Treatment-related Pneumonitis in Lung Cancer Patients

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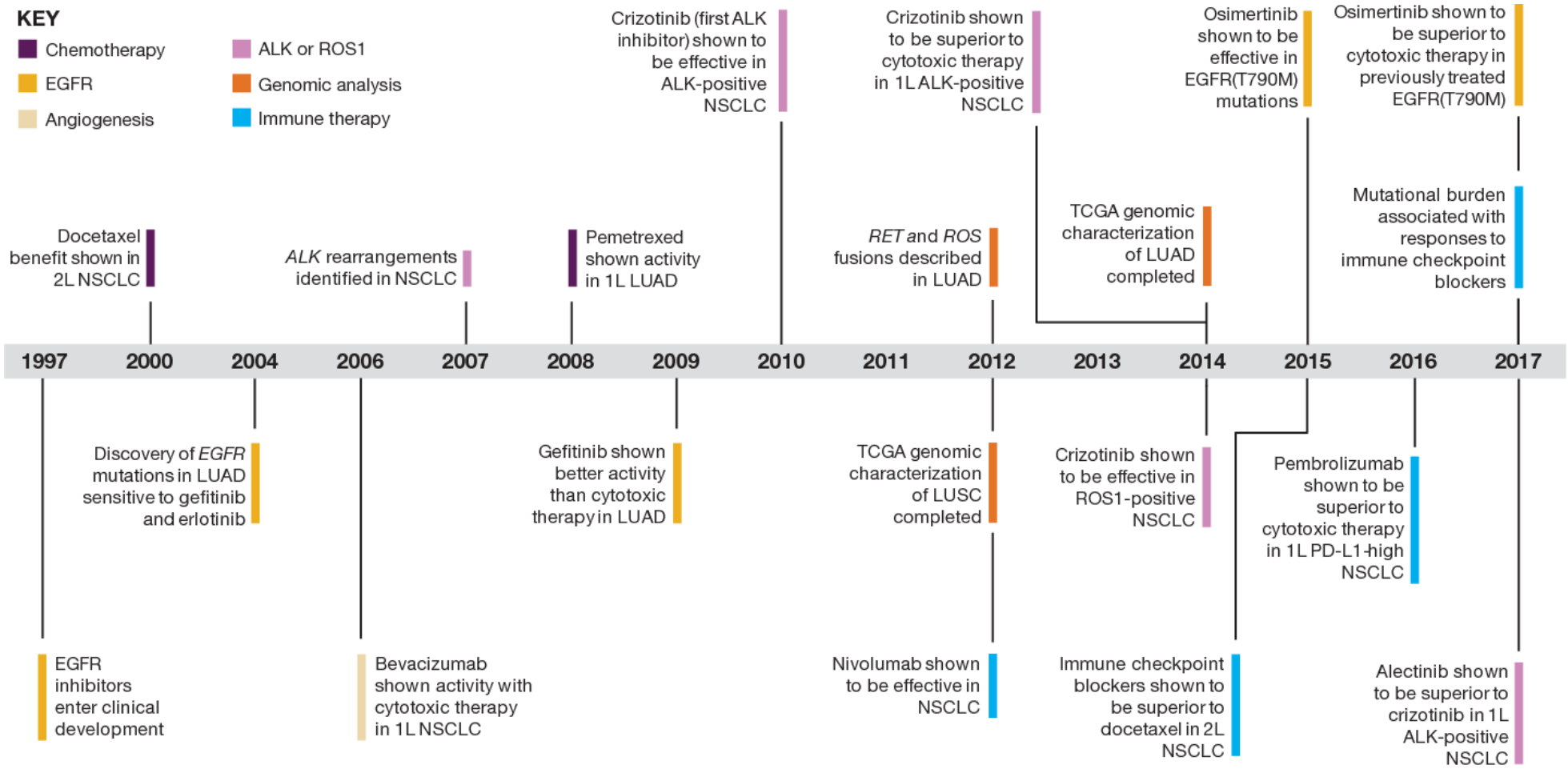


Treatment with chemotherapy, radiation therapy, and more recently, immunotherapy, has provided improvement in disease outcomes

Introduction

- The benefits of agents need always be weighted against the risks of toxicity.

- Drug-related pneumonitis is one of the major categories of adverse events during cancer therapy

Clinical manifestation

- Clinical courses
  - Variable, Non-specific
  - lung infiltration, shortness of breath, gas exchange abnormality
  - Timing of the symptoms can vary between weeks to months

  - Some patients required admission to the ICU
  - Others were treated successfully with oral corticosteroids on an OPD basis

Pathogenesis

- Poorly understand.
  - Direct toxic injury to pneumocytes or the aveloar capillary endothelium with subsequent release of cytokines and recruitment of inflammatory cells
  - The systemic releases of cytokines
  - Cell-mediated lung injury d/t activation of lymphocytes and alveolar macrophage
  - Oxidative injury from free oxygen radicals
  - Unintended dysregulation of the immune system and T-cell activation
  - Impair alveolar wall repair mechanisms
  - Radiation recall pneumonitis

Diagnosis

- Exclusion diagnosis
  - There are no specific findings to confirm a diagnosis of drug-induced pneumo nitis => to rule out infectious causes and recurrent malignancy.

Diagnosis

Radiographic findings can vary depending on the offending agent. (Patchy, unilateral or bilateral reticular markings, ground glass opacit ies or consolidation, pleural effusion, focal nodular consolidations…)

Nasal swab and PCR, infection panel testing

Sputum, blood and urine culture

Bronchoscopy & **BAL** are necessary to rule out other causes(infectio n, IIPs, etc.)

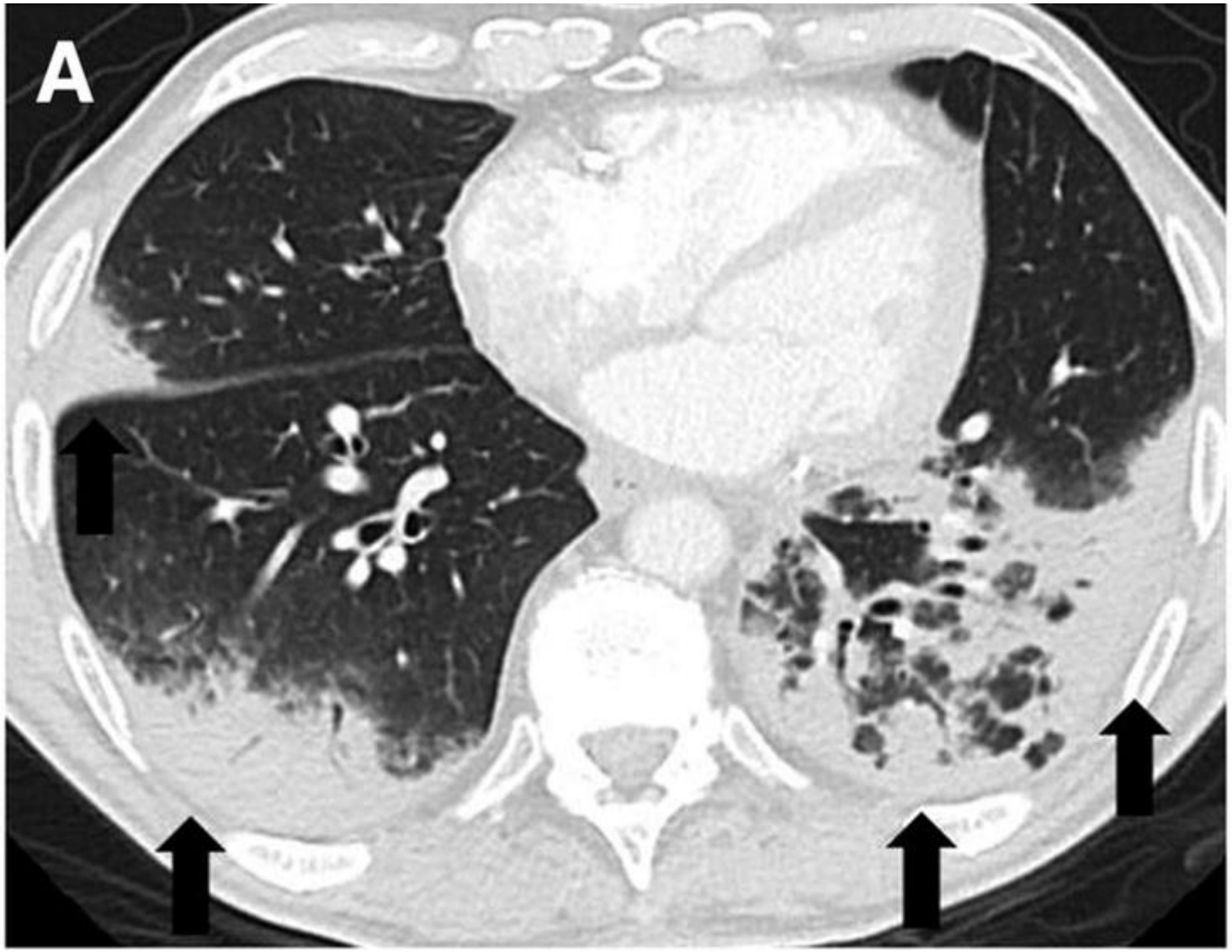
Pulmonary Function test
DLCO - decreased / Restrictive pattern.

Radiologic pattens of drug-induced pneumonitis

Radiographic Pattern	Findings on Chest CT Imaging
COP	Multifocal bilateral parenchymal consolidations with peripheral and lower lung distribution, which may be accompanied with GGOs and reticular opacities
NSIP	GGOs and reticular opacities predominantly in peripheral and lower lung distribution, which may be accompanied with traction bronchiectasis and lower lobe volume loss
HP	Diffuse GGOs and centrilobular nodularities, which may be accompanied by air trapping
AIP/ARDS	Diffuse or multifocal GGOs or consolidations predominantly in dependent lung regions, may be accompanied by lung volume loss and traction bronchiectasis

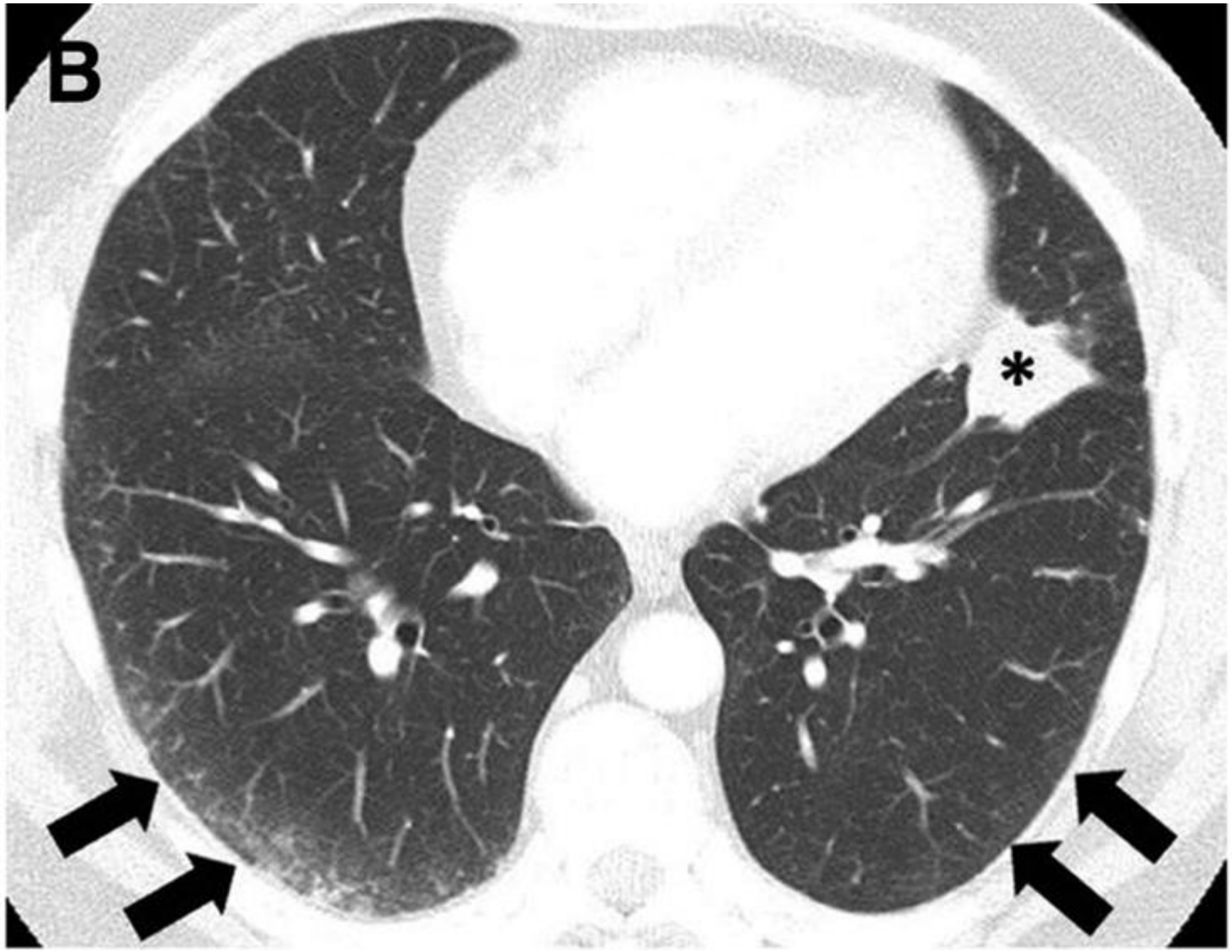
Radiographic manif estations

(A) COP pattern is characterized by multi focal bilateral parenchymal consolidatio ns with peripheral and lower lung distrib ution, with ground-glass opacities (GGOs) and reticular opacities (arrows).



