstitial pneumonia Desquamative interstitial pneumonia Pleuroparenchymal fibroelastosis
	Unclassifiable interstitial lung disease		
Autoimmune-related	Rapidly progressive interstitial lung disease (eg. anti-MDA5-antibody-associated amyopathic dermatomyositis and diffuse alveolar haemorrhage in ANCA-associated vasculitis or in systemic lupus erythematosus)	Connective tissue disease-associated interstitial lung disease (eg. rheumatoid arthritis, systemic sclerosis, idiopathic inflammatory myopathies, anti-synthetase syndrome, Sjögren's syndrome, and others)	
		ANCA-associated vasculitis-related interstitial lung disease	
Exposure-related	Hypersensitivity pneumonitis		
			Pneumoconiosis
			Respiratory bronchiolitis-interstitial lung disease
	Drug-induced lung injury (eg. chemotherapy, immune checkpoint inhibitors, biological agents, antirheumatic drugs, antibiotics, antithrombotic agents, cardiovascular drugs, and herbal medicine)		
		Radiation-induced lung injury	
			Postinfectious interstitial lung disease

Challenging diagnosis

- Nonspecific & Variable manifestation
- Difficulty in definitive diagnosis
 - challenge in assessing causality
 - time relationship
 - consideration of other potential causes
 - biologically explainable

<i>Causality term</i>	<i>Assessment criteria*</i>
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Recent update in ILD terminology

- Expert opinion of Fleischner Society
- Some controversial aspects
 - hypersensitivity pneumonitis (HP) vs. Bronchiolocentric interstitial pneumonia (BIP)



STATE OF THE ART

Standardized Clinical Terms and Definitions for Interstitial Lung Disease A Consensus Statement from the Fleischner Society

Christopher J. Ryerson¹, Alexander Bankier³, Mary Beth Beasley⁴, Kevin Brown⁵, Thomas Colby⁷, Vincent Cottin⁸, Sujal Desai⁹, Jeffrey Galvin^{11,12}, Linda B. Haramati¹⁴, Lida P. Hariri¹⁵, Yoshikazu Inoue^{16,17}, Takeshi Johkoh¹⁸, Ho Yun Lee^{19,20}, Ann Leung²¹, David Lynch⁶, Nestor Muller², Andrew Nicholson^{22,23}, Suhail Raof²⁵, Marie-Pierre Revel²⁶, Martine Remy-Jardin²⁷, Luca Richeldi²⁸, Jay H. Ryu²⁹, Mark Schiebler³⁰, Lynette Sholl³¹, Nicola Sverzellati^{32,33}, William Travis³⁴, Simon L. F. Walsh²⁴, Athol U. Wells¹⁰, Charles S. White¹³, and Kerri A. Johannson³⁵

Regarding drug-induced pneumonitis

- Induced vs. Associated
- Pneumonitis vs. Interstitial lung disease
- Needs to align terminology with oncologic field

Preferred Term	Preferred Abbreviations	Nonpreferred Alternatives
Drug-associated interstitial lung disease	Drug-associated ILD	<ul style="list-style-type: none">• Drug-induced lung disease• Medication-associated interstitial lung disease• Drug-associated lung injury• Medication-associated lung injury• Drug-related pneumonitis
Radiotherapy-associated lung injury	N/A	<ul style="list-style-type: none">• Radiotherapy-induced interstitial lung disease• Radiotherapy-associated interstitial lung disease• Radiotherapy-induced lung injury• Radiation-associated lung injury• Radiation-induced lung injury
Post–acute respiratory disease syndrome lung injury	Post-ARDS lung injury	<ul style="list-style-type: none">• Post-ARDS interstitial lung disease
Post–infectious lung injury	N/A	<ul style="list-style-type: none">• Post–infectious interstitial lung disease

Checklists for considering association with drugs

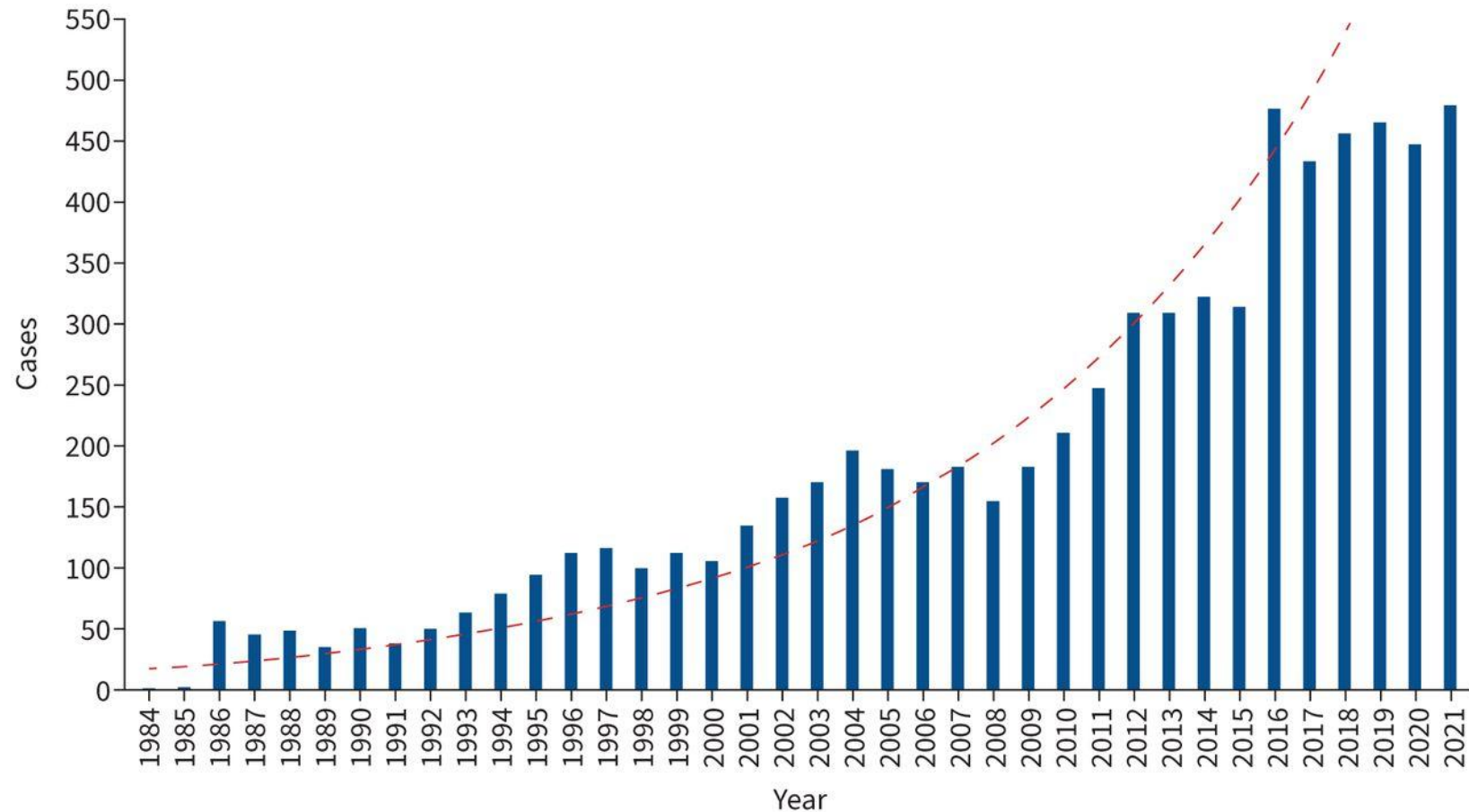
- Potential drug? Timing of exposure?
- Other causes?
- Discontinuation? Rechallenge?

Steps	Checklist	To do
1	Consider the possibility of DI-ILD in every patient with ILD	This must be a mandatory step in the diagnostic workup of any ILD
2	Check www.pneumotox.com	By pattern By drug
3	History of exposure to the drug	A meticulous inquiry is necessary Easier when there is only one drug Help from the pharmacist is helpful
4	Timing of drug exposure	DI-ILD develops usually within a few weeks to a few months after treatment initiation Generally, the patient is still taking the culprit medication

5	Clinical and imaging pattern	The DI-ILD patterns should match the literature (see www.pneumotox.com)
6	Exclusion of other causes for ILD	Essential: <ul style="list-style-type: none"> • Infection • Heart failure • Lymphangitic carcinomatosis • Underlying disease <ul style="list-style-type: none"> Cancer Connective tissue diseases (<i>i.e.</i> RA, SSc) IBD
7	Drug discontinuation	Mandatory: <ul style="list-style-type: none"> May need the help of colleagues specialised in the underlying disease (drug withdrawal and replacement) Improvement following drug discontinuation is the strongest diagnostic argument
8	Recurrence of symptoms after rechallenge with the drug	May be dangerous or even lethal Cannot be recommended

Epidemiologic data from France

- Nationwide data from France
- Overall increasing number of cases



Possible culprit drugs identified in France

- Nationwide data from France – Drugs suspected in at least 50 cases

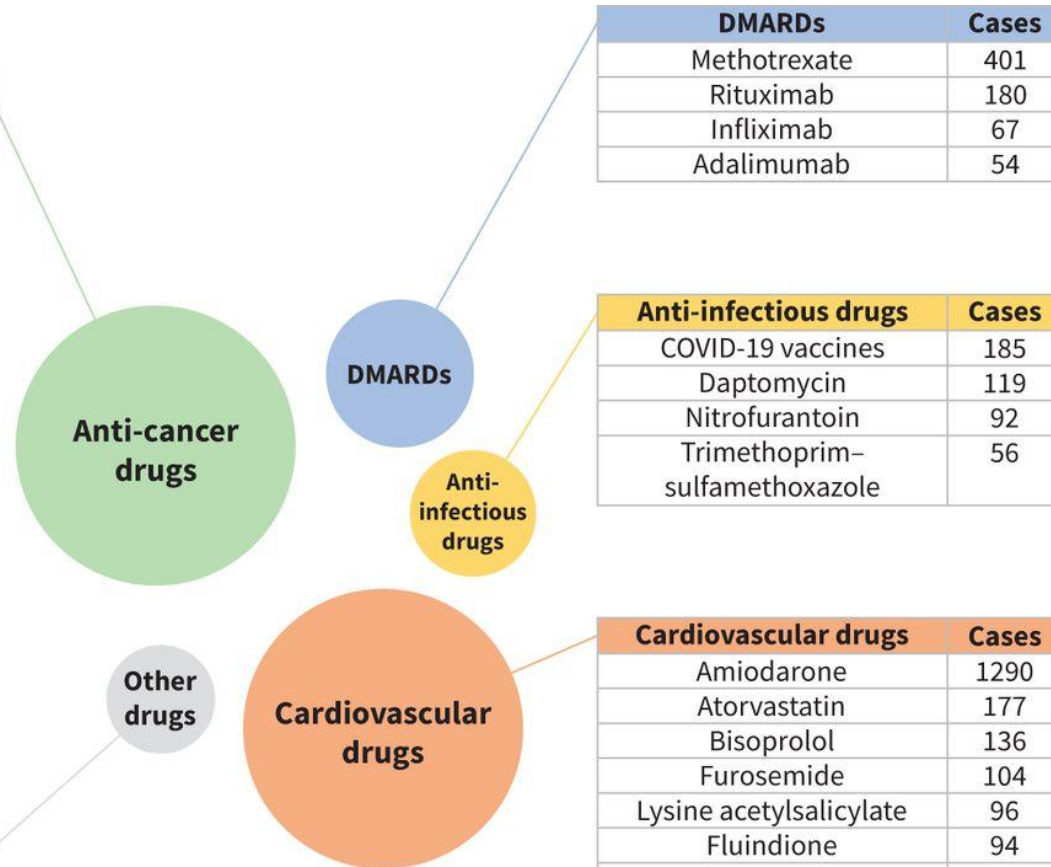
Anti-cancer drugs	Cases
Nivolumab	219
Gemcitabine	211
Bleomycin	206
Cyclophosphamide	173
Everolimus	148
Pembrolizumab	144
Docetaxel	139
Doxorubicin	130
Oxaliplatin	113
Paclitaxel	113
Fluorouracil	110
Cisplatin	83
Etoposide	70
Vinblastine	67
Trastuzumab	63
Cytarabine	62
Sirolimus	61
Dacarbazine	58
Carboplatin	57
Vincristine	56
Hydroxycarbamide	54
Pemetrexed	54