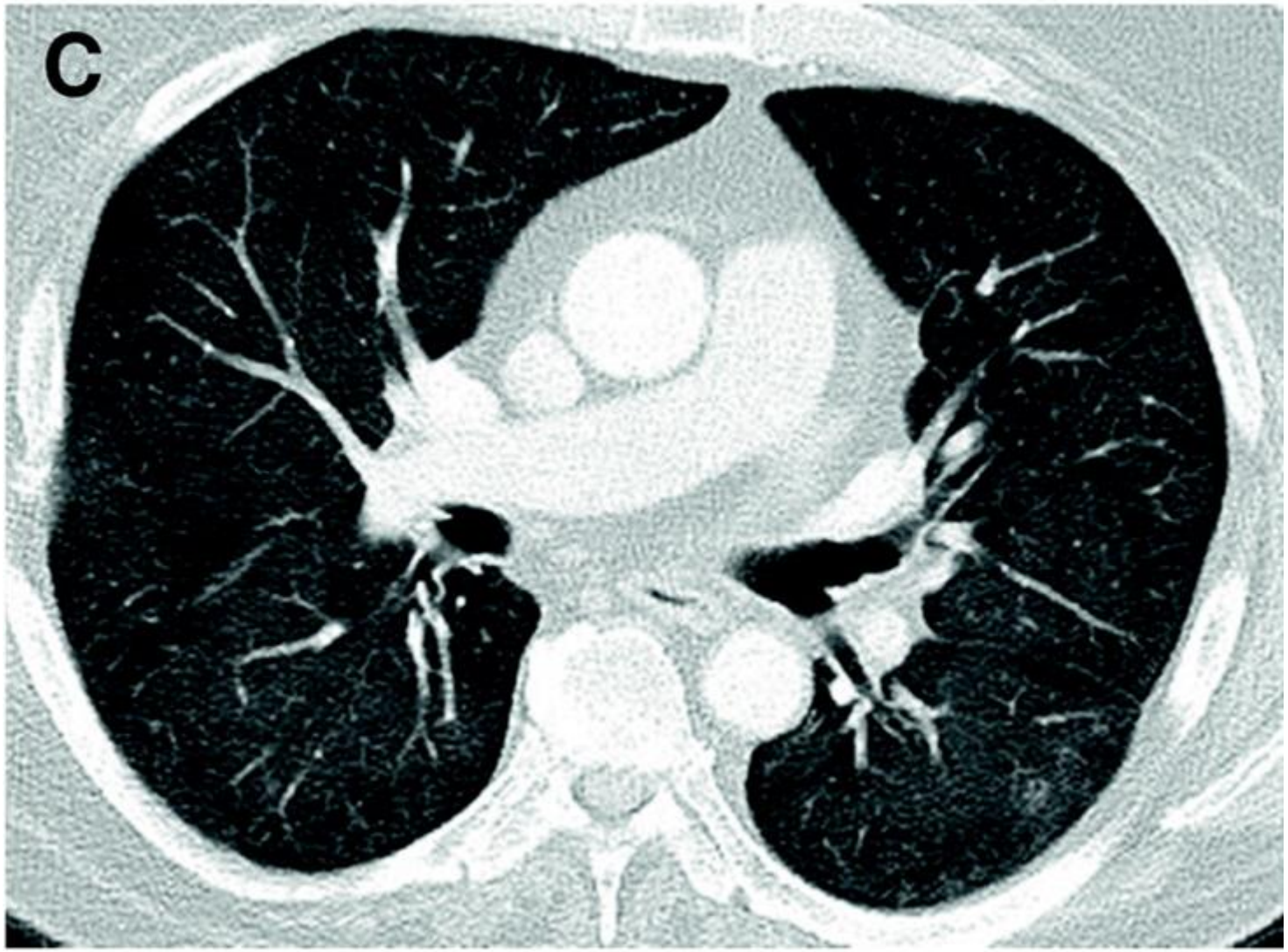
Radiographic manif estations

(B) NSIP pattern demonstrates GGOs an d reticular opacities predominantly in pe ripheral and lower lung distribution (arro ws). The asterisk indicates lung tumor b urden.



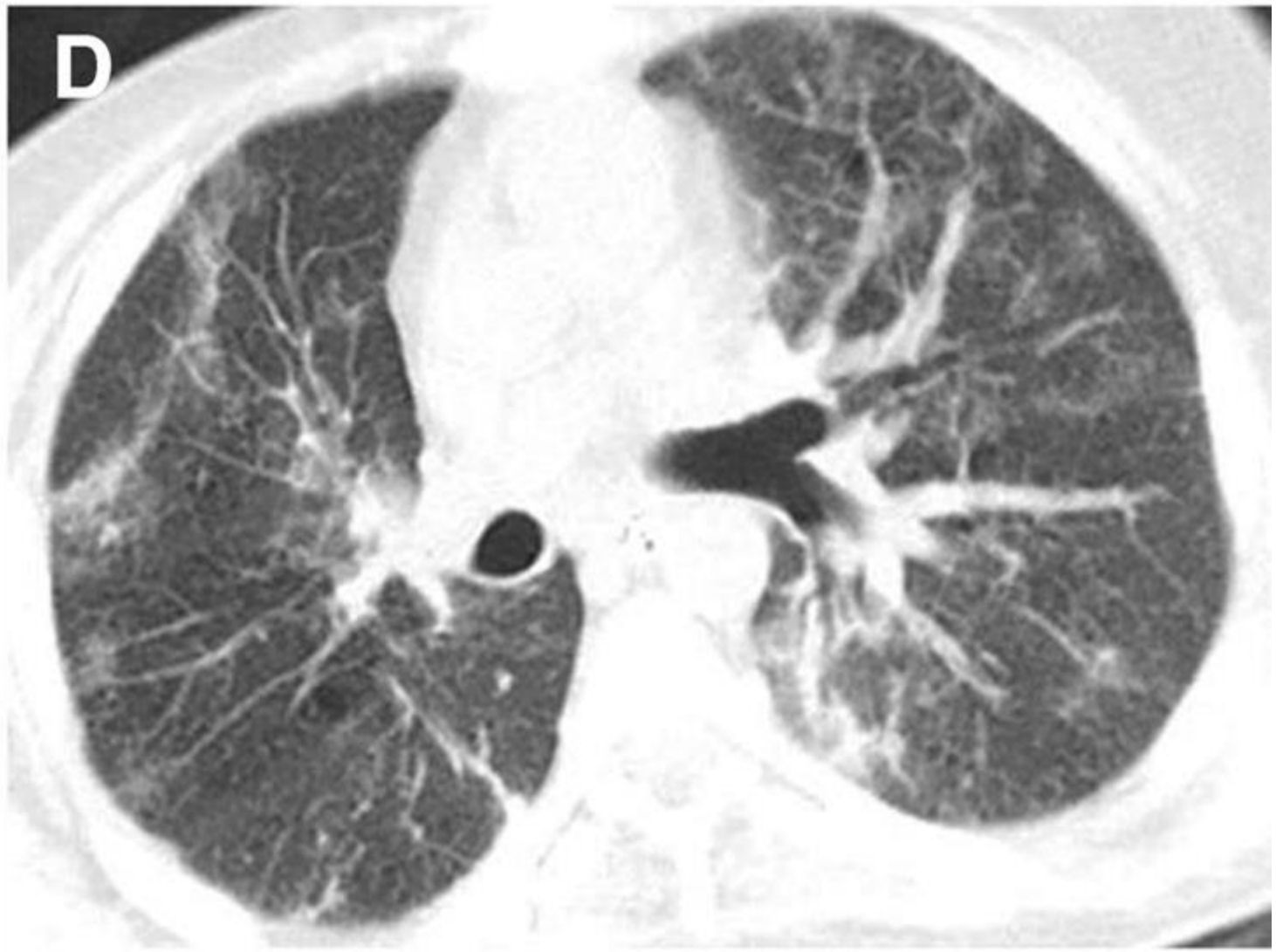
Radiographic manif estations

(C) HP pattern demonstrates diffuse GG Os and centrilobular nodularities, with sc attered areas of air trapping.



Radiographic manif estations

(D) AIP/ARDS pattern is characterized by diffuse or multifocal GGOs or consolidati ons, along with lung volume loss and tra ction bronchiectasis.



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MINI REVIEW

Drug-induced interstitial lung disease in tyrosine kinase inhibitor therapy for non-small cell lung cancer: a review on current insight

Ji Hye Min · Ho Yun Lee · Hoyeong Lim · Myung-Ju Ahn · Keunchil Park · Man Pyo Chung · Kyung Soo Lee

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Table 3 CT Features of molecularly targeted agent-induced interstitial lung disease

Patterns	Radiographic manifestations on CT
Progression of underlying PF	Obvious progression of reticular attenuation with interlobular septal thickening, architectural distortion with associated traction bronchiectasis, a honeycomb pattern, and GGO

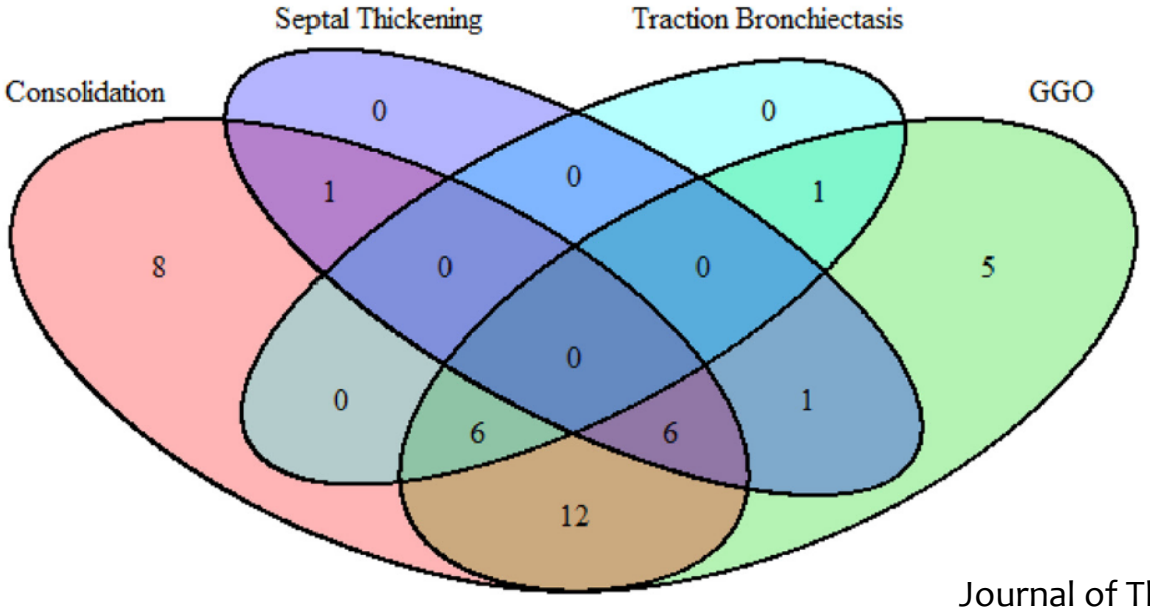
GGO ground-glass opacity, *NSIP* nonspecific interstitial pneumonia, *UIP* usual interstitial pneumonia, *PF* pulmonary fibrosis

Table 4 Patterns and their relative frequency of drug-induced interstitial lung disease associated with the use of various tyrosine kinase inhibitors

	DAD	BO	COP	HP	IP
Gefitinib	++			+	+
Erlotinib		+	+	+	
Sorofenib		+	+		+

DAD diffuse alveolar damage, *BO* broncholitis obliterans, *COP* cryptogenic organizing pneumonitis, *HP* hypersensitivity pneumonia, *IP* interstitial pneumonia

Plus signs indicate the relative frequency of the findings from occasional (++) to rare (+)



Journal of Thoracic Oncology Vol. 13 No. 12: 1930-1939

	Number (%)
Laterality	9 (2)
Left	12 (2)
Right	19 (45)
Bilateral	
Components of Infiltrate	
Ground-glass	31 (73)
Consolidation	33 (78)
Septal Thickening	8 (19)
Traction Bronchiectasis	7 (16)
Area of pneumonitis	
Peri-tumoral	6 (14)
Away from tumor	36 (86)

Figure 5. Venn diagram and table of radiographic data showing the laterality, infiltrate type, and relationship of infiltrates to primary tumor in patients with checkpoint inhibitor pneumonitis. Abbreviation: GGO, ground glass opacity.

Grading of drug-induced pneumonitis

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events

Grade	Description
1	Asymptomatic – clinical/diagnostic observations only
2	Symptomatic – limiting instrumental ADL; intervention indicated
3	Severe symptoms – limiting self-care ADL; oxygen indicated
4	Life-threatening respiratory failure – urgent intervention indicated (eg, intubation for MV)
5	Fatal – death

Grading Criteria for Pneumonitis[59]

Abbreviations: ADL = activity of daily living; MV = mechanical ventilation.

Treatments

- No specific treatments
  - Drug discontinuation
    - The risks, benefits, and availability of alternative treatements…
  - Systemic glucocorticoids
    - Depends on the severity and rapidity of worsening of pulmonary impairments
    - No established treatment schedule
      - Prednisone 40-60mg daily; intravenous(eg, methyl-Pd with doses up to 1gm daily for 3 days)
  - Supportive care
    - Supplemental oxygen, inhaled bronchodilating medication, mechanical ventilation…
  - Rechallenge
    - Case by case basis

Treatment-related Pneumonitis

- Chemotherapy-Induced Pneumonitis
- Target-therapy-Induced Pneumonitis
- Immunotherapy-Induced Pneumonitis

Chemotherapy-Induced Pneumonitis

Chemotherapy-Induced Pneumonitis

10~20% of all cancer patients treated with cytotoxic chemotherapy d evelop some form of lung toxicity.
It is estimated to occur in 3% of NSCLC patients.