Other drugs	Cases
Prednisone	88
Nilutamide	76
Methylprednisolone	58
Paracetamol	58
Metformin	55
Esomeprazole	53

DMARDs	Cases
Methotrexate	401
Rituximab	180
Infliximab	67
Adalimumab	54

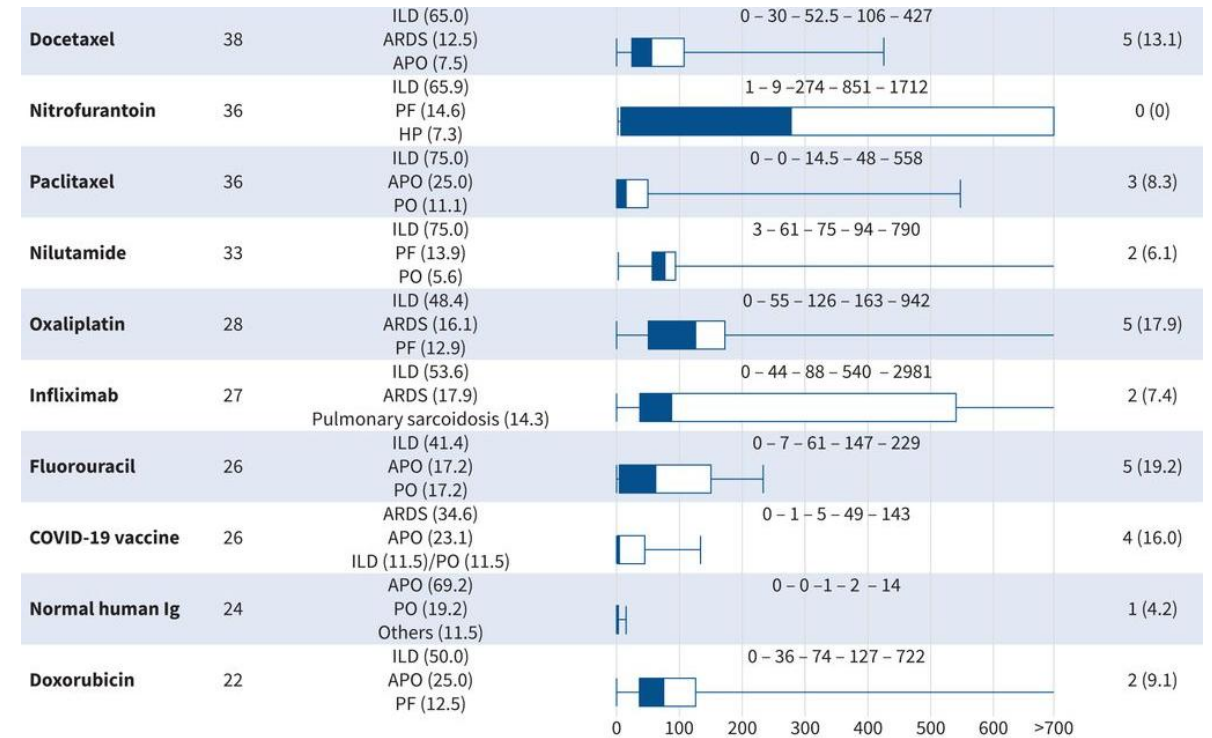
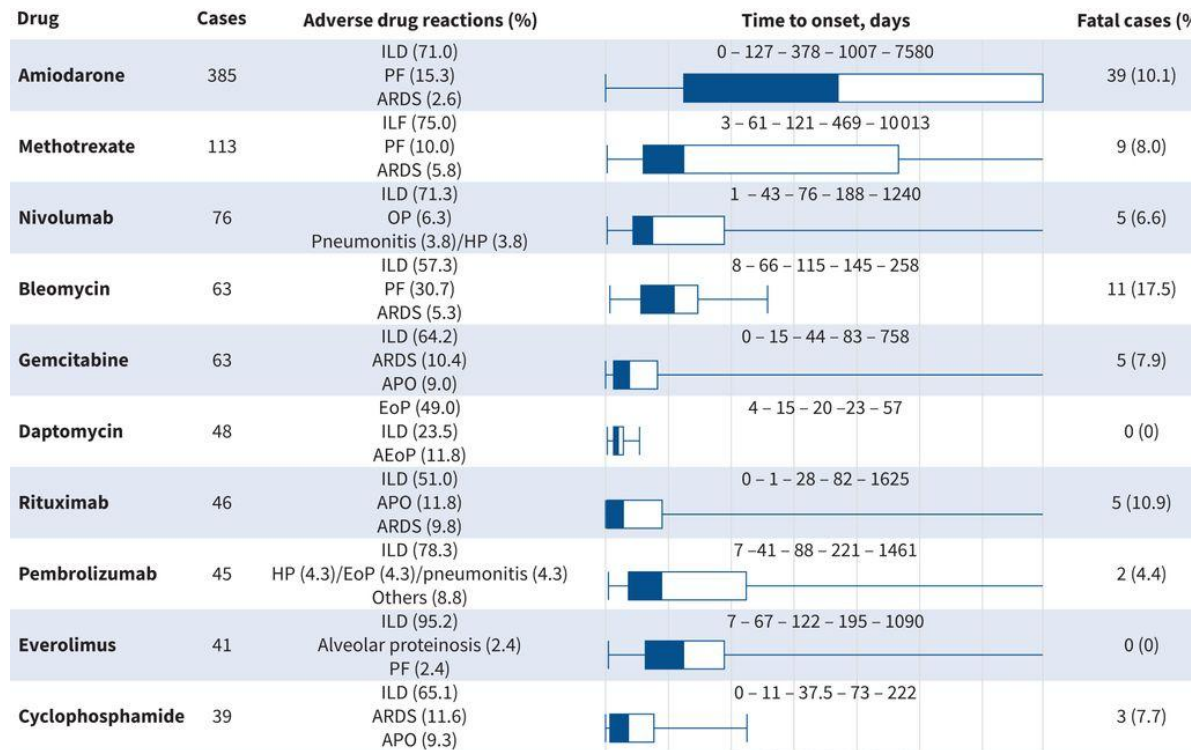
Anti-infectious drugs	Cases
COVID-19 vaccines	185
Daptomycin	119
Nitrofurantoin	92
Trimethoprim-sulfamethoxazole	56

Cardiovascular drugs	Cases
Amiodarone	1290
Atorvastatin	177
Bisoprolol	136
Furosemide	104
Lysine acetylsalicylate	96
Fluindione	94
Pravastatin	78
Simvastatin	76
Flecainide	73
Atenolol	63
Rosuvastatin	57
Ramipril	57
Amlodipine	50



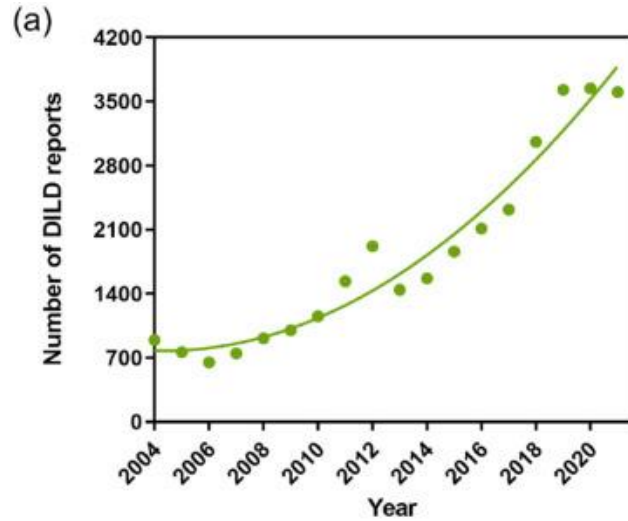
Most suspected drugs in France

- Nationwide data from France – Most common drugs imputed as “at least plausible”
- Variable time to onset