Pathophysiology is pooly understood.

Multiple mechanism have been proposed.

=> Mediated by the systemic release of cytokines
-> direct injury to the pneumocytes, activation of lymphocytes & alv eolar macrophages, generation of oxygen free radicals.

Chemotherapy-Induced Lung injury

Clinical presentation of Lung injury; variable

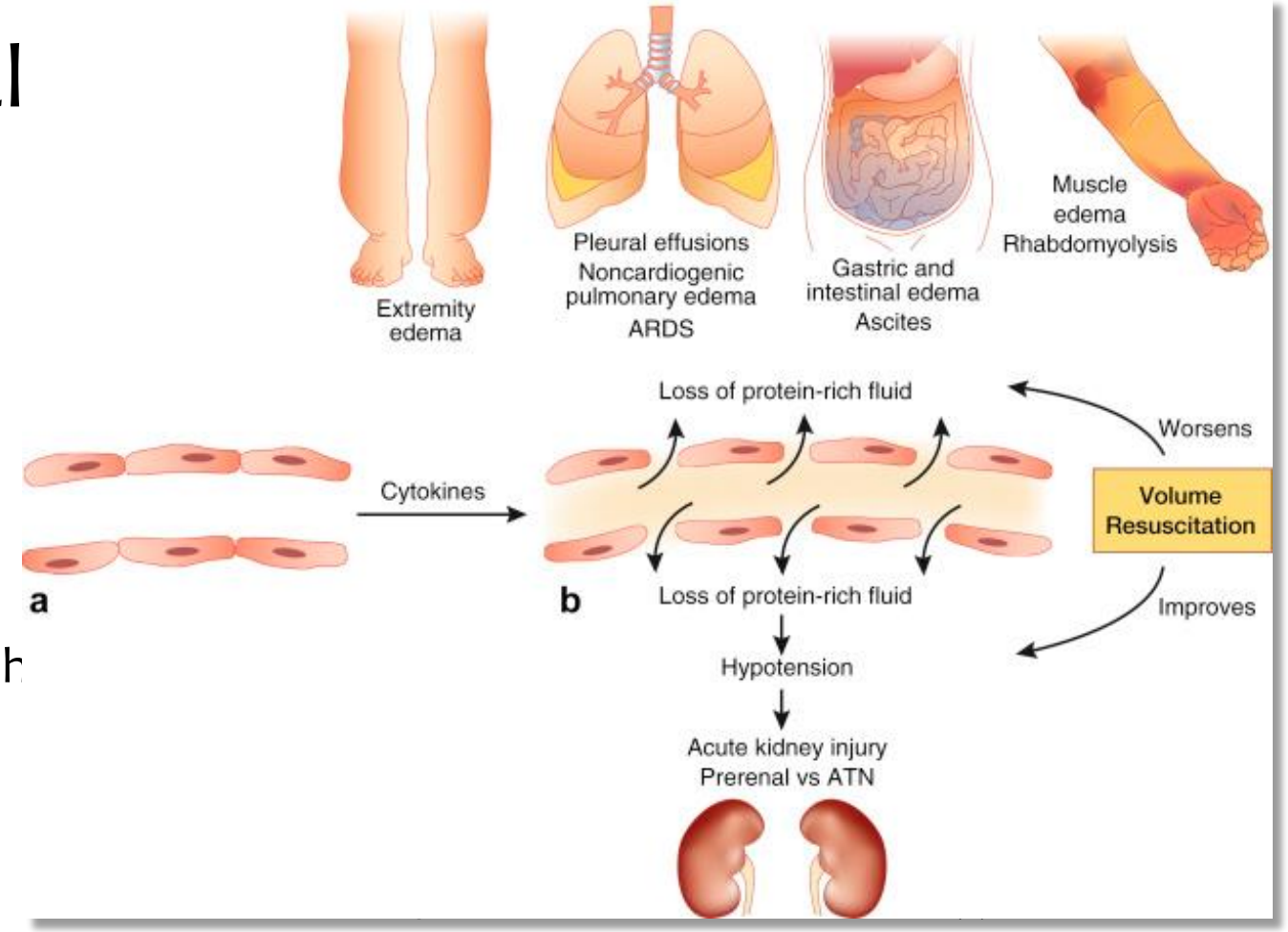
1) acute bronchoconstriction
2) alveolar hemorrhage
3) eosinophilic pneumonia
4) hypersensitivity
5) interstitial pneumonitis
6) capillary leak syndrome
7) pulmonary veno-occlusive disease

Taxanes, namely pacl

- Disrupt microtubule function
- Pulmonary complication : < 5%
- m/c type : interstitial pneumonitis
- Duration : within days to weeks

Paclitaxel

- d/t immune-mediated dealyed h



Docetaxel

- Capillary leak syndrome ; exclusively
  - Fluid retention and non-cardiogenic pulmonary edema and/or pleural effusion

Constantopoulos S, et al. Respiration. 2000;67(6):680–3.
Amathieu R, et al. Ann Fr Anesth Reanim. 2007;26(2):180–1.

Gemcitabine

- Pyrimidine analog
  - Nearly 25% of patients develop pulmonary Sxs
  - Only 1-2% : significant pulmonary toxicities

Aapro MS et al. Anti-Cancer Drugs. 1998;9(3):191–201.
Roychowdhury DF, et al. Investig New Drugs. 2002;20(3):311–5.
Pavlakis N, et al. Cancer. 1997;80(2):286–91.
LinskensRK, et al. Neth J Med. 2000;56(6):232–5.
Marruchella A, et al. Eur Respir J. 1998;11(2):504–6.
Barlesi F, et al. Fundam Clin Pharmacol. 2004;18(1):85–91.
Boiselle PM, et al. J Comput Assist Tomogr. 2000;24(6):977–80.
Sauer-Heilborn A, et al. J Cancer Res Clin Oncol. 1999;125(11):637–40.

  - A potent radiosensitizer; increase RT toxicity, radiation recall
  - Radiation-induced lung injury

Umemura S, et al. J Cancer Res Clin Oncol. 2011;137(10):1469–75.
Blackstock AW, et al. Int J Radiat Oncol Biol Phys. 2001;51(5):1281–9.
van Putten JW, et al. Clin Cancer Res. 2003;9(7):2472–7.
Shewach DS, et al. Investig New Drugs. 1996;14(3):257–63.
Vokes EE, et al. J Clin Oncol. 2002;20(20):4191–8.
JeterMD, et al. Int J Radiat Oncol Biol Phys. 2002;53(2):394–400.

Gemcitabine

- Tx. : Generally supportive & discontinuation of the drug

- Mortality rate with severe gemcitabine lung toxicity → 20 %

Barlesi F. et al. Fundam Clin Pharmacol 2004;18:85

- Reintroduction of Gemcitabine : contraindicated

Etoposide

- Topoisomerase 2 inhibitor.
- 1-3% suffer pulmonary toxicity
- oral administration have higher incidence

- Vehicle may be causing hypersensitivity reaction
- RT pneumonitis risk ↑

Gurjal A, et al. Lung Cancer. 1999;26(2):109–12.
Hatakeyama S, et al. Nihon Kyobu Shikkan Gakkai Zasshi. 1997;35(2):210–4.
Uchida T, et al. Gan To Kagaku Ryoho. 1996;23(14):1967–70.

- Treatment: discontinuation of the drug

PEMETREXED

- A multisite folic acid inhibitor
  - Acute and Subacute pulmonary fibrosis, Acute respiratory distress syndrome, Diffuse alveolar hemorrhage

Hochstrasser A, et al. Chemotherapy 2012;58:84

Kim KH et al. Cancer Res Treat 2013;45:74

Loriot Y et al. Clin Lung Cancer 2009;10:364

Nagata K, et al. J Thorac Oncol 2010;5:1714

Kurimoto R, et al. Intern Med 2015;54:833

- Treatment
  - Prompt discontinuation of drug and initiation of glucocorticoid(limited benefit)

Nagata K, et al. J Thorac Oncol 2010;5:1714

Khakal B, et al. Clin Pract 2011;1:e106

Irinotecan and Topotecan

Pulmonary toxicity

(non specific onset of cough, shortness of breath, fever)

Irinotecan	Any grade : 0 – 20% Severe : 1 – 2 %
Topotecan	Rare association

- Tx. : Discontinuation of the drug & glucocorticoid

Yamada M, et al. Br J Cancer 2002;87:258

Fukuoka M, et al. J Clin Oncol 1992;10:16

Madarnas Y, et al. Anticancer Drugs 2000;11:709

Rothenberg ML, et al. J Clin Oncol 1996;14:1128

Pitot HC, et al. J Clin Oncol 1997;15:2910

Michielin O, et al. Lancet Oncol 2004;5:322

VINCA ALKALOIDS

- Rare cases of lung toxicity
  - Vinblastine --- Bronchoconstriction, interstitial pneumonitis, lung nodules, and noncardiogenic pulmonary edema

Hoelzer KL, et al. Drug Intell Clin Pharm 1986;20:287
Rao SX, et al. Arch Intern Med 1985;145:1905

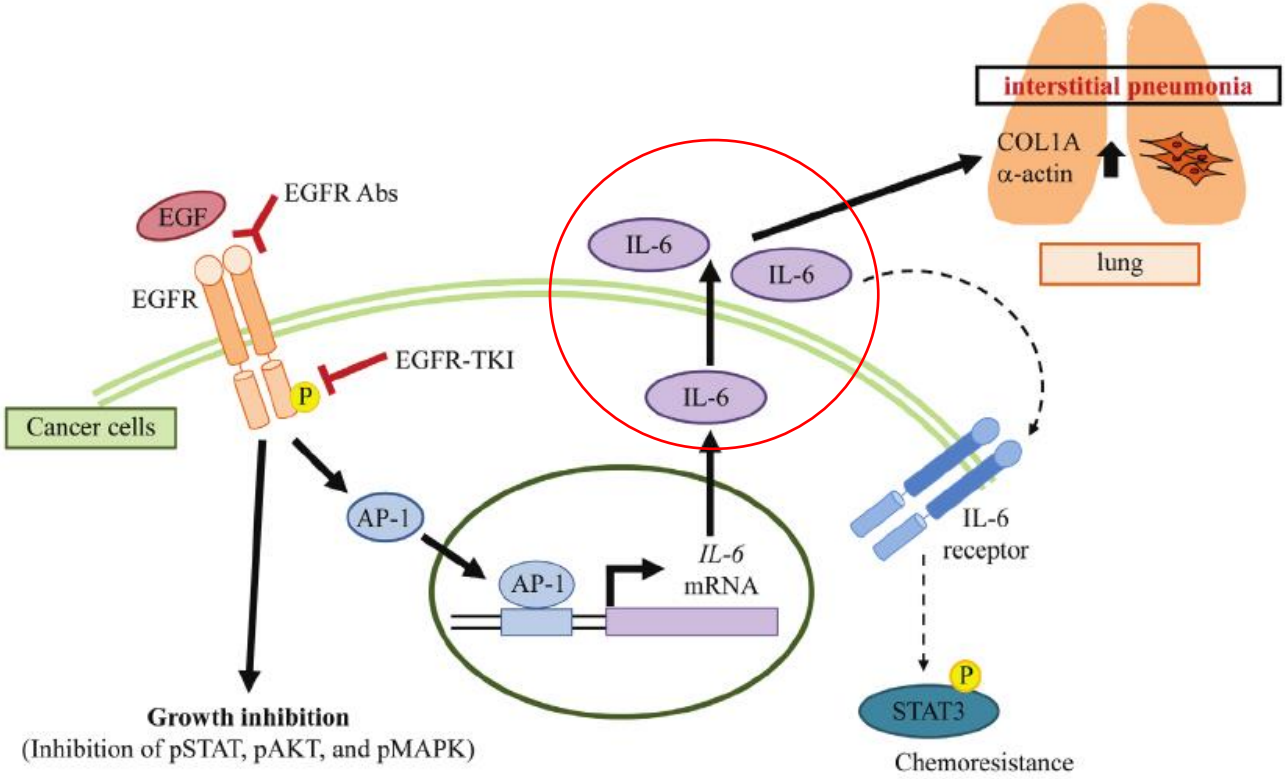
  - Vinorelbine --- interstitial pneumonitis as a single agent

Igishi T, et al. J Thorac Oncol 2009;4:376
Furuse K, et al. Lung Cancer 1994;11:385
Yanagitani N et al. Gan To Kagaku Ryoho 2008;35:1619