Epidemiologic data from FDA data

- FDA Adverse Event Reporting System (FAERS) data



Reporter country

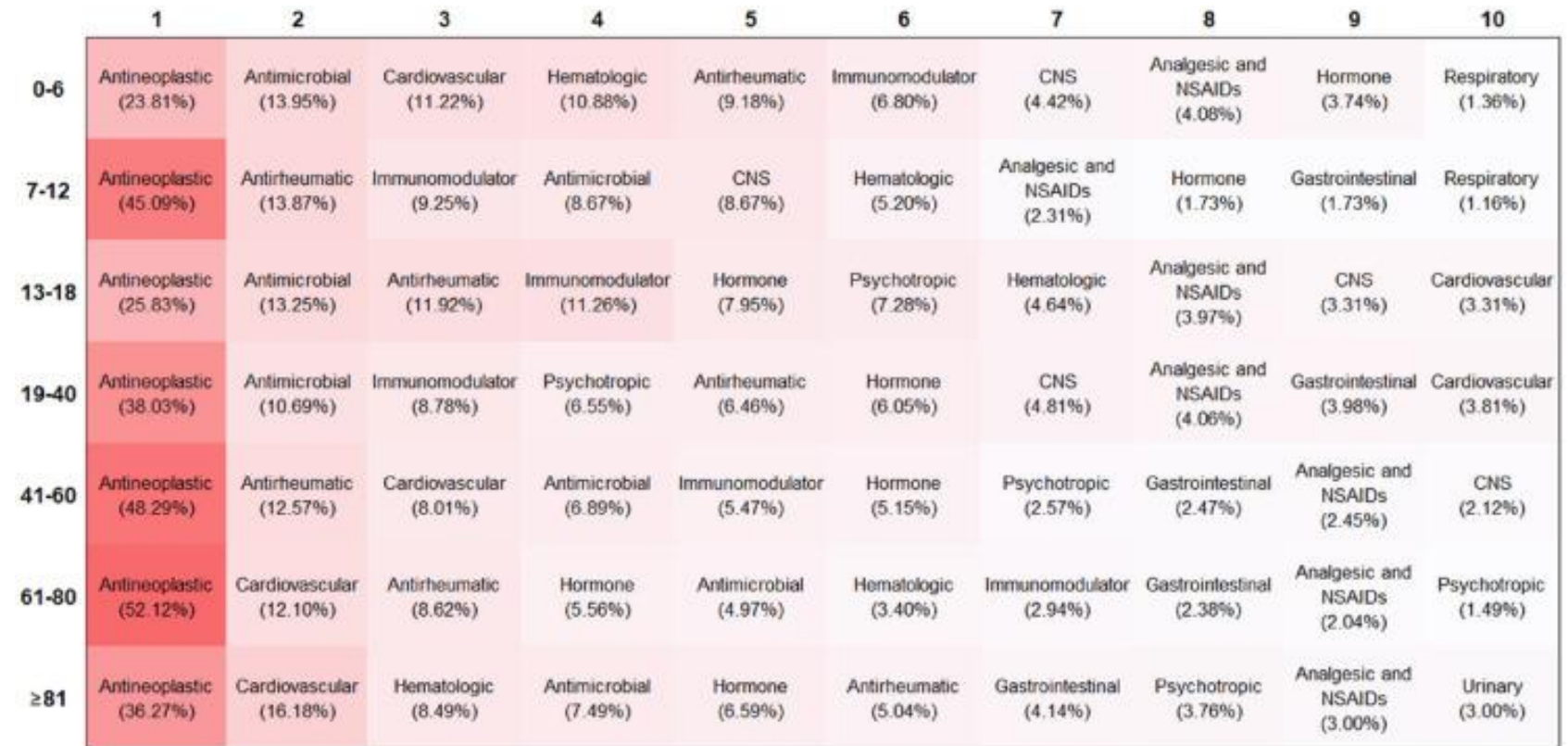
Japan 14,483 (44.13%)

United States 4424 (13.48%)

France 3799 (11.57%)

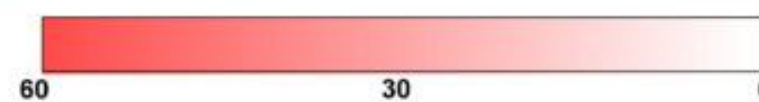
Others 8780 (26.75%)

Unknown 1335 (4.07%)



Age group (years)

Percent (%)



Commonly reported drugs in FDA data

- FDA Adverse Event Reporting System (FAERS) data

Drug name	Total adverse event reports	DILD reports [%]	Japan DILD reports [%, n=31,486 ^a]
Overall database from 2004 to 2021	43,046,990	32,821 [0.08%]	14,483 [46.00%]
Methotrexate	343,703	891 [0.26%]	39 [4.53%]
Doxorubicin	81,024	844 (1.04%)	138 [16.57%]
Pembrolizumab	70,054	783 (1.12%)	673 [85.95%]
Nivolumab	130,296	708 [0.54%]	549 [77.54%]
Amiodarone	53,830	634 (1.18%)	43 [7.08%]
Etanercept	1,301,974	607 [0.05%]	218 [36.64%]
Adalimumab	1,528,994	565 [0.04%]	87 [15.88%]
Everolimus	121,289	524 [0.43%]	286 [54.68%]
Tocilizumab	165,928	494 [0.30%]	265 [53.64%]

Drug name	Total adverse event reports	DILD reports [%]	Japan DILD reports [%, n=31,486 ^a]
Rituximab	256,867	487 [0.19%]	33 [6.86%]
Bevacizumab	163,636	470 [0.29%]	342 [73.08%]
Docetaxel	159,218	448 [0.28%]	241 [58.92%]
Infliximab	402,189	411 [0.10%]	133 [37.15%]
Oxaliplatin	81,014	366 [0.45%]	190 [52.20%]
Abatacept	179,763	357 [0.20%]	164 [45.94%]
Osimertinib	23,759	343 (1.44%)	241 [70.26%]
Paclitaxel	75,462	341 [0.45%]	204 [60.00%]
Atorvastatin	203,754	323 [0.16%]	74 [24.18%]
Erlotinib hydrochloride	111,517	299 [0.27%]	133 [45.08%]
Cyclosporine	109,612	291 [0.27%]	198 [70.46%]

Drugs with highest signal strength in FDA data

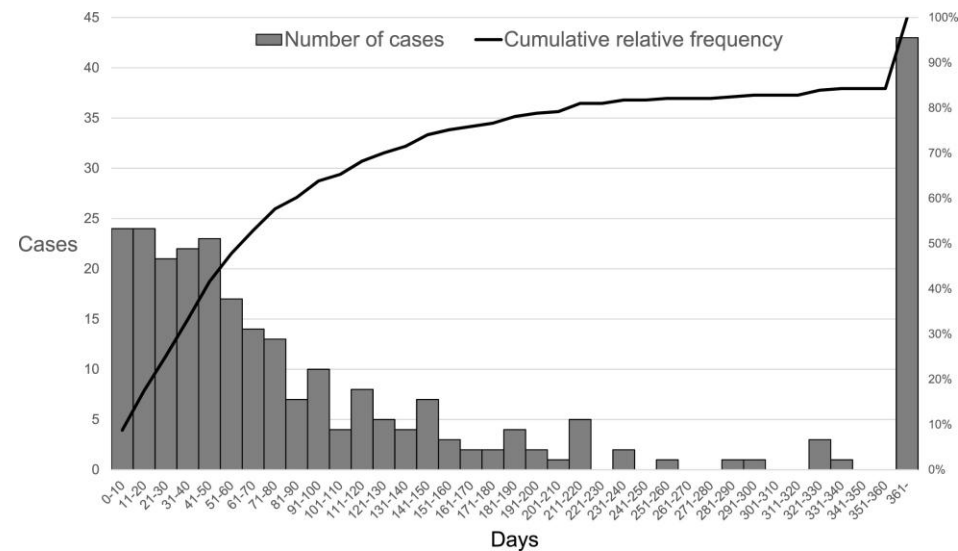
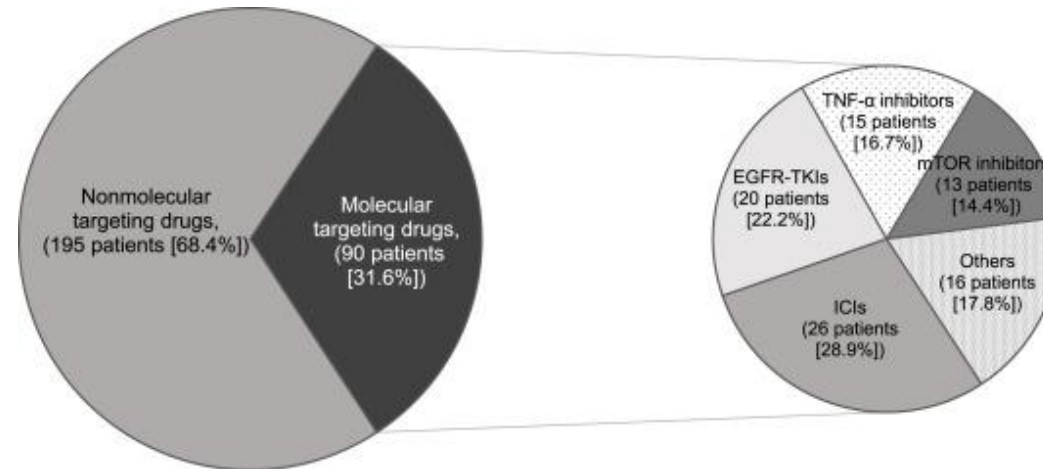
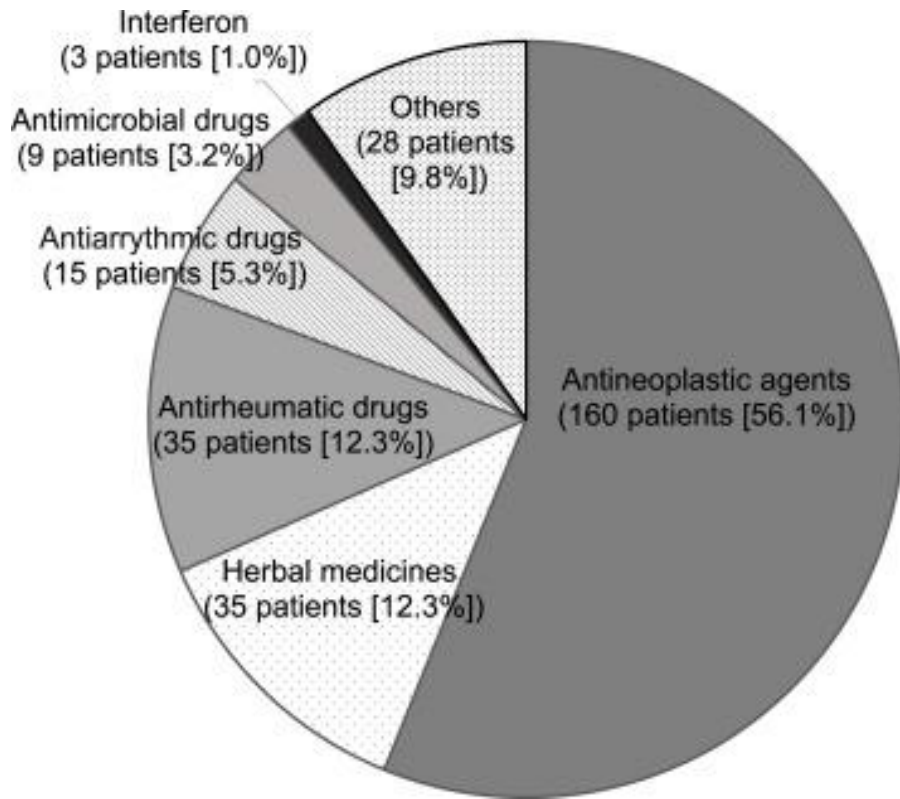
- FDA Adverse Event Reporting System (FAERS) data
- Reporting odds ratio (ROR), Proportional reporting ratio (PRR)