Target-therapy-Induced Pneumonitis

Pathogenesis

- **Decreased alveolar regeneration**
  - A process normally regulated by EGFR



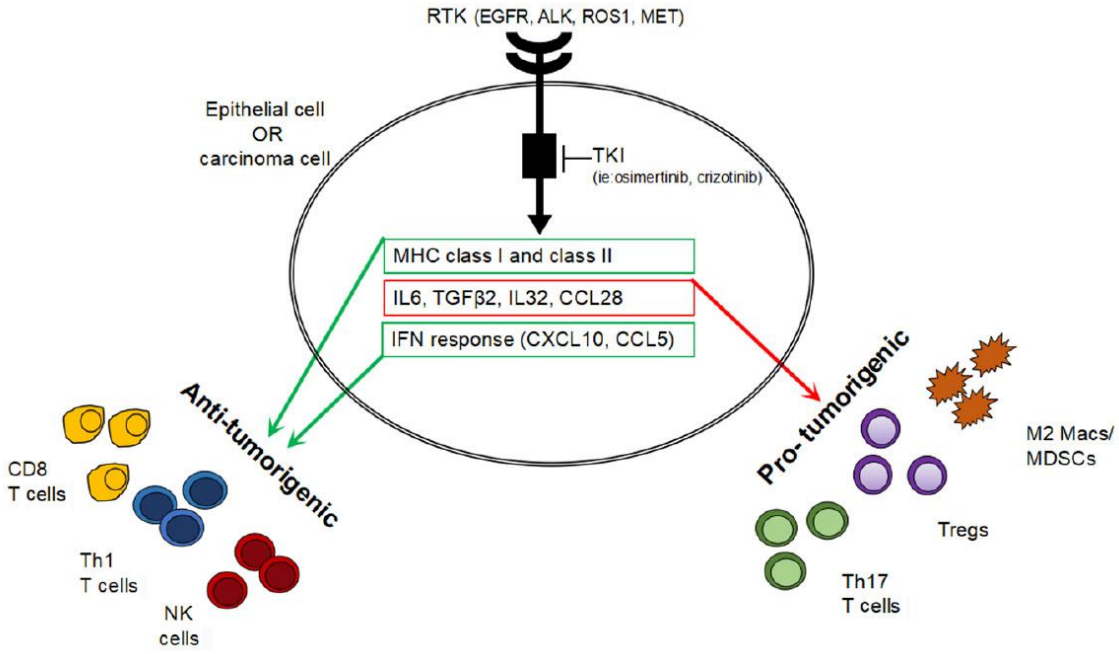


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Table 1 Reported incidence, mortality rate, and risk factors of gefitinib-induced interstitial lung disease from clinical trials conducted in Japan

Year	Study group	Period	*n*	No. cases ILD (%)	Mortality (%)	Onset	Risk factors
2004	WJTOG [10][a]	2002/8–2002/12	1,976	64 (3.2%)	25 (1.3%)	NA	Preexisting pulmonary fibrosis, male, smoker
2004	NCCH [9][b]	2002/7–2002/12	112	6 (5.4%)	4 (3.6%)	Acute	Preexisting pulmonary fibrosis
2005	JMTO [24][c]	2002/7–2003/2	399	33 (8.3%)	17 (4.3%)	NA	Preexisting pulmonary fibrosis, decrease of serum albumins, concomitant radiotherapy, absence of history of chemotherapy
2005	OLCSG [7][d]	2000/11–2003/10	330	15 (4.5%)	8 (2.4%)	NA	Preexisting pulmonary fibrosis, poor PS, prior thoracic irradiation
2006	WJTOG [6][a]	2002/8–2002/12	1,976	70 (3.5%)	31 (1.6%)	31 d (18–50)	Preexisting pulmonary fibrosis, male, smoker
2010	OLCSG [8][d]	2000/11–2003/10	330	8 (2.4%)	5 (1.5%)	13 d (4–23)	Preexisting pulmonary fibrosis, poor PS

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Table 2 Reported individual cases of erlotinib-associated interstitial lung disease

Case	Year	Sex	Age	Smoke	Underlying comorbidity	Previous treatment	Onset	Respiratory symptom	Treatment	Outcome	Pathology
1 [12]	2007	M	66	Ex-smoker	No PF	Chemo	5 d	Mild fever, dry cough	Steroid	Improved	NA
2 [12]	2007	F	46	Nonsmoker	No PF	No	6 d	Mild fever, dry cough, short of breath	Steroid	Improved[a]	NA
3 [5]	2007	M	60	Ex-smoker	PF	op	4 w	Dyspnea, hypoxemia	Steroid	Death	DAD
4 [4]	2007	M	55	Smoker	COPD	chemo	2 m	Nonproductive cough, severe dyspnea after 2 ws	Steroid (2 ws later)	Death	DAD (after 3 ws)
5 [51]	2009	M	60	Smoker	No PF	chemo	9 d	Exertional dyspnea	Steroid	Improved	NA
							24 d	Dyspnea, dry cough	Steroid	Improved	Interstitial pneumonia
6 [13]	2010	M	63	Nonsmoker	No PF	chemo	7 w	Dyspnea, progressive respiratory failure	Steroid	Improved	NA
7 [11]	2010	M	53	Smoker	No PF	chemo	3 w	Cough, fever	Steroid	Improved	NA

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DAD diffuse alveolar damage, *BO* broncholitis obliterans, *COP* cryptogenic organizing pneumonitis, *HP* hypersensitivity pneumonia, *IP* interstitial pneumonia

Plus signs indicate the relative frequency of the findings from occasional (++) to rare (+)

Research Article

Pneumonitis in advanced non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitor: Meta-analysis of 153 cohorts with 15,713 patients

Meta-analysis of incidence and risk factors of EGFR-TKI pneumonitis in NSCLC

Chong Hyun Suh[a], Hye Sun Park[b], Kyung Won Kim[a], Junhee Pyo[c], Hiroto Hatabu[b,1], Mizuki Nishino[b,*,1]

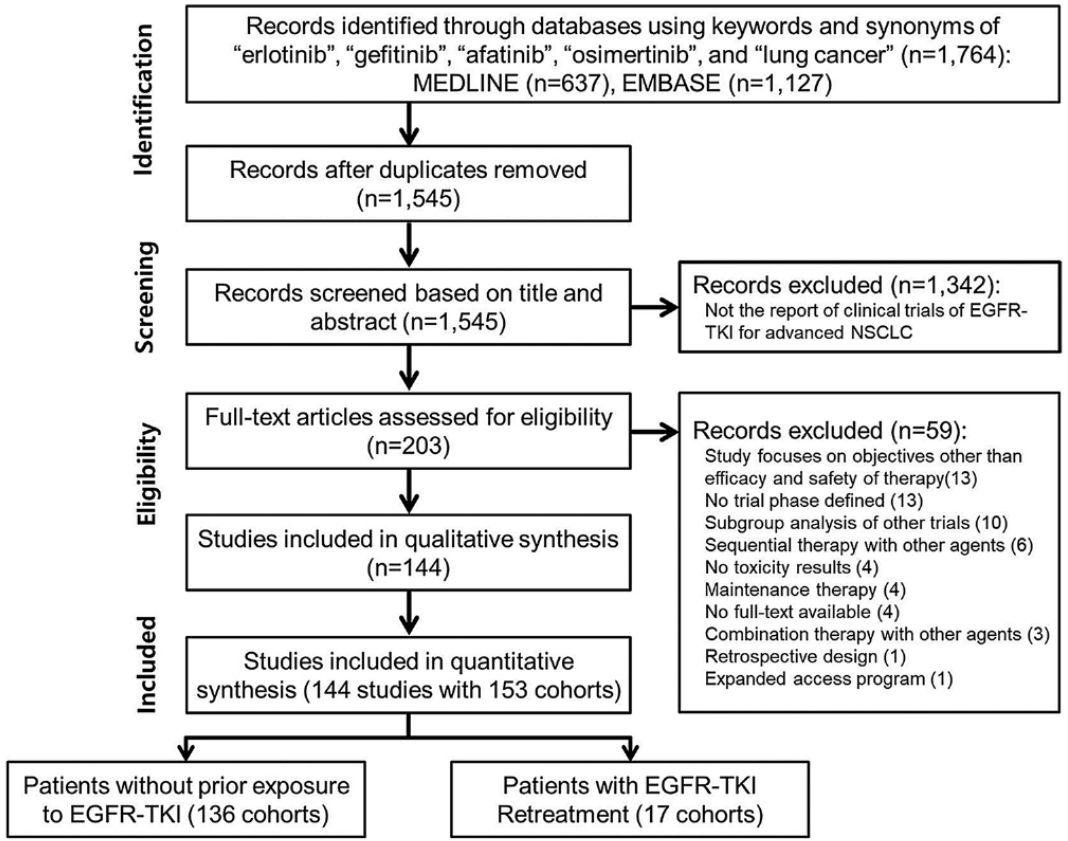

Fig. 1. Flow diagram of study inclusion.

Table 1
Characteristics of eligible trial cohorts.

Study Characteristics		Cohorts without prior exposure to EGFR-TKI (n = 136)
Phase	II	107 (79%)[a]
	III	29 (21%)
EGFR-TKI agents	Erlotinib	75 (55%)
	Gefitinib	53 (39%)
	Afatinib	8 (6%)
Treatment line	Prior chemotherapy	69 (51%)
	First-line	49 (36%)
	Mixed[b]	18 (13%)
EGFR mutation status	No mutants	9 (7%)
	All mutants	33 (24%)
	Mixed/unknown[d]	94 (69%)
Countries	Non-Japan study	95 (70%)
	Japan study	36 (26%)
	Japan plus other countries	5 (4%)

Study Characteristics		Cohorts with prior EGFR-TKI (EGFR-TKI retreatment) (n = 17)
Phase	I	2 (12%)
	II	13 (76%)[c]
	III	2 (12%)[c]
EGFR-TKI agents	Erlotinib	6 (35%)
	Gefitinib	4 (24%)
	Afatinib	5 (29%)
	Osimertinib	2 (12%)
EGFR mutation status	No mutants	0 (0%)
	All mutants	5 (29%)
	Mixed/unknown^	12 (71%)
Countries	Non-Japan study	11 (65%)
	Japan study	4 (24%)
	Multiple countries including Japan	2 (12%)

[a] Two phase I/II studies were included as phase II.
[b] Studies included both the patients with prior chemotherapy and those with first-line therapy.
[c] One study with phase I/II was included as phase II studies and one study with phase II/III was included as phase III studies.
[d] Studies included patients with and without EGFR mutations and/or patients with unknown EGFR mutation status.

Table 2
Results of multiple subgroup analysis for the incidence of EGFR-TKI related pneumonitis.

Subgroup	All-grade pneumonitis		High-grade pneumonitis		Grade 5 pneumonitis	
	No. of studies	Incidence (%) (95% CI)	No. of studies	Incidence (%) (95% CI)	No. of studies	Incidence (%) (95% CI)
Overall						
EGFR-TK						
Treatmer						
Country						
EGFR mu						
Phase						

EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.
CI: Confidence interval.
[a] $I^2 > 50\%$ indicating substantial heterogeneity.
[b] Not all studies provided the number of patients with pneumonitis in all three grade categories (all grade, high grade, and grade 5). Therefore, for each grade group of pneumonitis, the studies reporting the number of pneumonitis in the groups were including the analyses, generating different numbers of studies for three groups.

Table 4
Results of multivariate meta-regression for the incidence of EGFR-TKI related pneumonitis.

Variable		All-grade pneumonitis		High-grade pneumonitis		Grade 5 pneumonitis	
		Odds Radio (95% CI)	*P* value	Odds Radio (95% CI)	*P* value	Odds Radio (95% CI)	*P* value
EGFR-TKI	Erlotinib	REF		REF		REF	
	Afatinib	0.76 (0.26-2.26)	0.62	1.01 (0.25-4.05)	0.98	0.68 (0.07-5.95)	0.73
	Gefitinib	1.08 (0.68-1.71)	0.76	1.18 (0.65-2.16)	0.58	1.44 (0.69-3.02)	0.33
Treatment line	Prior chemotherapy	REF		REF		REF	
	First-line	1.16 (0.70-1.90)	0.56	1.84 (0.99-3.42)	0.05	1.63 (0.78-3.41)	0.19
	Mixed	1.59 (0.74-3.38)	0.23	1.69 (0.65-4.38)	0.28	1.15 (0.30-4.34)	0.84
Country	Non-Japan study	REF		REF		REF	
	Japan study	5.04 (3.14-8.11)	< 0.001	4.45 (2.50-7.93)	< 0.001	4.55 (2.20-9.44)	< 0.001
	Multiple countries including Japan	2.76 (1.21-6.31)	0.01	4.94 (0.70-21.17)	0.12	0.66 (0.17-2.78)	0.60

EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.
REF: reference group.