Drug name	Total adverse event reports	DILD reports (%)	Japan DILD reports (% <i>n</i> = 31,486 ^a)	ROR (95% CI)	PRR (χ^2)
Fam-trastuzumab deruxtecan-nxki	2392	96 (4.01%)	15 (15.63%)	56.50 (46.01–69.39)	54.28 (4957.35)
Ramucirumab	6614	170 (2.57%)	164 (96.47%)	36.28 (31.14–42.27)	35.37 (5637.04)
Eribulin	6252	137 (2.19%)	131 (95.62%)	30.57 (25.79–36.22)	29.92 (3812.85)
Osimertinib	23,759	343 (1.44%)	241 (70.26%)	19.69 (17.68–21.92)	19.42 (5887.47)
Riluzole	2010	40 (1.99%)	26 (70.27%)	26.71 (19.53–36.53)	26.20 (968.99)
Durvalumab	11157	155 (1.39%)	118 (76.13%)	18.07 (15.41–21.19)	17.83 (2439.19)
Amiodarone	53,830	634 (1.18%)	43 (7.08%)	15.95 (14.74–17.26)	15.77 (8608.73)
Linagliptin/metformin hydrochloride	2706	44 (1.63%)	42 (95.45%)	22.65 (16.81–30.52)	22.30 (894.08)
Temsirolimus	8750	113 (1.29%)	52 (46.02%)	17.54 (14.56–21.12)	17.33 (1733.29)
Pembrolizumab	70,054	783 (1.12%)	673 (85.95%)	15.98 (14.87–17.16)	15.81 (10,463.82)
Atezolizumab	26,163	285 (1.09%)	235 (82.46%)	14.54 (12.93–16.36)	14.40 (3498.46)

Drug name	Total adverse event reports	DILD reports (%)	Japan DILD reports (% <i>n</i> = 31,486 ^a)	ROR (95% CI)	PRR (χ^2)
Doxorubicin	81,024	844 (1.04%)	138 (16.57%)	14.17 (13.23–15.18)	14.03 (9960.03)
Ursodiol	4598	59 (1.28%)	56 (98.25%)	17.11 (13.23–22.12)	16.90 (881.73)
Panitumumab	24,553	256 (1.04%)	231 (90.23%)	14.15 (12.50–16.01)	14.01 (3069.96)
Alogliptin benzoate	2692	35 (1.30%)	35 (100.00%)	18.28 (13.09–25.52)	18.05 (563.29)
Bleomycin sulfate	3505	43 (1.23%)	15 (36.59%)	16.34 (12.09–22.08)	16.15 (610.83)
Pertuzumab	12,910	120 (0.93%)	84 (70.00%)	12.93 (10.80–15.48)	12.82 (1302.07)
Defibrotide sodium	4905	53 (1.08%)	2 (3.77%)	14.25 (10.87–18.69)	14.11 (643.95)
Bicalutamide	9447	86 (0.91%)	46 (61.33%)	12.10 (9.78–14.97)	12.00 (865.46)
Ampicillin sodium/sulbactam sodium	1774	21 (1.18%)	19 (100.00%)	15.75 (10.24–24.22)	15.57 (286.45)

Epidemiologic data from Japan

- Relatively more frequent reports of drug-induced pneumonitis in Japan
- Genetic factors in East Asian? or only in Japanese?



Epidemiologic data from Korea

- HIRA data – Only anti-neoplastic drugs
- Some differences with Japanese data

	n	Incidence rate per 1,000 person-years ^{a)}		Mantel–Haenszel Odds Ratio ^{a)}	95% CI	<i>P</i> value	
All	2,634	4.12					
Sex							
Male	1,763	5.93					
Female	871	2.55					
Age, years							
<40	31	1.00	Antibody-drug conjugates	5.63	2.57	12.31	<0.0001
40–49	139	1.42	HER2 antibodies	0.98	0.76	1.26	0.87
50–59	397	2.31	Immune checkpoint inhibitors	1.77	1.48	2.13	<0.0001
60–69	942	5.08	mTOR inhibitors	6.30	4.00	9.92	<0.0001
70–79	913	7.30	CDK4/6 inhibitors	1.45	0.98	2.16	0.06
≥80	212	7.45	ALK or EGFR inhibitors	0.77	0.64	0.93	0.01
Cancer site			Multikinase inhibitors	0.90	0.66	1.23	0.52
Lung	767	12.16	Cytotoxic agents	0.80	0.72	0.88	<0.0001
Stomach	185	3.52	VEGF inhibitors	0.83	0.48	1.44	0.50
Prostate	76	10.35					
Colon and rectum	425	3.11					
Liver	316	3.81					
Thyroid	18	2.45					
Pancreas	155	6.12					
Kidney	56	6.97					
Gallbladder etc.	85	4.24					
Bladder	127	4.57					
Breast	383	2.13					
Corpus uteri and cervix uteri	41	1.45					

Pathogenesis & Risk factors

- Pathogenesis mostly unknown
 - may involve cytotoxic damage to epithelial and endothelial cells & immune dysregulation
- Risk factors

Advanced age (> 40 years of age)

Renal dysfunction (GFR < 80 mL/min)

Dose-dependent toxicity

Genetic predisposition (familial pulmonary fibrosis, Japanese descent)

Previous radiotherapy

Preexisting ILD

Exposure to high FiO₂

Concurrent administration of pneumotoxic drugs

Poor performance status or advanced lung cancer

Smoking

COPD

Recent interests in antibody-drug conjugates (ADC)

- ADC – Biological missile → New era of targeted cancer therapy
- Pulmonary toxicities reported from ADCs targeting HER2

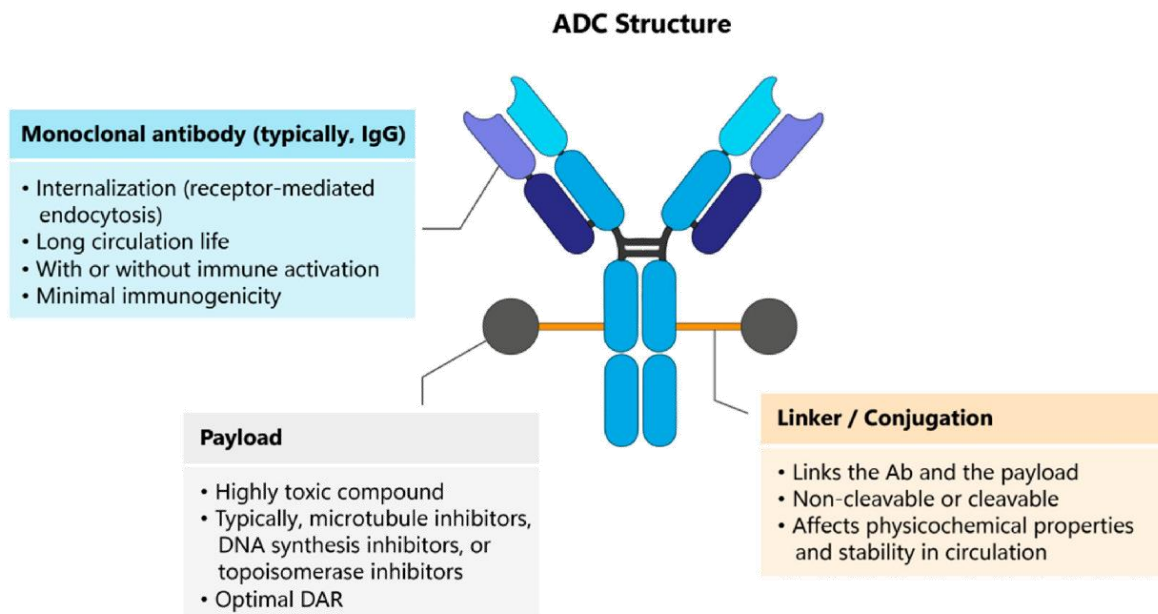
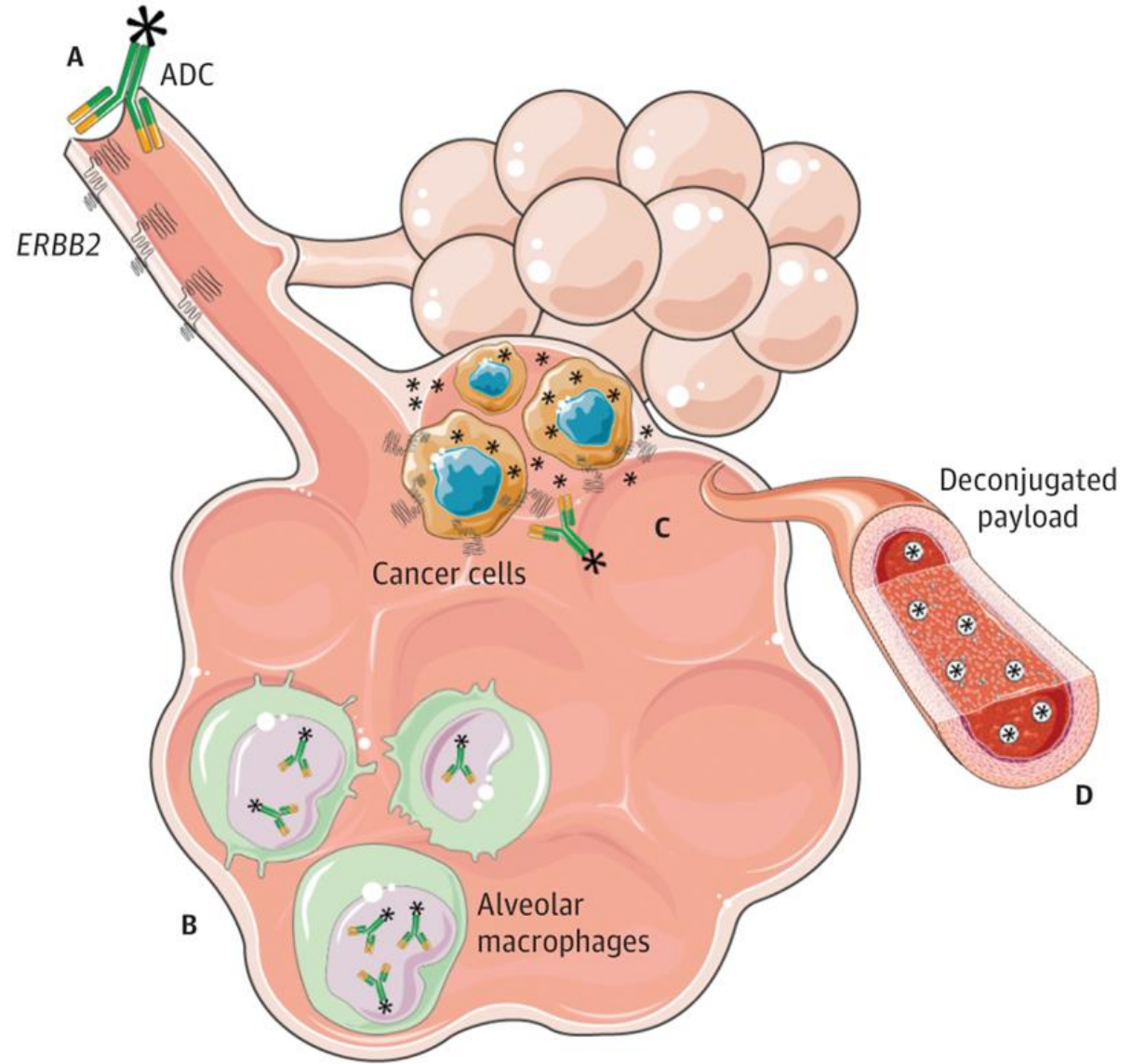


Table. Rate of ILD or Pneumonitis Reported in Trials Testing Anti-ERBB2 Antibody-Drug Conjugates

Drug	Setting	No. of patients	No. (%)	
			Incidence of all-grade ILD	Incidence of fatal ILD
Trastuzumab emtansine ¹⁴	Advanced ERBB2-positive breast cancer	3290	15 (0.5)	6 (0.2)
Trastuzumab emtansine ³⁶	Early ERBB2-positive breast cancer	740	19 (2.6)	0
Trastuzumab emtansine with atezolizumab ³⁷	Advanced ERBB2-positive breast cancer	202	8 (4.0)	0
Trastuzumab deruxtecan ³⁸	Advanced ERBB2-positive breast cancer	184	28 (15.2)	5 (2.7)
Trastuzumab deruxtecan ⁴	Advanced ERBB2-positive gastric cancer	125	12 (10.0)	0
Trastuzumab deruxtecan ⁶	Advanced ERBB2-mutant lung cancer	91	24 (26.4)	2 (2.2)
Trastuzumab deruxtecan ⁸	Advanced ERBB2-positive and ERBB2-expressing colorectal cancer	78	5 (6.4)	2 (2.6)
Trastuzumab deruxtecan ³⁹	Advanced ERBB2-positive breast cancer	257	27 (10.5)	0
Trastuzumab deruxtecan with nivolumab ⁴⁰	Advanced ERBB2-positive and ERBB2-expressing breast cancer	48	5 (10.4)	1 (2.1)
Trastuzumab duocarmazine ¹¹	ERBB2-positive or ERBB2-expressing advanced cancer	185	4 (2.2)	1 (0.5)
Trastuzumab duocarmazine ⁴¹	Advanced ERBB2-positive breast cancer	288	22 (7.6)	2 (0.7)

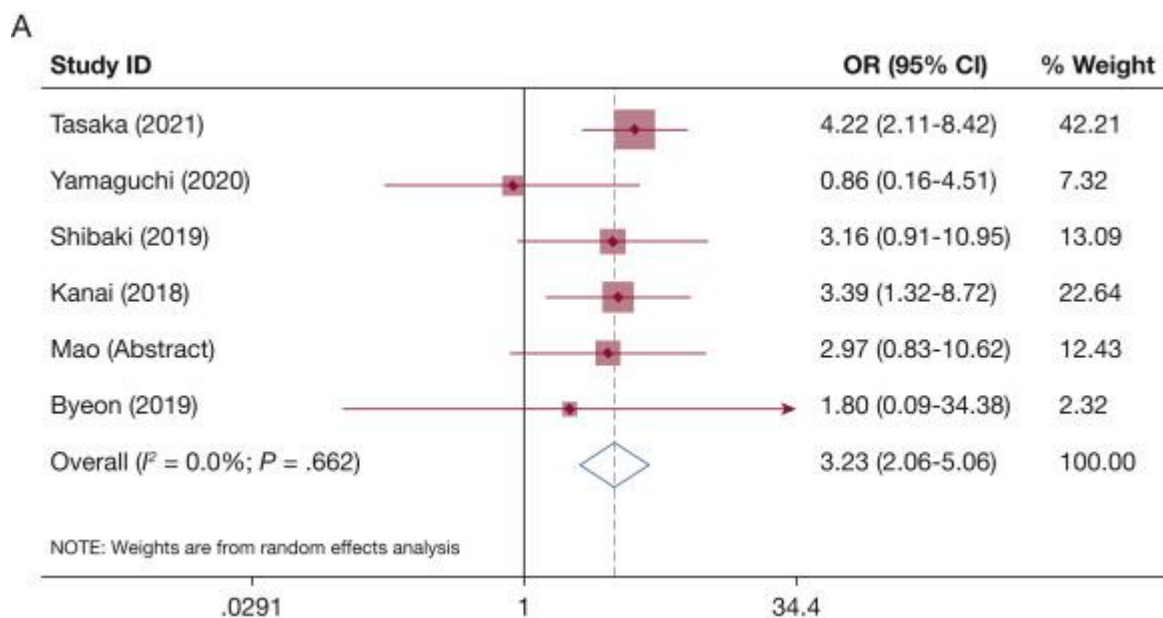
Suggested mechanisms of ADC-related lung injury

- Multiple potential mechanisms
 - target-dependent uptake of ADC
 - target-independent uptake of ADC
 - bystander killing by free payload released from tumor cell
 - circulating free payload due to deconjugation of ADC

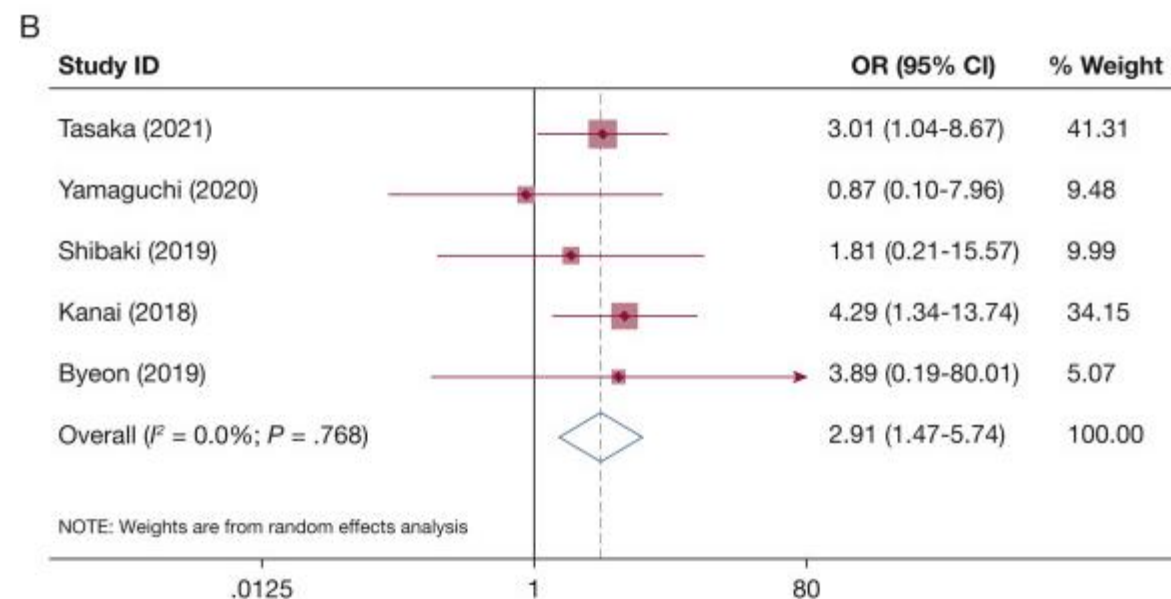


Impact of underlying ILD

- Consistent data regarding immune checkpoint inhibitors
- Not enough data regarding other potential culprit drugs



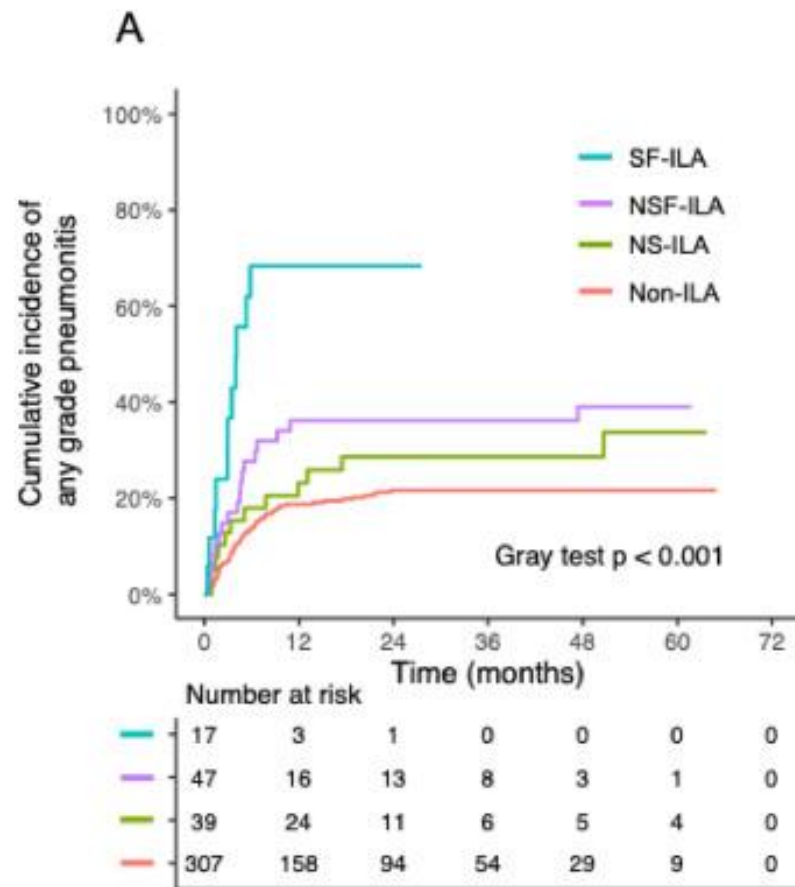
Any grade



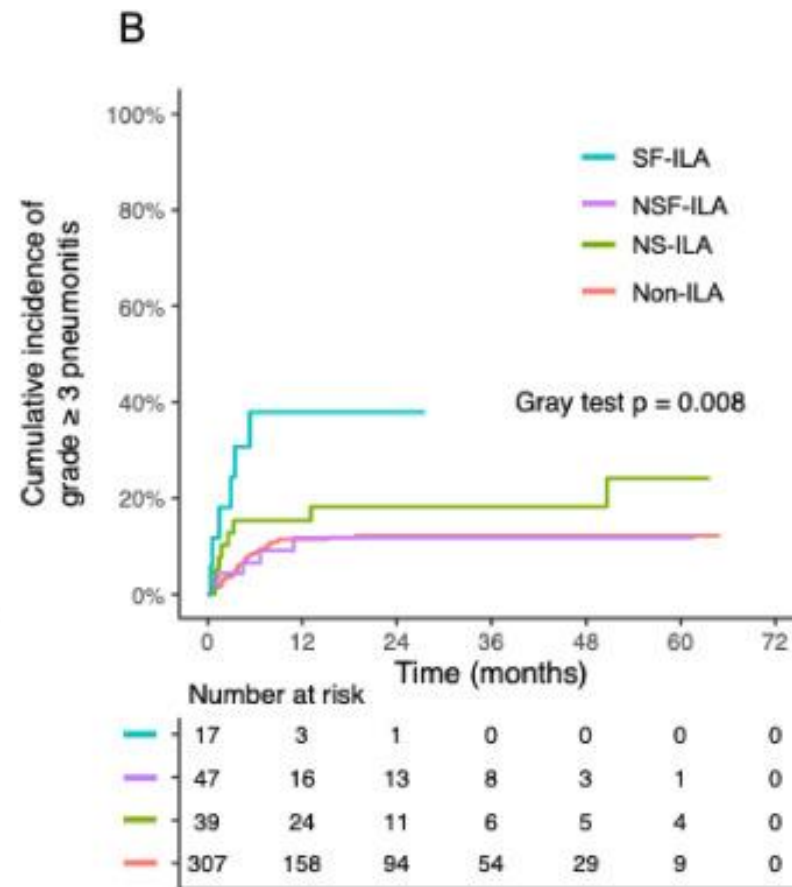
Grade 3 or more

Impact of underlying ILA

- Only limited data regarding immune checkpoint inhibitors
 - especially higher risk in subpleural fibrotic ILA