ORIGINAL ARTICLE

Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced *EGFR*-Mutated Non–Small Cell Lung Cancer

Pei Ni Ding, MBBChir,[a,b] Sarah J. Lord, MSc,[a,c] Val Gebski, MStat,[a] Matthew Links, PhD,[d] Victoria Bray, PhD,[b] Richard J. Gralla, MD,[e] James Chih-Hsin Yang, PhD,[f] Chee Khoon Lee, PhD[a,d,*]

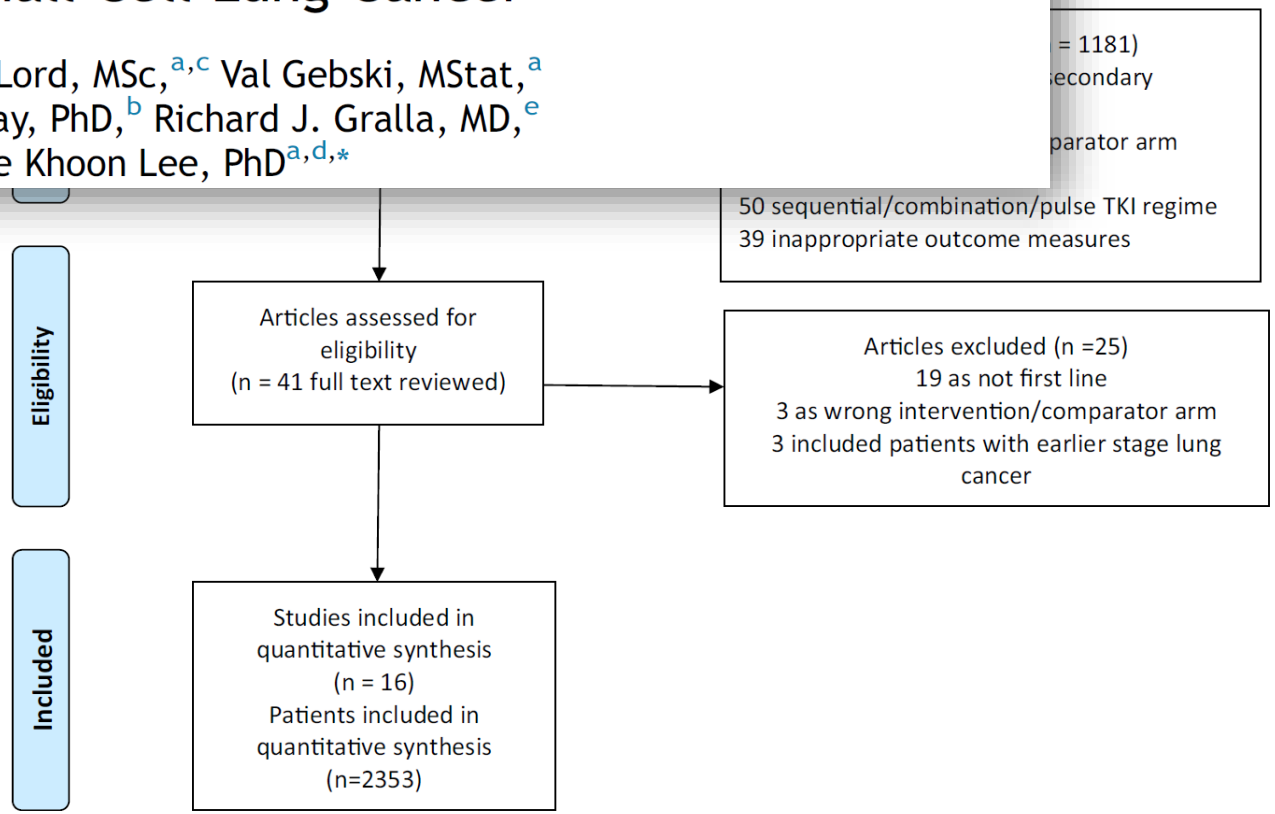

Figure 1. Flow diagram showing inclusion and exclusion of studies. TKI, tyrosine kinase inhibitor.

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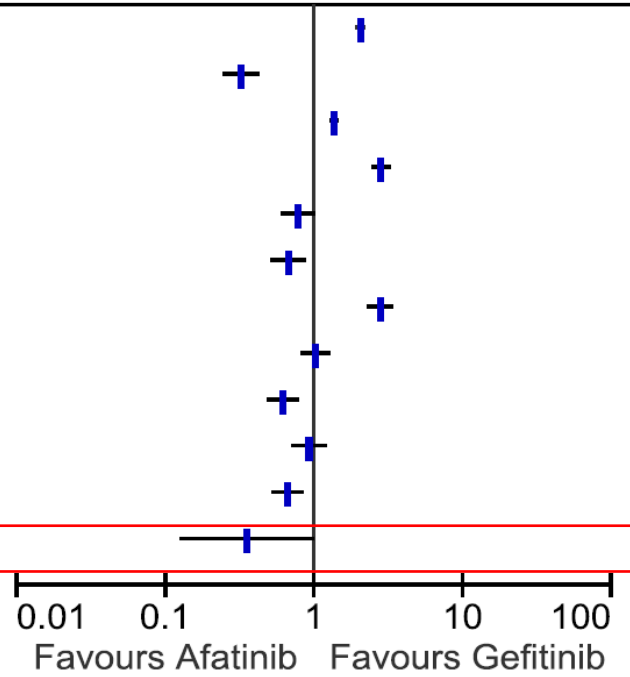
						edian)	Asian (%)	Male (%)	Present or Former Smokers (%)	ECOG PS 0 or 1 (%)
Afatinib trials										
LUX-Lung 3	Sequist (2013)[12]	345	229	Afatinib vs. CisPem	11	61	72	36	33	100
LUX-Lung 6	Wu (2014)[11]	364	239	Afatinib vs. CisG	14.2	58	100	36	25	100
Gefitinib trials										
INVITE	Crinò (2008)[14]	196	94	Gefitinib vs. V	2.7[a]	74	18	77	83	76
IPASS	Mok (2009)[15]	1217	607	Gefitinib vs. CP	5.6	57	100	21	6	90
INSTEP	Goss (2009)[16]	201	100	Gefitinib vs. placebo	1.8	75	4	61	90	0
NEJ002	Maemondo (2010)[17]	230	114	Gefitinib vs. CP	11	64[b]	100	37	34	99
64IFCT-0301	Morere (2010)[18]	125	43	Gefitinib vs. G vs D	3	70	NK	88	95	0
First-Signal	Han (2012)[13]	313	159	Gefitinib vs. CisG	5.8	57	100	12	NK	91
WJTOG 3405	Mitsudomi (2010)[19]	175	87	Gefitinib vs. CisD	5.9	64	100	31	29	100
Erlotinib trials										
	Chen (2012)[20]	113	57	Erlotinib vs. V	3.8	77	100	83	79	81
EURTAC	Rosell (2012)[21]	173	84	Erlotinib vs. platinum-G or platinum-D	8.2	65	0	33	34	86
	Lilenbaum (2008)[22]	103	52	Erlotinib vs. CP	1.7	NK	NK	44	89	0
OPTIMAL	Zhou (2011)[23]	165	82	Erlotinib vs. CG	13.9	57	100	41	28	91
TOPICAL	Lee (2010)[24]	670	334	Erlotinib vs. placebo	2.8[a]	77	2	61	94	15
	Heigener (2014)[25]	284	144	Erlotinib vs. CV	2.4[a]	76	0	68	82	100
ENSURE	Wu (2015)[26]	214	110	Erlotinib vs. CisG	11[a]	58	100	38	28	94

ORIGINAL ARTICLE

Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced *EGFR*-Mutated Non–Small Cell Lung Cancer

A Afatinib vs Gefitinib

Toxicity outcome	Afatinib Events	Afatinib Total	Gefitinib Events	Gefitinib Total	Risk Ratio[95%CI]
Diarrhoea	429	468	535	1204	2.06 [1.93, 2.21]
Elevated liver enzymes	48	239	124	201	0.33 [0.25, 0.43]
Rash	397	468	746	1204	1.37 [1.29, 1.45]
Stomatitis	289	468	186	853	2.83 [2.45, 3.28]
Fatigue	64	468	211	1204	0.78 [0.60, 1.01]
Nausea	59	468	204	1090	0.67 [0.51, 0.88]
Paronychia	208	468	110	694	2.80 [2.30, 3.42]
Dry skin	67	229	298	1047	1.03 [0.82, 1.28]
Pruritus	69	468	206	866	0.62 [0.48, 0.79]
Vomiting	62	468	143	1003	0.93 [0.70, 1.23]
Appetite loss	71	468	253	1117	0.67 [0.53, 0.85]
Pneumonitis	4	468	29	1204	0.35 [0.13, 1.00]

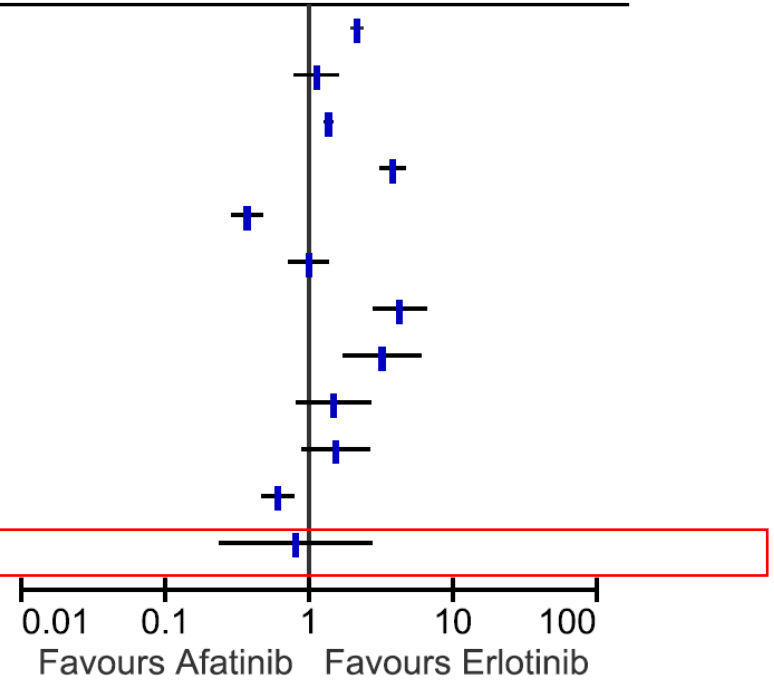


ORIGINAL ARTICLE

Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced *EGFR*-Mutated Non-Small Cell Lung Cancer

B Afatinib vs Erlotinib

Toxicity outcome	Afatinib Events	Afatinib Total	Erlotinib Events	Erlotinib Total	Risk Ratio[95%CI]
Diarrhoea	429	468	281	662	2.16 [1.97, 2.37]
Elevated liver enzymes	48	239	49	276	1.13 [0.79, 1.62]
Rash	397	468	446	719	1.37 [1.28, 1.46]
Stomatitis	289	468	85	525	3.81 [3.10, 4.69]
Fatigue	64	468	244	662	0.37 [0.29, 0.48]
Nausea	59	468	73	578	1.00 [0.72, 1.38]
Paronychia	208	468	20	192	4.27 [2.78, 6.54]
Dry skin	67	229	10	110	3.22 [1.72, 6.01]
Pruritus	69	468	11	110	1.47 [0.81, 2.69]
Vomiting	62	468	14	162	1.53 [0.88, 2.66]
Appetite loss	71	468	146	580	0.60 [0.47, 0.78]
Pneumonitis	4	468	7	662	0.81 [0.24, 2.75]

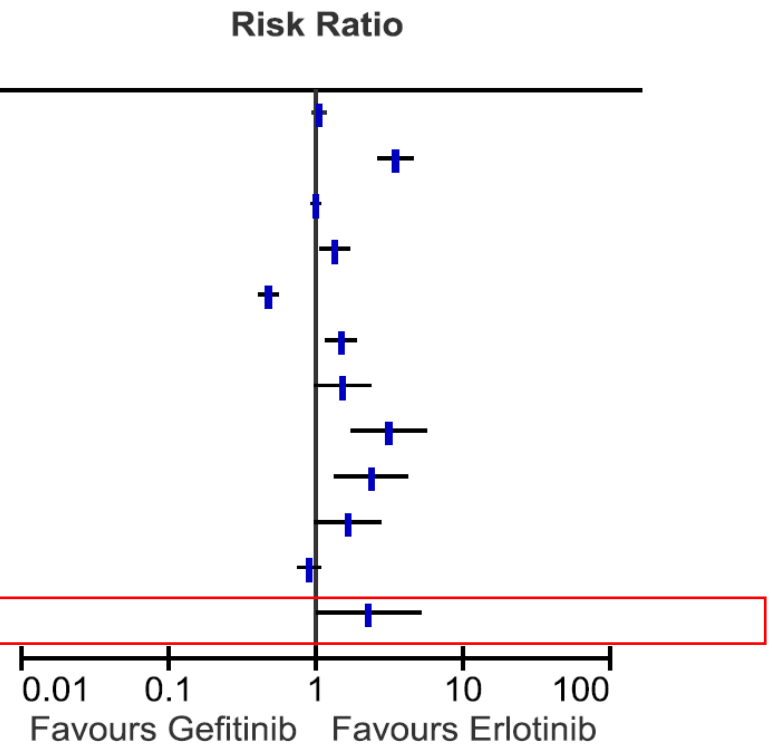


ORIGINAL ARTICLE

Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced *EGFR*-Mutated Non–Small Cell Lung Cancer

C Gefitinib vs Erlotinib

Toxicity outcome	Gefitinib Events	Gefitinib Total	Erlotinib Events	Erlotinib Total	Risk Ratio [95%CI]
Diarrhoea	535	1204	281	662	1.05 [0.94, 1.17]
Elevated liver enzymes	124	201	49	276	3.47 [2.64, 4.58]
Rash	746	1204	446	719	1.00 [0.93, 1.07]
Stomatitis	186	853	85	525	1.35 [1.07, 1.70]
Fatigue	211	1204	244	662	0.48 [0.41, 0.56]
Nausea	204	1090	73	578	1.48 [1.16, 1.90]
Paronychia	110	694	20	192	1.52 [0.97, 2.38]
Dry skin	298	1047	10	110	3.13 [1.72, 5.70]
Pruritus	206	866	11	110	2.38 [1.34, 4.22]
Vomiting	143	1003	14	162	1.65 [0.98, 2.78]
Appetite loss	253	1117	146	580	0.90 [0.75, 1.07]
Pneumonitis	29	1204	7	662	2.28 [1.00, 5.17]



EGFR-TKI

- Acute onset of dyspnea, cough, and pyrexia
- Develops within 3 weeks to 7 weeks

- **Gefitinib;** overall 1%
  - In the ISEL trial; 1%, similar in the two treatment groups
  - In IPASS trial; 2.6%(gefitinib) vs 1.4%(paclitaxel/carboplatin)

- **Erlotinib;** overall 1.1%
  - In EURTAC trial; 1%(erlotinib), 1st line Tx.
  - In BR.21 trial; 3%(erlotinib), 2nd, 3rd line Tx.
  - In the SATURN trial; 2%(erlotinib) vs. <1%(placebo)
- **Osimertinib;** ~ 3%

- **Risk factors :** Asian ethnicity, male gender, smoking, a presence of ILD

- Nearly ⅓ of patients who develop pulmonary complications of **gefitinib** died as a consequence

The incidence of ALK inhibitor-related pneumonitis in advanced non-small-cell lung cancer patients: A systematic review and meta-analysis☆

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Table 1
Characteristics of the eligible trial cohorts.