Any grade



Grade 3 or more

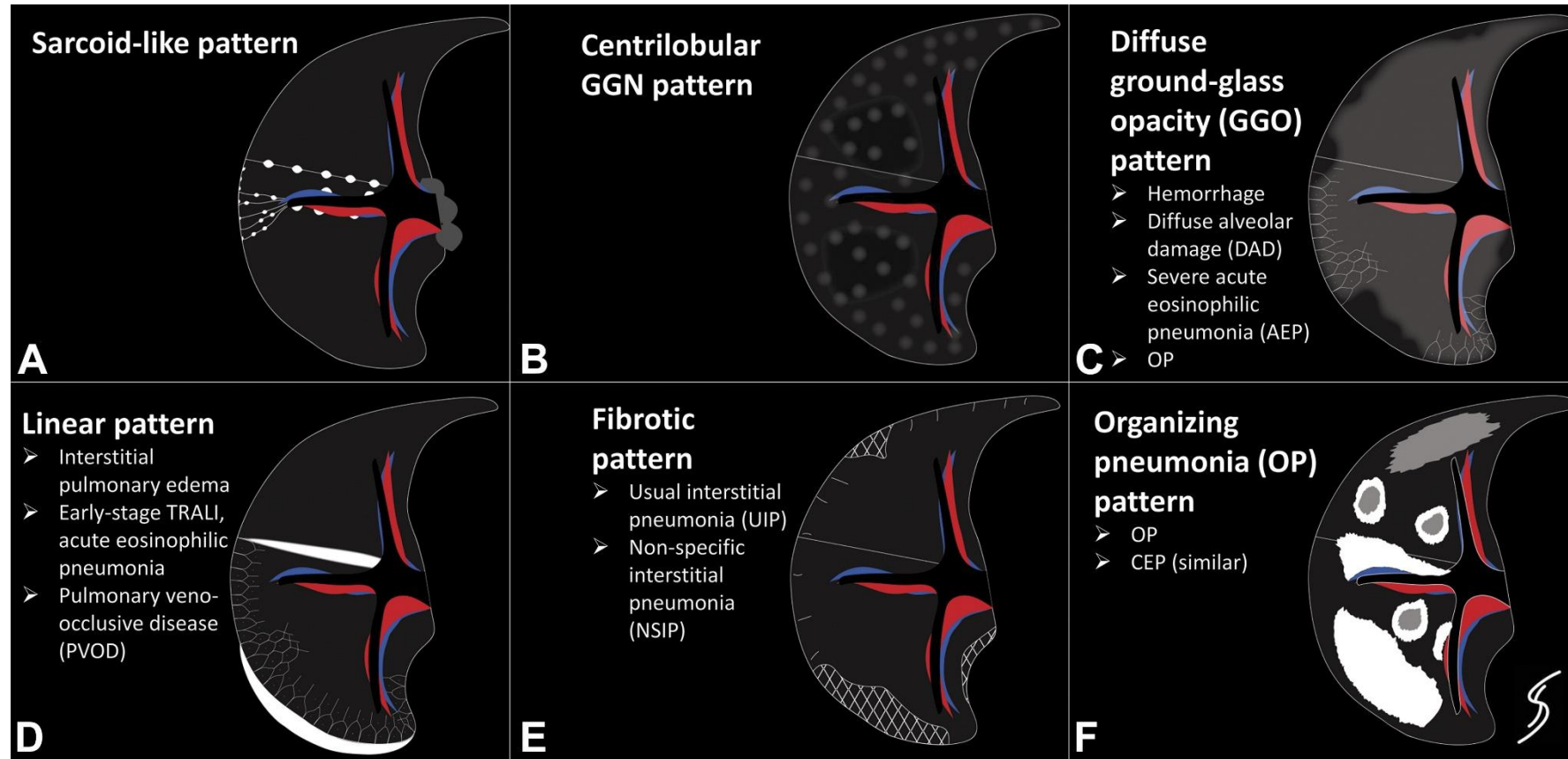
Clinical manifestation

- Highly variable
 - some associations between certain drug and disease pattern, but not so definite

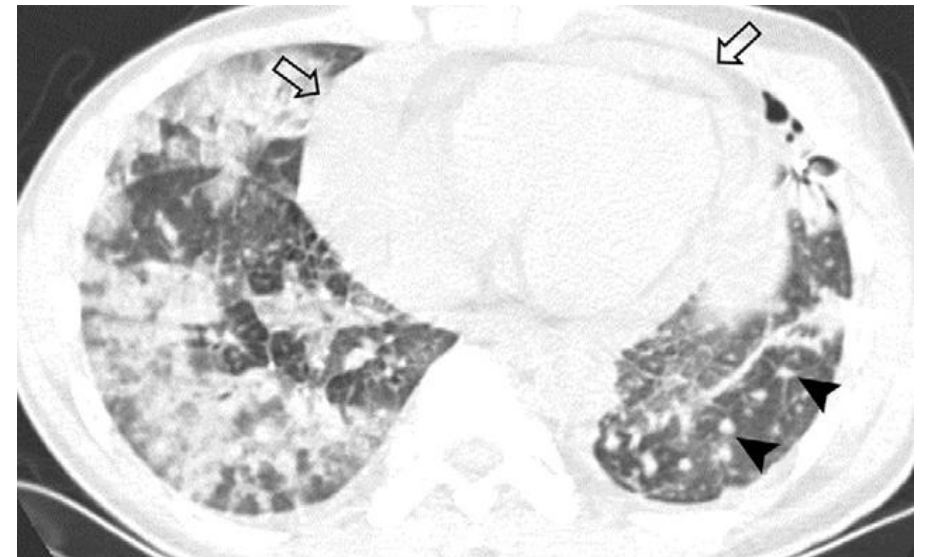
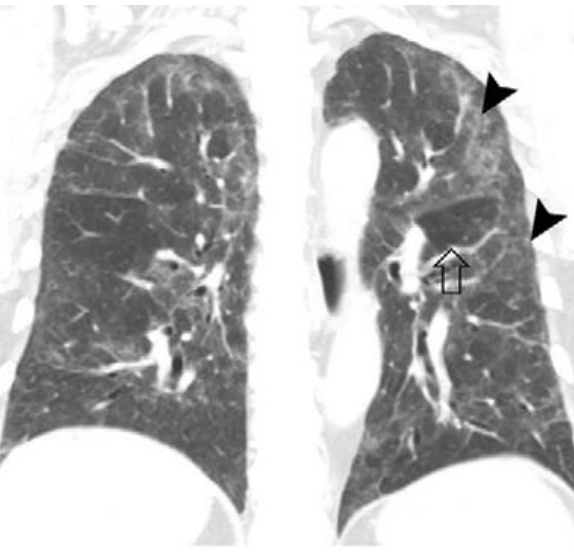
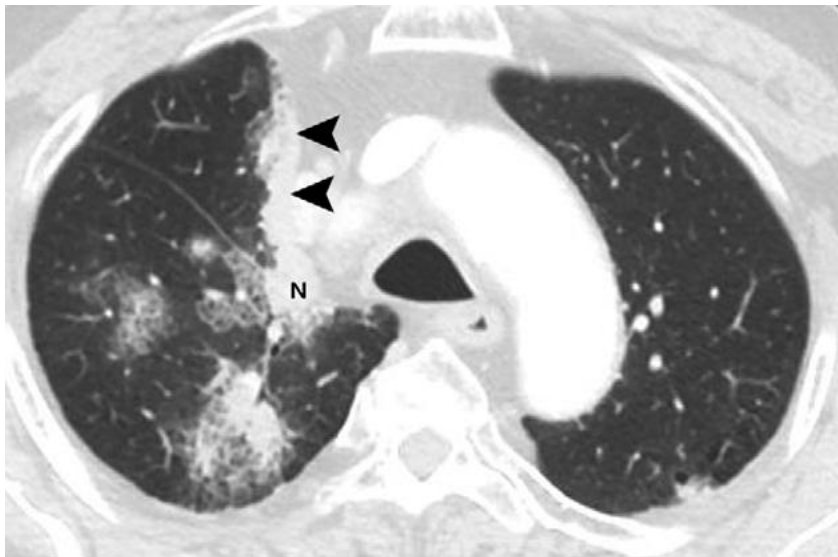
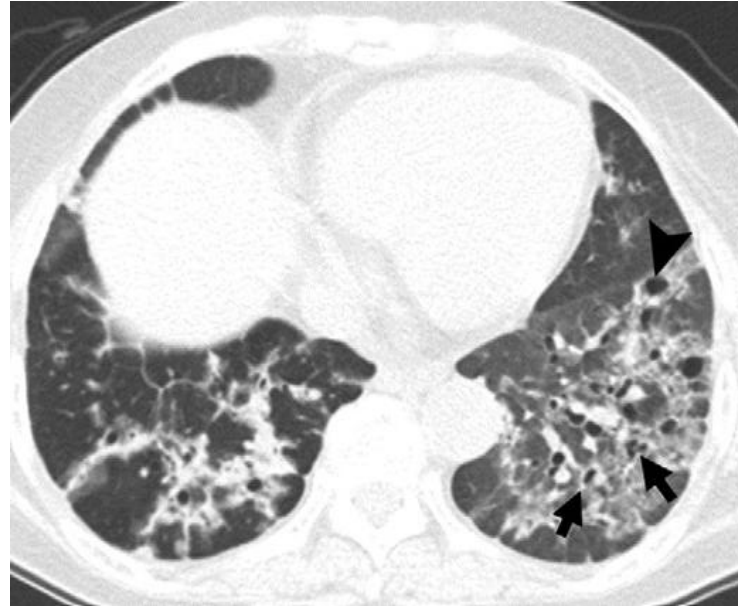
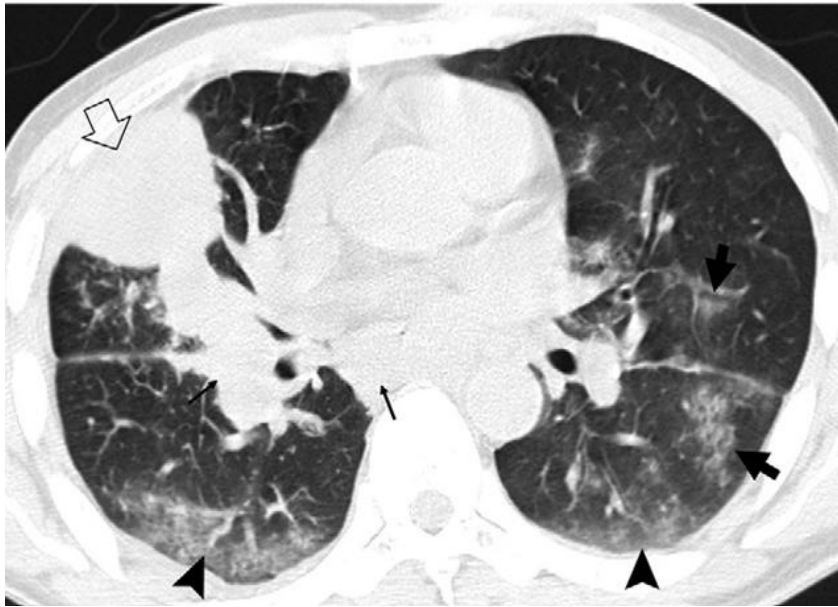
Acute or subacute ILD (including ARDS)	<ul style="list-style-type: none">• >350 suspected drugs• Amiodarone, chemotherapy (most drugs), ICIs, TKIs (including crizotinib, EGFR inhibitors erlotinib, gefitinib), mTOR inhibitors, rituximab, statins, methotrexate, nitrofurantoin, TNF-α antagonists• Do not forget: BCG therapy, tobacco smoke, e-cigarettes and vaping, vitamin E acetate, heroin, radiation therapy, silicone fluid
Pulmonary fibrosis	<ul style="list-style-type: none">• >80 suspected drugs• Chemotherapy (including alkylating agent cyclophosphamide, carmustine (BCNU), lomustine (CCNU), busulfan, bleomycin, gemcitabine) amiodarone, nitrofurantoin, bone marrow transplantation• Do not forget: paraquat, radiation to the chest, tobacco smoke
Eosinophilic pneumonia (including acute eosinophilic pneumonia and DRESS)	<ul style="list-style-type: none">• >200 suspected drugs• Antibiotics (minocycline, azathioprine, β-lactam), amiodarone, anticonvulsant, antidepressants, NSAIDs, chloroquine, leukotriene receptors antagonists, mesalazine, nitrofurantoin, tryptophan• Do not forget: tobacco smoke
Organising pneumonia	<ul style="list-style-type: none">• >100 suspected drugs• Amiodarone, antineoplastics including ICIs, statins, rituximab, sirolimus• Do not forget: radiation therapy to the breast
Noncardiogenic pulmonary oedema	<ul style="list-style-type: none">• >200 suspected drugs• All-trans-retinoic acid, aspirin, β_2-agonists (<i>i.v.</i> as tocolytic therapy), chemotherapy, hydrochlorothiazide, <i>i.v.</i> epoprostenol• Do not forget: cocaine, heroin, chlorine gas, various inhaled chemicals, TRALI, vasodilators in patients with pulmonary hypertension
Diffuse alveolar haemorrhage	<ul style="list-style-type: none">• >150 suspected drugs• Amiodarone, anticoagulants, antiplatelet agents, abciximab, ticlopidine, fibrinolytic agents, VEGF-inhibitors (bevacizumab), erlotinib, mTOR inhibitors, propylthiouracil• Do not forget: brodifacoum, superwarfarin (anticoagulant rodenticide), cocaine
Granulomatosis, sarcoid-like granulomatosis	<ul style="list-style-type: none">• >40 suspected drugs• TNF-α antagonists, ICIs, daclizumab, interferon• Do not forget: BCG therapy (bladder instillation)
Lupus-like syndrome	<ul style="list-style-type: none">• >80 suspected drugs• Hydralazine, TNF-α antagonists, isoniazid, minocycline, sulfasalazine, procainamide, β-blockers, ICIs• Do not forget: timolol ocular drops
Auto-immune conditions including ANCA+	<ul style="list-style-type: none">• >20 suspected drugs• Nitrofurantoin, TNF-α antagonists, propylthiouracil, minocycline, alemtuzumab• Do not forget: adulterant levamisole-induced vasculitis (cocaine users)
Pleuroparenchymal fibroelastosis	<ul style="list-style-type: none">• ~10 suspected drugs• Cyclophosphamide and other alkylating agents• Do not forget: bone marrow transplantation (both allogenic and autologous) and lung transplantation

Diagnostic approach

- Suspicion is always most important – Temporal association
- Chest imaging – Various patterns : prognostic information
- Histopathologic exam – Rarely needed

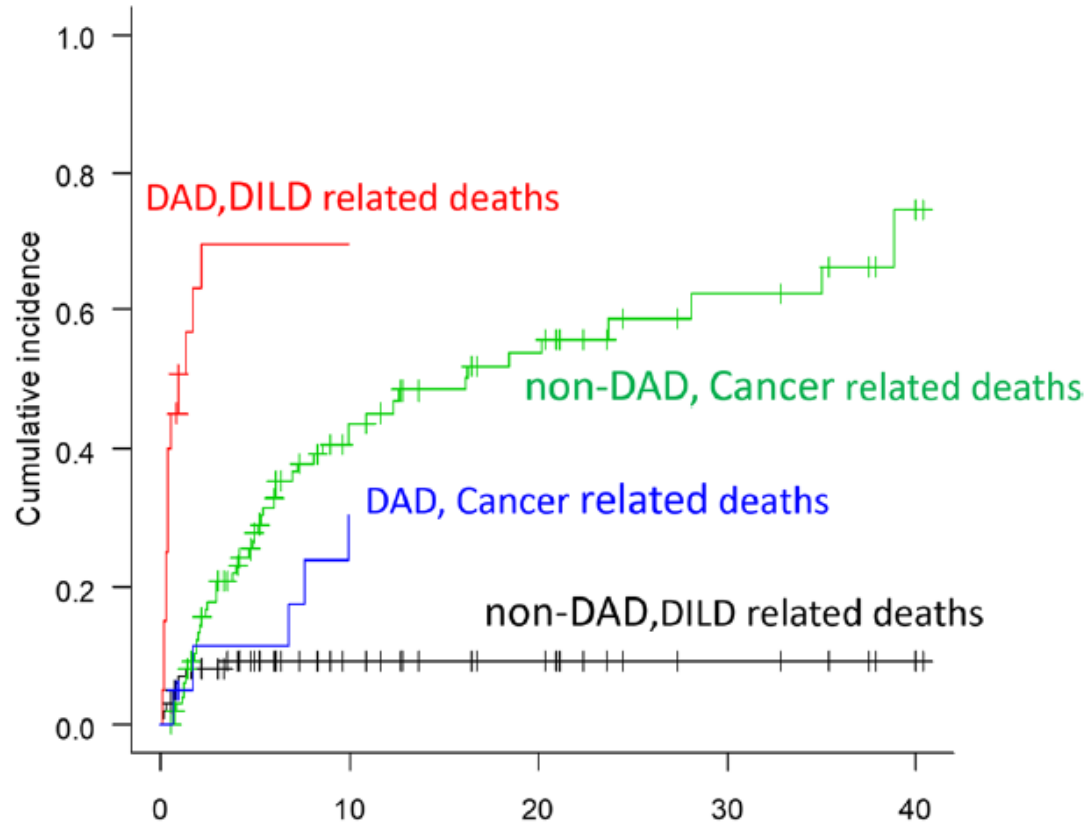


Chest CT patterns



Prognostic impact of chest CT finding

- Diffuse alveolar damage (DAD) pattern has worse prognosis



Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	<i>P</i> value	Hazard ratio	95% CI	<i>P</i> value
Sex						
Male	1	0.01–0.73	0.02	1	0.05–3.6	0.42
Female	0.09	0.44				
History of lung surgery						
Absence	1	1.05–5.66	0.04	1	0.59–5.21	0.31
Presence	2.44	1.76				
History of interstitial lung disease						
Absence	1	2.24–12.67	<0.01	1	1.27–8.10	0.01
Presence	5.33	3.2				
Smoking history						
Absence	1	1.18–22.63	0.03	1	0.23–6.88	0.78
Presence	5.18	1.26				
Performance status						
0–1	1	2.32–16.46	<0.01	1	1.10–13.17	0.03
≥2	6.18	3.81				
DAD pattern on CT						
Absence	1	4.82–26.20	<0.01	1	1.17–11.03	0.02
Presence	11.24	3.59				