Author (publication year)	Drug	Treatment line	Country	Phase	Total patients	All-grade pneumonitis	High-grade pneumonitis	Grade 5 pneumonitis
Camidge DR, et al. (2012)	Crizotinib	Mixed treatment	Multiple countries including Japan	I	149	at least 4*	3	0
Cho BC, et al. (2017)	Ceritinib	Mixed treatment	Non-Japan study	I	135	0	0	0
Crino L, et al. (2016)	Ceritinib	ALK inhibitor retreatment	Multiple countries including Japan	II	140	2	1	0
Gadgeel SM, et al. (2014)	Alectinib	ALK inhibitor retreatment	Non-Japan study	I /II	47	0	0	0
Hida T, et al. (2016)	Alectinib	Mixed treatment	Japan	I	35	1	0	0
Hida T, et al. (2017)	Alectinib	Mixed treatment	Japan	III	103	8	5	0
Hida T, et al. (2017)	Crizotinib	Mixed treatment	Japan	III	104	8	3	0
Iwama E, et al. (2017)	Alectinib	Mixed treatment	Japan	II	18	not mentioned	not mentioned	0
Kim DW, et al. (2016)	Ceritinib	Mixed treatment	Non-Japan study	I	246	9	8	1
Kim DW, et al. (2017)	Brigatinib	ALK inhibitor retreatment	Multiple countries including Japan	II	219	9	4	0
Nishio M, et al. (2015)	Ceritinib	Mixed treatment	Japan	I	20	not mentioned	not mentioned	0
Ou SH, et al. (2016)	Alectinib	ALK inhibitor retreatment	Non-Japan study	II	138	not mentioned	not mentioned	0
Peters S, et al. (2017)	Crizotinib	First-line	Non-Japan study	III	151	4	3	not mentioned
Peters S, et al. (2017)	Alectinib	First-line	Non-Japan study	III	152	2	0	0
Shaw AT, et al. (2013)	Crizotinib	Prior chemotherapy	Multiple countries including Japan	III	172	2	2	2
Shaw AT, et al. (2016)	Alectinib	ALK inhibitor retreatment	Non-Japan study	II	87	0	0	0
Shaw AT, et al. (2017)	Ceritinib	ALK inhibitor retreatment	Multiple countries including Japan	III	115	1	1	0
Solomon BJ, et al. (2014)	Crizotinib	First-line	Multiple countries including Japan	III	171	3	3	1
Soria JC, et al. (2017)	Ceritinib	First-line	Multiple countries including Japan	III	189	4	1	1
Tamura T, et al. (2017)	Alectinib	Mixed treatment	Japan	I /II	46	1	not mentioned	0

ALK: anaplastic lymphoma kinase.
* For the case with "at least 4" pneumonitis, we used "4" as the number of pneumonitis.

Fig. 1. Flow diagram of study inclusion.

Table 2
Results of multiple subgroup analyses for the incidence of ALK inhibitor-related pneumonitis.

Group/Subgroup		All-grade pneumonitis			High-grade pneumonitis			Grade 5 pneumonitis		
		No. of studies	No. of patients	Incidence (%) (95% CI)	No. of studies	No. of patients	Incidence (%) (95% CI)	No. of studies	No. of patients	Incidence (%) (95% CI)
Overall group		17[#]	2261	2.14 (1.37-3.34)[*]	16[#]	2215	1.33 (0.80-2.21)	19[#]	2286	0.22 (0.09-0.52)
ALK inhibitors	Alectinib	6	470	1.62 (0.48-5.29)[*]	5	424	0.08 (0.00-28.58)[*]	8	626	0.00 (NA)
	Ceritinib	5	825	1.62 (0.72-3.59)	5	825	0.88 (0.27-2.78)	6	845	0.24 (0.06-0.94)
	Crizotinib	5	747	2.68 (1.45-4.90)	5	747	1.87 (1.11-3.14)	4	596	0.50 (0.16-1.55)
	Brigatinib	1	219	4.11 (NA)	1	219	1.83 (NA)	1	219	0.00 (NA)
Treatment line	First-line	4	663	1.96 (1.14-3.35)	4	663	1.05 (0.46-2.42)	3	512	0.39 (0.10-1.55)
	ALK-first line with prior chemotherapy	1	172	1.16 (NA)	1	172	1.16 (NA)	1	172	1.16 (NA)
	ALK ≥ 2	5	608	1.24 (0.35-4.27)	5	608	0.99 (0.44-2.18)	6	746	0.00 (NA)
	Mixed	7	818	3.29 (1.70-6.30)*	6	772	2.32 (1.25-4.28)	9	856	0.12 (0.02-0.82)

1. The overall incidence of ALK inhibitor pneumonitis was 2.14% in patients with advanced NSCLS.

2. The patients from Japanese cohorts had a higher incidence of ALK-inhibitor pneumonitis

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Table 4
Results of multivariate meta-regression analyses for the incidence of ALK inhibitor-related pneumonitis.

Subgroup		All-grade pneumonitis		High-grade pneumonitis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Drug	Alectinib	REF		REF	
	Ceritinib	1.959 (0.773, 4.962)	0.156	2.282 (0.584, 8.903)	0.235
	Crizotinib	1.958 (0.895, 4.283)	0.092	2.730 (0.740, 10.069)	0.131
	Brigatinib	4.827 (1.553, 14.999)	0.007	3.976 (0.646, 24.466)	0.137
Country	Non-Japan study	REF		REF	
	Japan study	4.329 (1.918, 9.770)	< 0.001	3.130 (0.888, 11.034)	0.076
	Multiple countries including Japan	0.770 (0.368, 1.611)	0.489	0.712 (0.264, 1.917)	0.502

OR: odds ratio, ALK: anaplastic lymphoma kinase, REF: reference group.

Lung Cancer 132 (2019) 79–86

Anaplastic Lymphoma Kinase (ALK)

Crizotinib, ceritinib, alectinib, and brigatinib

- Options for advanced or metastatic NSCLC with EML4-ALK fusion oncogene
- Crizotinib is approved for ROS-1-mutated NSCLC

Crizotinib

- 3% of patients : pneumonitis
- 1.5% of patients : severe, life-threatening, or fatal pneumonitis

Ceritinib: 4% of patients, grade 3 or 4 pneumonitis

Brigatinib: 3.7% of patients, grade 3 or 4 pneumonitis

Alectinib: 1% of patients, grade 3 or 4 pneumonitis

Immunotherapy-Induced Pneumonitis

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

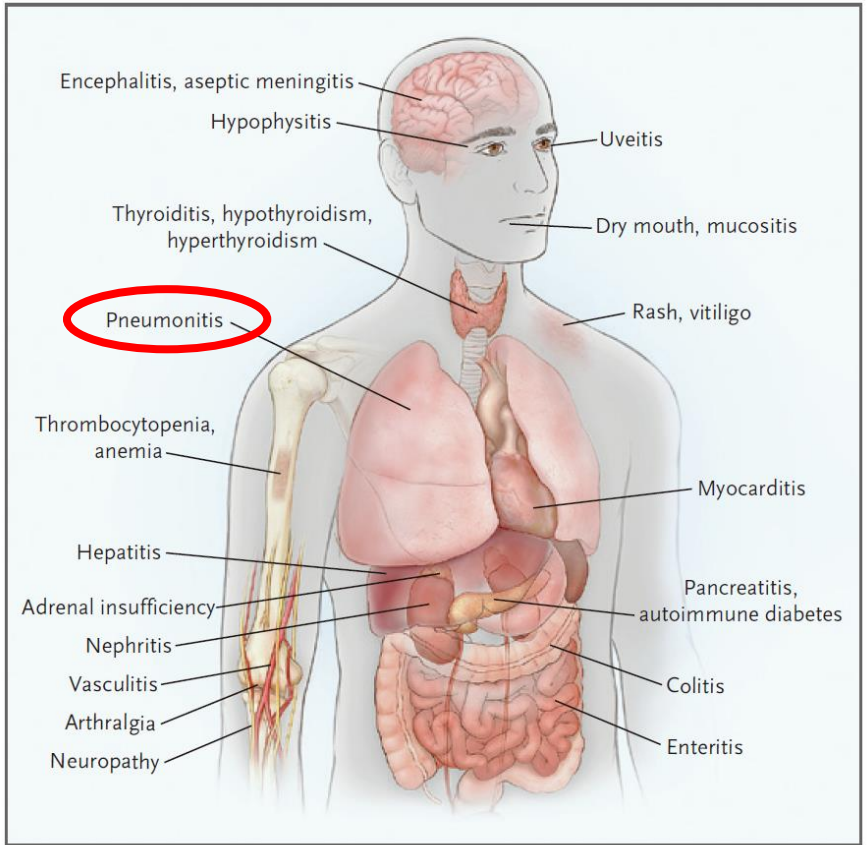


Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

N Engl J Med 2018;378:158-68.

Pathophysiology

- The precise pathophysiology is unknown
- Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved

  - T-cell activity ↑
  - Preexisting autoantibodies ↑
  - Inflammatory cytokines ↑
  - Complement-mediated inflammation d/t direct binding of an antibody against CTLA-4 expressed on normal tissue (pituitary gland)

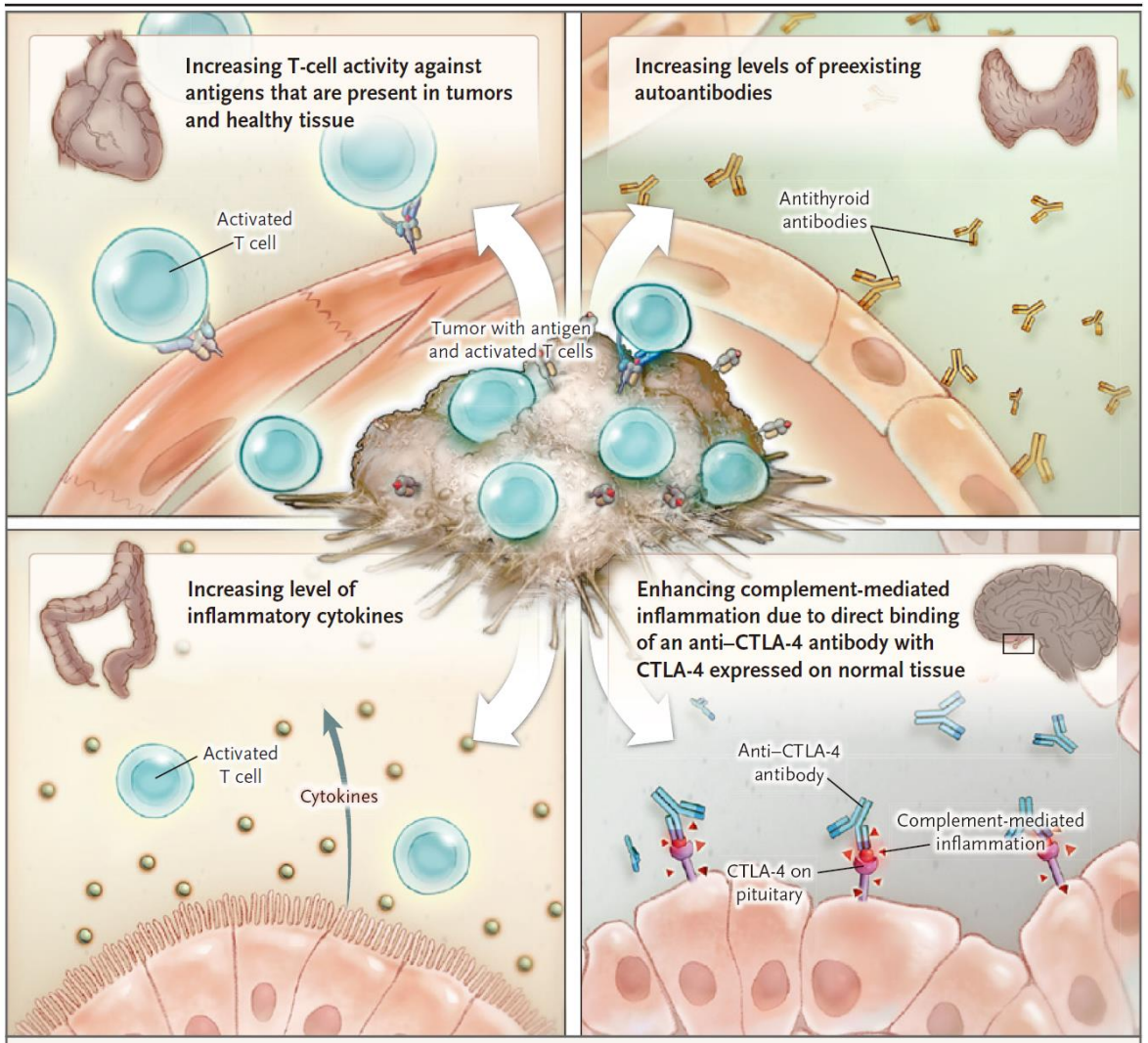


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

N Engl J Med 2018;378:158-68.

Pathophysiology

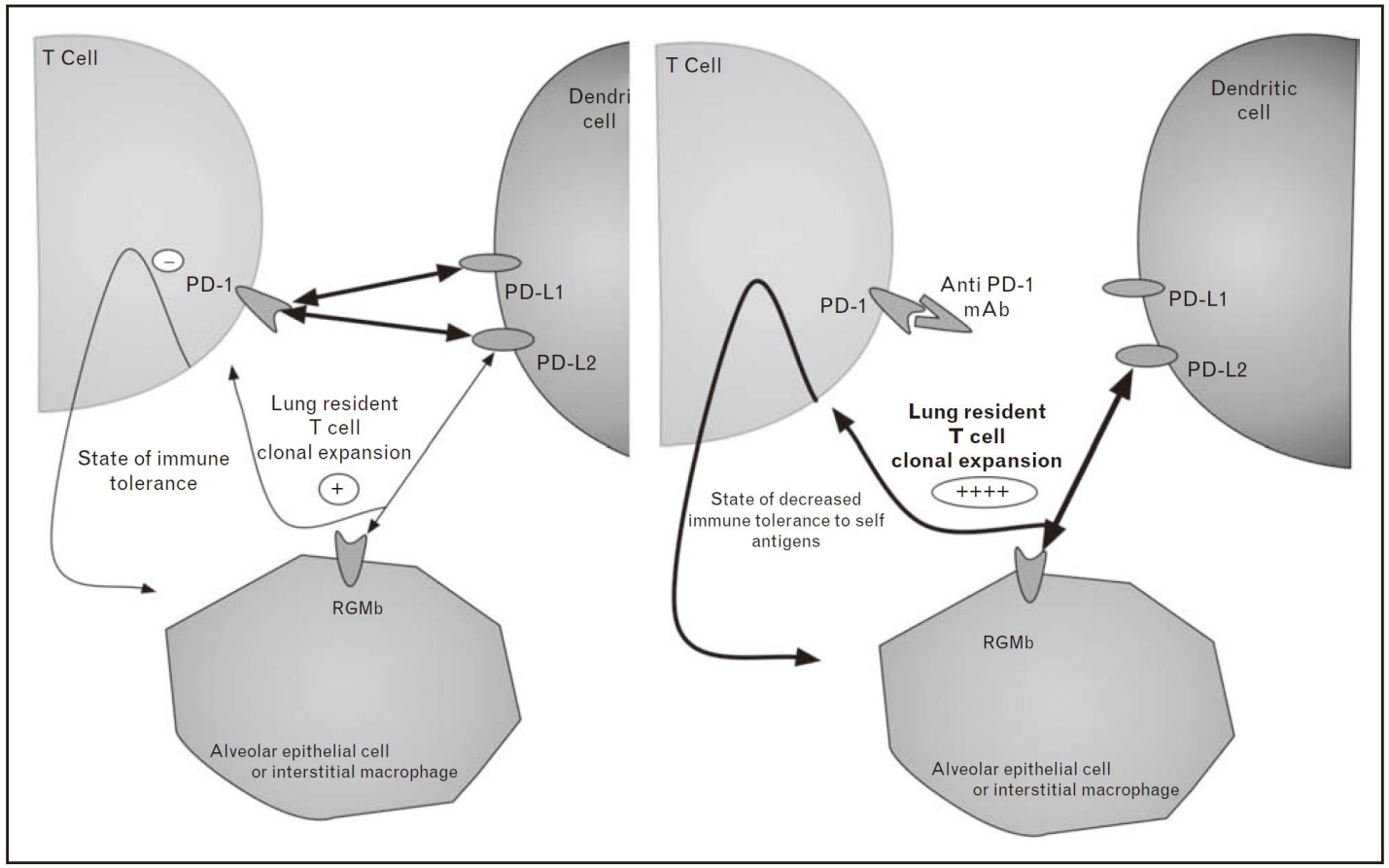


FIGURE 1. Interaction between programmed cell death protein 1 (PD1) on T cells and its ligands [programmed cell death protein 1 ligand 1 (PD-L1) and PD-L2] on dendritic cells/tumor cells. Perturbation of the PD-1 axis through the use of anti-PD-1 agents results in a higher rate of PD-L2 availability, which can have increased interaction with repulsive guidance molecule b (RGMb), thus leading to vigorous clonal expansion of lung resident T cells and subsequent pneumonitis in the absence of PD-1-mediated tolerance to self-antigens.

Curr Opin Oncol 2016, 28:269–277

Incidence of pneumonitis according to cancer types

Table 3. Incidence of Pneumonitis in Patients Treated With Programmed Death-1 Inhibitor Therapy in Melanoma, Lung Cancer, and Renal Cell Carcinoma

Regimen	Tumor Type	Total No. of Patients	All-Grade Pneumonitis		Grade ≥ 3 Pneumonitis	
			No.	% (95% CI)	No.	% (95% CI)
Monotherapy	All three tumors	3,921	105	2.7 (1.9 to 3.6)	31	0.8 (0.4 to 1.2)
	Melanoma	2,155	35	1.6 (1.3 to 2.2)	5	0.2 (0.1 to 0.4)
	Lung	1,159	45	4.1 (2.4 to 6.3)*	20	1.8 (1.0 to 2.6)*
	Renal cell carcinoma	607	25	4.1 (2.9 to 4.8)*	6	0.8 (0.0 to 1.5)
Combination therapy	Melanoma	575	38	6.6 (4.7 to 8.7)*	9	1.7 (0.8 to 2.9)*

*Significantly higher incidence of pneumonitis compared with the reference group (melanoma monotherapy group). Modified from Nishino et al.[21]

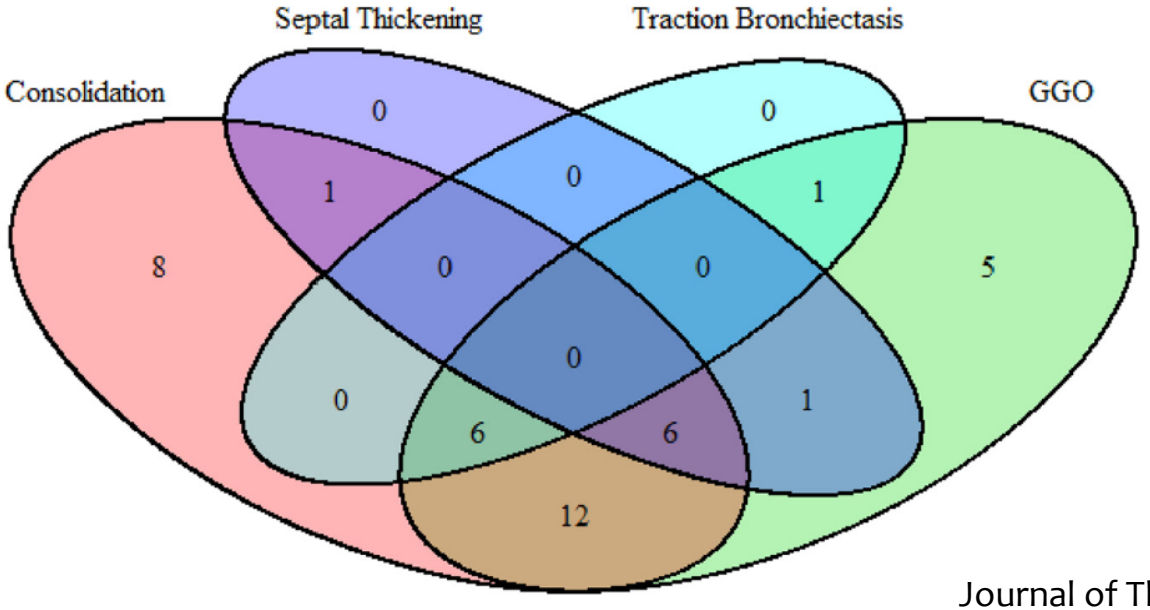
Onset of pneumonitis in IO Tx

- 170 patients who were treated in 10 trials of nivolumab
  - Either alone or in combination with other ICIs

- 20 patients developed pneumonitis
  - 10 with melanoma, 6 with lymphoma, 4 with lung cancer

- Time from initiation of therapy to pneumonitis
  - Widely from 0.5 to 11.5 months(median 2.6 months)
  - Shorter in patients with lung cancer(1.1 vs 3.1 months, respectively)

Clin Cancer Res 22:6051-6060, 2016



Journal of Thoracic Oncology Vol. 13 No. 12: 1930-1939

	Number (%)
Laterality	9 (2)
Left	12 (2)
Right	19 (45)
Bilateral	
Components of Infiltrate	
Ground-glass	31 (73)
Consolidation	33 (78)
Septal Thickening	8 (19)
Traction Bronchiectasis	7 (16)
Area of pneumonitis	
Peri-tumoral	6 (14)
Away from tumor	36 (86)

Figure 5. Venn diagram and table of radiographic data showing the laterality, infiltrate type, and relationship of infiltrates to primary tumor in patients with checkpoint inhibitor pneumonitis. Abbreviation: GGO, ground glass opacity.

CURRENT OPINION

Immune-media… checkpoint inh… …s of

Samer Tabo…

PD-1 inhibitors

Table 1. Immune-mediated p…

PD-1 inhibitor/ phase	Pneumonitis any grade % (*n*)	Pneumonitis grade 3/4% (*n*)	Outcome
Nivolumab/phase I [22]	3 (9)	1 (3)	Death of patients with grade 3/4 toxicities
	1.9 (2)	0	Resolution of irAEs after treatment
Nivolumab/phase I [26]	4 (16)	1 (6)	Resolution of irAEs after treatment
Nivolumab/phase III [28]	2.2 (6)	0.3 (1)	Resolution of irAEs after treatment
Nivolumab/phase III [36]	1.5 (3)	0	Resolution of irAEs after treatment
Nivolumab/phase III [34]	1.3 (4)	0.3 (1)	
Nivolumab	6.4 (20)	1 (3)	Resolution of irAEs after treatment
Nivolumab/ipilimumab/ phase III [20]	10.6 (11)	2.1 (2)	One treatment-related death
Nivolumab/ipilimumab/ phase III [21]	3.4 (10)	1.7 (5)	Resolution of irAEs after treatment
Nivolumab phase III [31]	4.5 (6)	0.7 (1)	Resolution of irAEs after treatment
Nivolumab/phase III [32]	7 (4)		
Pembrolizumab/phase I [30]	3.6 (2)	0	One treatment-related death
	0		
	4.5 (13)	1.8 (9)	One treatment-related death
Pembrolizumab/phase I [27]	2.5 (5)		
	1.6 (3)	0	Resolution of irAEs after treatment
	1.6 (3)	1.1 (2)	
Pembrolizumab/phase II [29]	4.6 (16)	2 (7)	Three treatment-related deaths
	4.3 (15)	2 (7)	
Pembrolizumab/phase II/III [33]	1 (6)	0.1 (1)	Resolution of irAEs after treatment

irAEs, immune-related adverse events; N…

	Pneumonitis any grade % (*n*)	Pneumonitis grade 3/4% (*n*)	Outcome
	3 (9)	1 (3)	Death of patients with grade 3/4 toxicities
	1.9 (2)	0	Resolution of irAEs after treatment
	4 (16)	1 (6)	Resolution of irAEs after treatment
	2.2 (6)	0.3 (1)	Resolution of irAEs after treatment
	1.5 (3)	0	Resolution of irAEs after treatment
3	1.3 (4)	0.3 (1)	
13	6.4 (20)	1 (3)	Resolution of irAEs after treatment
	10.6 (11)	2.1 (2)	One treatment-related death
	3.4 (10)	1.7 (5)	Resolution of irAEs after treatment
	4.5 (6)	0.7 (1)	Resolution of irAEs after treatment
	7 (4)		
	3.6 (2)	0	One treatment-related death
	0		
	0		
	4.5 (13)	1.8 (9)	One treatment-related death
	2.5 (5)		
	1.6 (3)	0	Resolution of irAEs after treatment
	1.6 (3)	1.1 (2)	
	4.6 (16)	2 (7)	Three treatment-related deaths
	4.3 (15)	2 (7)	
	1 (6)	0.1 (1)	Resolution of irAEs after treatment

Curr Opin Oncol 2016, 28:269–277

CTLA-4 inhibitors

Table 2. Immune-mediated p…ibitors

Anti-CTLA4/phase	S…	Pneumonitis any grade % (*n*)	Pneumonitis grade 3/4% (*n*)	Outcome	…atients receiving ICI (*n*)	Pneumonitis any grade % (*n*)	Pneumonitis grade 3/4% (*n*)	Outcome
Ipilimumab/phase III [4]	A…	0	0	–	540	0	0	–
Ipilimumab/phase III [5]	A…	0	0	–	247	0	0	–
Ipilimumab/phase III [17]	A…	1.3 (5)	0.3 (1)	Resolution after treatment	399	1.3 (5)	0.3 (1)	Resolution after treatment
Ipilimumab/phase I [19]	R…	3 (1)	3 (1)	Resolution after treatment	29	3 (1)	3 (1)	Resolution after treatment
Nivolumab + Ipilimumab	A…	6.4 (20)	1 (3)	Resolution of irAEs after treatment	…ation n = 313	6.4 (20)	1 (3)	Resolution of irAEs after treatment
Ipilimumab/phase III [20]		1.6 (5)	0.3 (1)		…mab: *n* = 311	1.6 (5)	0.3 (1)	
Nivolumab + Ipilimumab	A…	10.6 (11)	2.1 (2)	One treatment-related death	…ation: *n* = 94	10.6 (11)	2.1 (2)	One treatment-related death
Ipilimumab/phase III [21]		4.3 (2)	2.1 (1)		…mab: *n* = 46	4.3 (2)	2.1 (1)	
Ipilimumab/phase III [35]	A…	0.4 (1)	0.4 (1)	Resolution of irAEs after treatment	256	0.4 (1)	0.4 (1)	Resolution of irAEs after treatment
Tremelimumab/phase III [18]	A…	0	0	–	325	0	0	–

allo-H…

Anti-PD-1 related pneumonitis has been reported more frequently than anti-PD-L1 and anti-CTLA4 induced pneumonitis.