Role of bronchoscopy

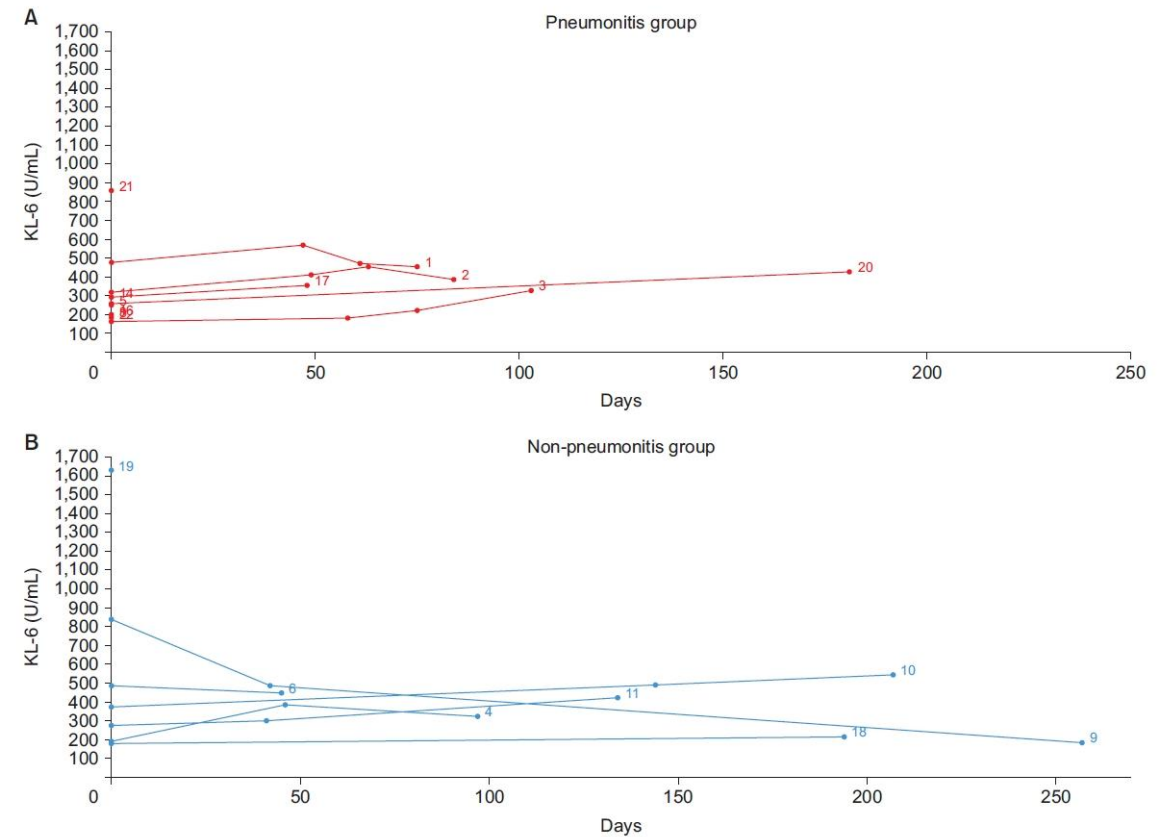
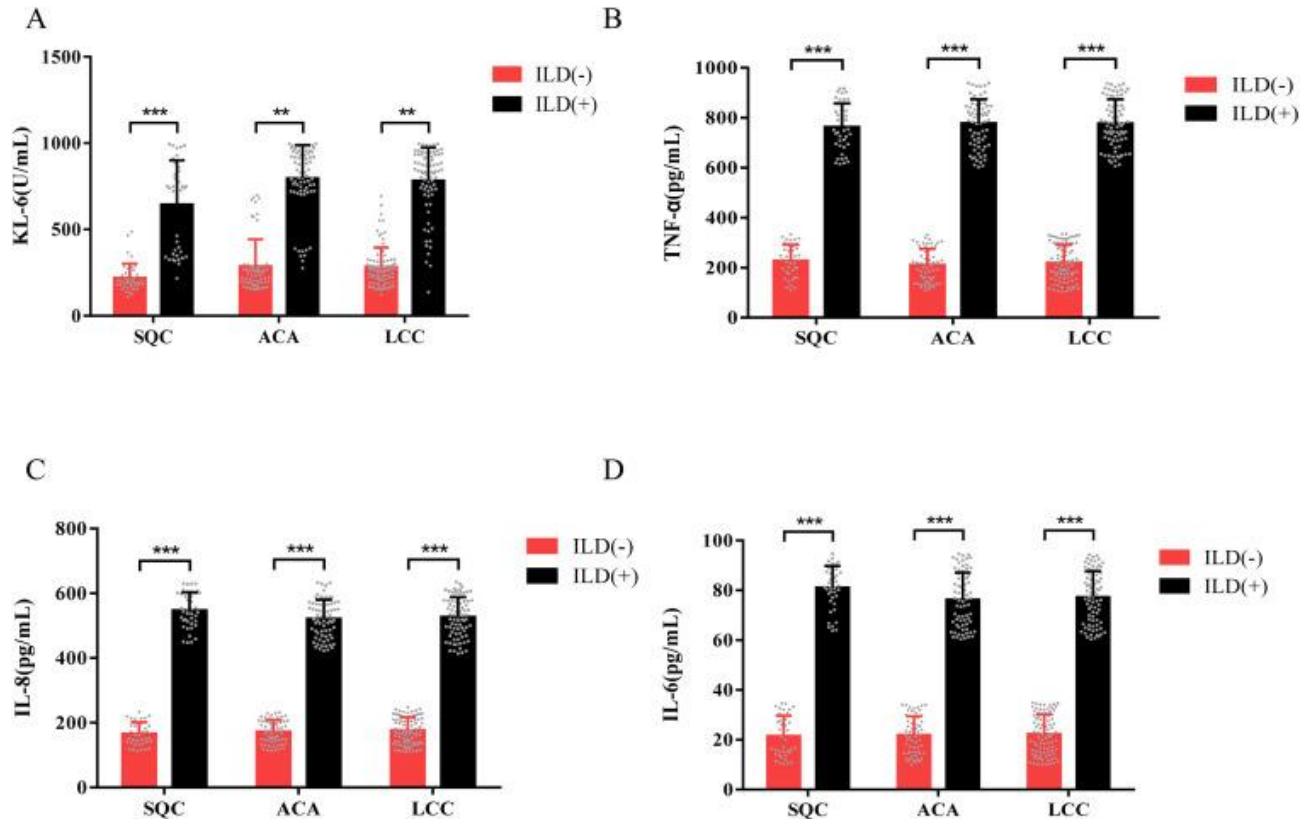
- Exclusion of alternative diagnoses
 - opportunistic infection, especially Pneumocystis
- BAL fluid lymphocytosis
 - often CD8 predominance
- Consideration of risk vs. benefit

Variable	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Brain metastasis	1.27 (0.80–2.02)	0.307		
Surgery	0.41 (0.22–0.73)	0.006	0.42 (0.22–0.79)	0.008
CTx	1.43 (0.57–3.60)	0.450		
RTx	1.95 (1.18–3.25)	0.001		
CCRTx	2.59 (1.58–4.25)	<0.001	2.09 (1.27–3.43)	0.004
Lymphopenia (<1000 cells/ μ L)	2.68 (1.23–5.82)	0.013		
Steroid \geq 20 mg/d and \geq 3 wks [†]	2.49 (1.42–4.37)	0.002	1.96 (1.06–3.63)	0.032
PJP prophylaxis	0.33 (0.10–1.09)	0.068		

	Patients with prolonged use of a moderate-to-high corticosteroid dose (n = 6)	Patients without prolonged use of a moderate-to-high corticosteroid dose (n = 14)	Total (n = 20)
Age (years), median (range)	56 (46–76)	67 (40–90)	66 (40–90)
Cancer type, n (%)			
Lung cancer	1 (17)	5 (36)	6 (30)
Breast cancer	1 (17)	2 (14)	3 (15)
Esophageal cancer	0 (0)	2 (14)	2 (10)
Pancreatic cancer	1 (17)	1 (7)	2 (10)
Others ^a	3 (50)	4 (29)	7 (35)
ALC, n (%)			
< 500	3 (50)	9 (64)	12 (60)
500–999	2 (33)	4 (29)	6 (30)
\geq 1000	1 (17)	1 (7)	2 (10)

Potential role of KL-6

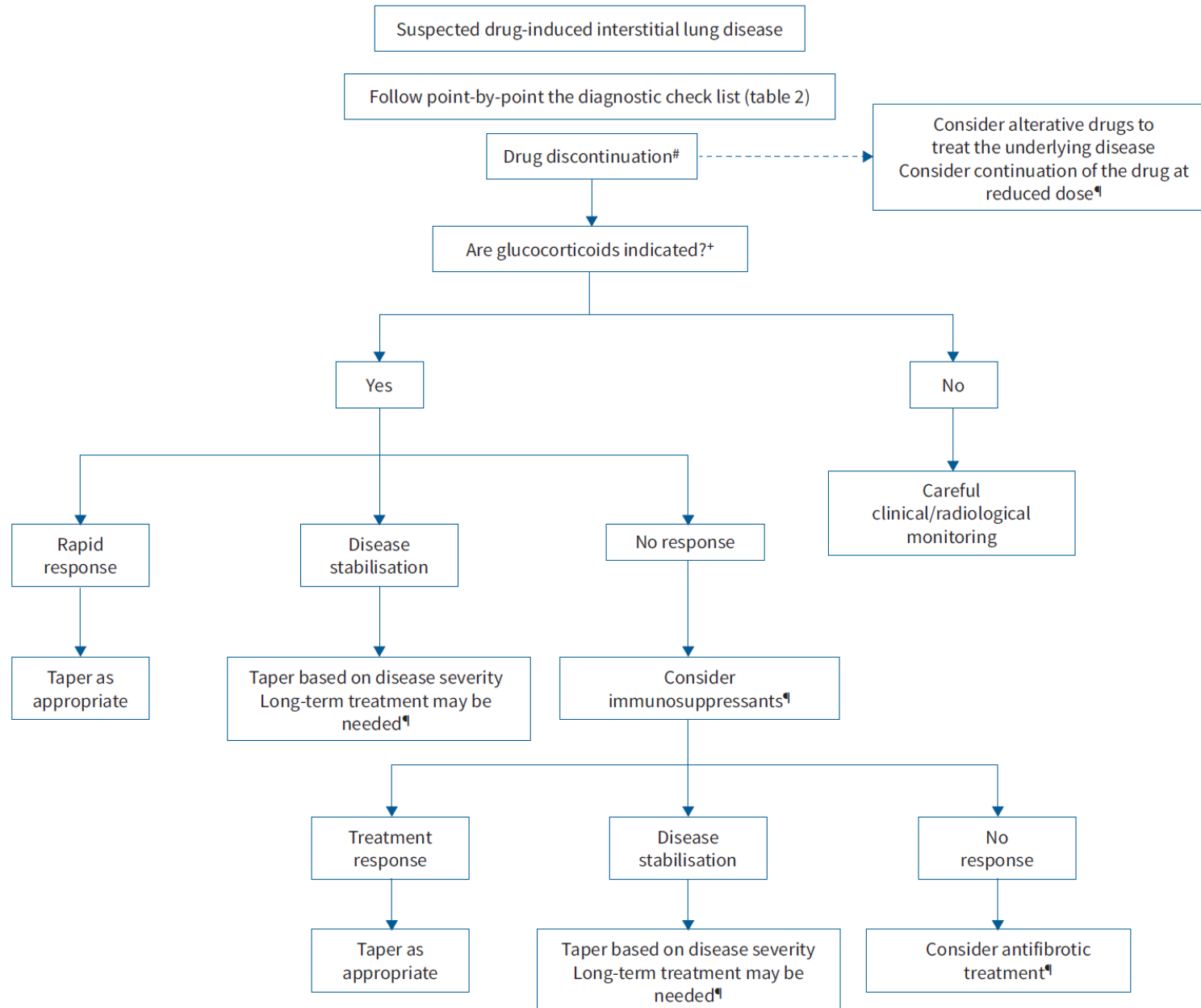
- Well-known biomarkers of ILD
- Limited data in immune checkpoint inhibitors



Therapeutic approach

- Drug discontinuation ± Rechallenge
- Glucocorticoid therapy
 - dosage based on severity
 - routinely prednisolone 0.5~1.0 mg/kg/day
 - pulse therapy in severe cases (ex. methylpredisolone 500~1000 mg/day)
 - gradual tapering based on clinical course
- Additional immunosuppressants
 - infliximab, mycophenolate, calcineurin inhibitor, IVIG, etc. → not well studied
- Antifibrotics
 - theoretically can be helpful in progressive pulmonary fibrosis → not well studied

Overall management flowchart



Multi-disciplinary discussion

- Particularly in cases of anti-neoplastic drugs
- Lung condition vs. Tumor control
- Curative setting vs. Palliative setting
- Expected survival
- Next line treatment options



Thank you for your attention