PD-L1 inhibitors

Table 3. Immune-mediated p…itors

Agent/phase	Pneumonitis any grade % (*n*)	Pneumonitis grade 3/4% (*n*)	Outcome	Patients receiving ICI (*n*)	Pneumonitis any grade % (*n*)	Pneumonitis grade 3/4% (*n*)	Outcome
BMS-936559/phase I [37]	0	0	–	207	0	0	–
Durvalumab/phase I [39]	0	0	–	346	0	0	–
Durvalumab/phase I/II [40]	1 (2)	0	No treatment-related deaths	198	1 (2)	0	No treatment-related deaths
Atezolizumab/phase I [38]	0	0	–	68	0	0	–
Atezolizumab/phase II [42▪]	–	2%[a]	–	287	–	2%[a]	–
Atezolizumab/phase II [41▪]	–	0.6%[a]	–	659	–	0.6%[a]	–

irAEs, immune-related adverse events;
[a]Ongoing trials with insufficient data i…

Curr Opin Oncol 2016, 28:269–277

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TABLE 1] Characteristics of All Included Studies

NCT No.	Study/Year of Publication	Study Phase	PD-1/PD-L1 Inhibitor	Mean Age, y	Male, %	Comparator Group	Type of Study	Follow-Up Time, wk	Line of Therapy	No. of Patients Evaluated for Safety	Pneumonitis of Any Grade, No. of Patients	Grade 3-4 Pneumonitis, No. of Patients
NCT01673867	Borghaei et al[5] /2015	Phase III	Nivolumab	61	52	Docetaxel	RCT	56	Advanced	287	8	3
NCT01642004	Brahmer et al[4] /2015	Phase III	Nivolumab	62	82	Docetaxel	RCT	48	Advanced	131	6	1
NCT01721759	Rizvi et al[24] /2015	Phase II	Nivolumab	65	73	None	Single-arm trial	47	Advanced	117	6	4
NCT00730639	Gettinger et al[23] /2015	Phase I	Nivolumab	65	79	None	Single-arm trial	168	Advanced	129	10	3
NCT01454102	Gettinger et al[22] /2016	Phase I	Nivolumab	67	50	None	Single-arm trial	60	First line	52	3	1
NCT01295827	Garon et al[25] /2015	Phase I	Nivolumab	64	53	None	Single-arm trial	48	Advanced	495	18	9
NCT01905657	Herbst et al[18] /2016	Phase III	Pembrolizumab	63	62	Docetaxel	RCT	56	Advanced	682	31	14
CTI132072	Nishio et al[21] /2015	Phase II	Nivolumab	65	91	None	Single-arm trial	36	Advanced	35	1	0
CTI 132073	Nishio et al[21] /2015	Phase II	Nivolumab	64	65	None	Single-arm trial	37	Advanced	76	0	0
NCT02031458	Besse et al[19] /2015	Phase II	Atezolizumab	64	59	None	Single-arm trial	37	Advanced	659	10	0
NCT01903993	Fehrenbacher et al[26] /2016	Phase II	Atezolizumab	62	65	None	Single-arm trial	56	Advanced	144	4	1
NCT01846416	Spigel et al[17] /2015	Phase II	Atezolizumab	66	58	None	Single-arm trial	26	Advanced	137	NA	1
	et al /2014						trial					
NCT01693562	Rizvi et al[15] /2015	Phase I	Durvalumab	64	53	None	Single-arm trial	42	Advanced	228	3	0
NCT02066636	Bauer et al[9] /2015	Phase IIIB/IV	Nivolumab	66	54	None	Single-arm trial	10	Advanced	807	8	2
NCT01772004	Verschraegen et al[14] /2016	Phase I	Avelumab	70	51	None	Single-arm trial	13	First line	145	3	0
NCT02142738	Reck et al[12] /2016	Phase III	Pembrolizumab	64.5	92	Platinum-based chemotherapy	RCT	48	First line	154	9	4
NCT02008227	Rittmeyer et al[11] /2017	Phase III	Atezolizumab	63	61	Docetaxel	RCT	82	Advanced	609	6	4
NCT02041533	Socinski et al[10] /2016	Phase III	Niviouma b	63	68	Platinum-based double chemotherapy	RCT	78	First line	267	14	1

NA = not available; NCT = national clinical trial; PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; RCT = randomized clinical trial.

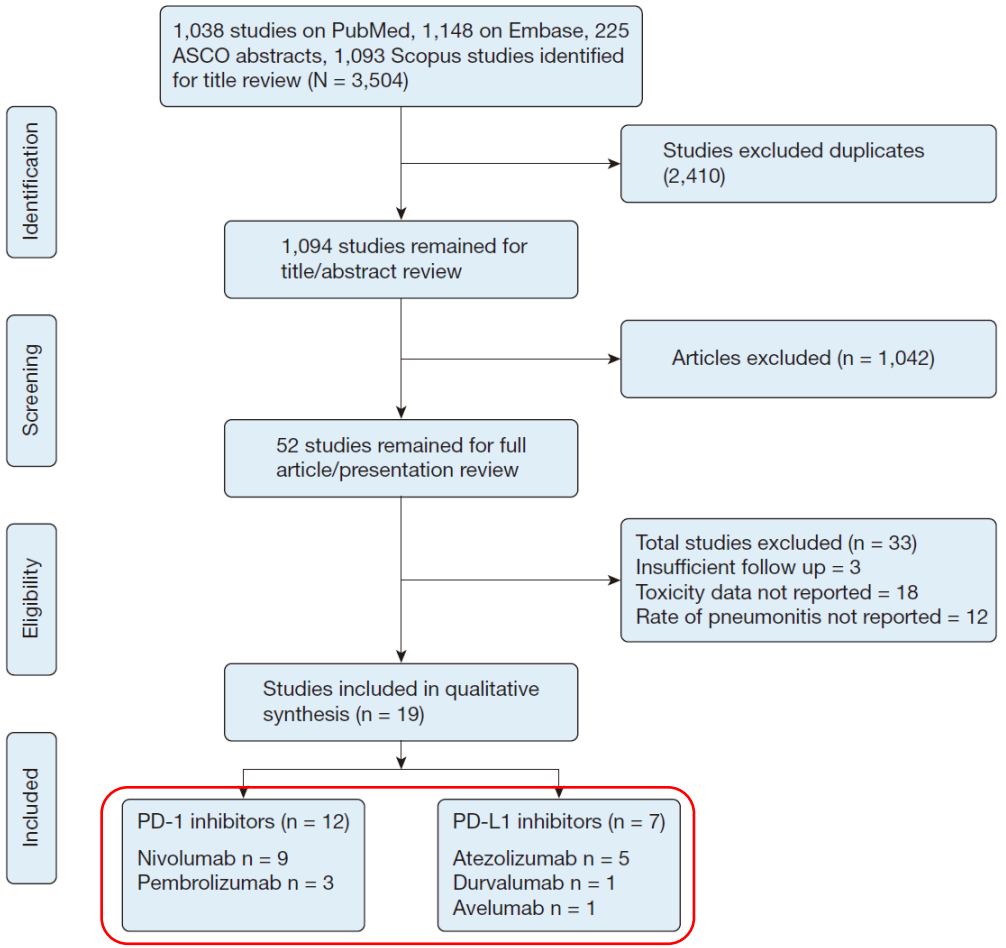

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. ASCO = American Society of Clinical Oncology; PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1.*

CHEST 2017; 152(2):271-281

[Original Research **Lung Cancer**]

CHEST

Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer

A Systematic Review and Meta-Analysis of Trials

Monica Khunger, MD; Sagar Rakshit, MD; Vinay Pasupuleti, MD, PhD; Adrian V. Hernandez, MD, PhD; Peter Mazzone, MD, MPH, FCCP; James Stevenson, MD; Nathan A. Pennell, MD, PhD; and Vamsidhar Velcheti, MD

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

See Table 1 legend for expansion of abbreviations.

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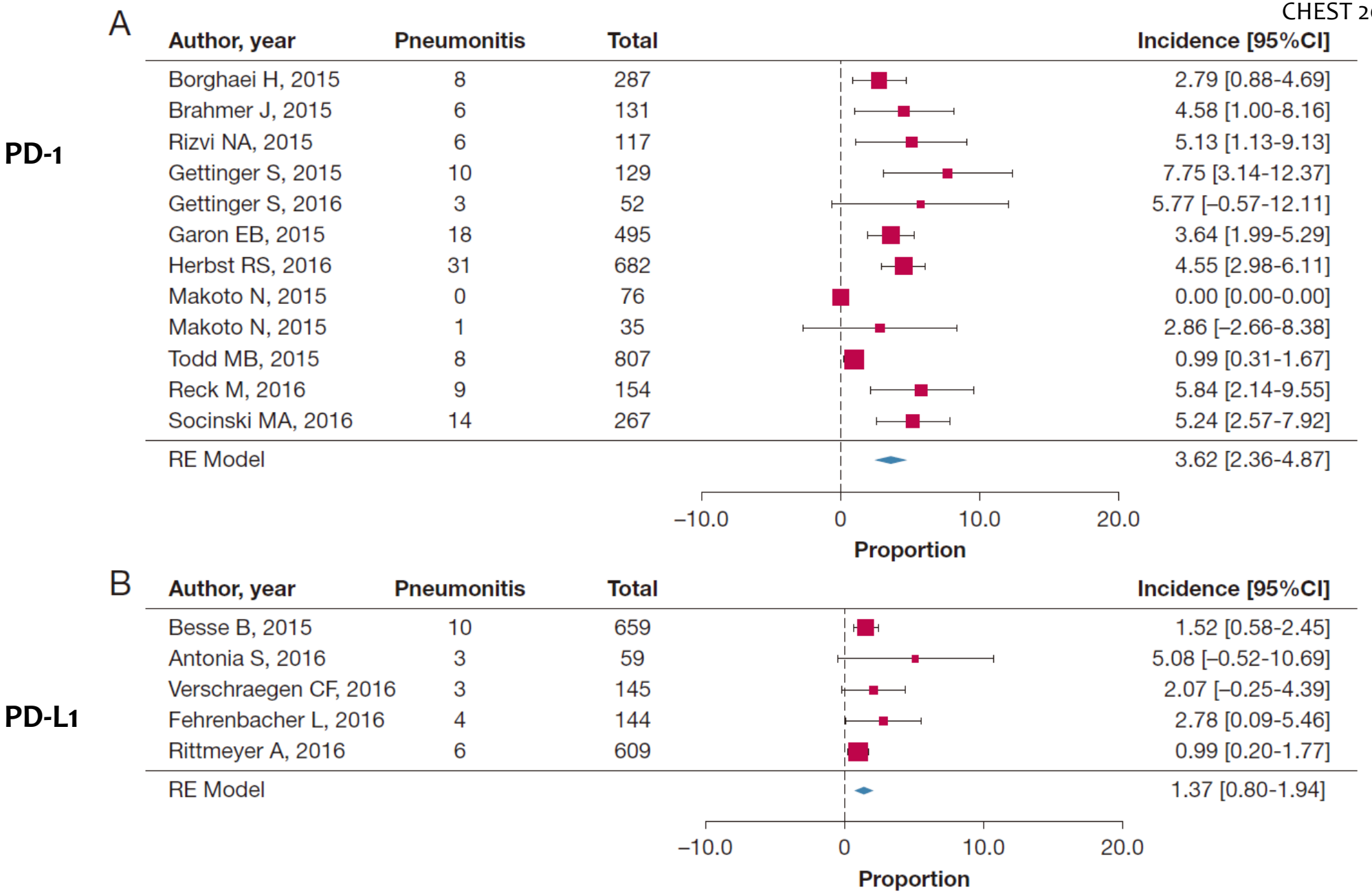

Figure 3 – *Incidence of all grade pneumonitis in studies of programmed death 1 inhibitors (A) and programmed death-ligand 1 inhibitors (B). RE = random effects.*

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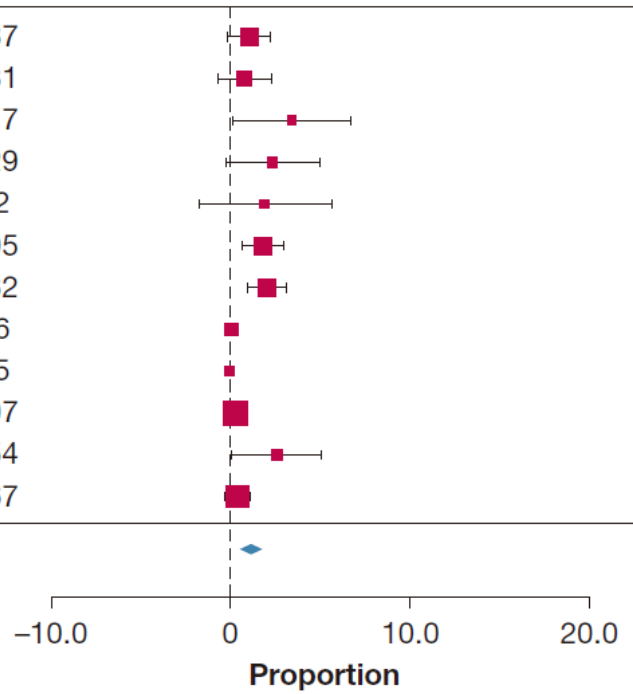
PD-1

A

Author, year	3–4 Pneum	Total	Incidence [95%CI]
Borghaei H, 2015	3	287	1.05 [–0.13-2.22]
Brahmer J, 2015	1	131	0.76 [–0.73-2.25]
Rizvi NA, 2015	4	117	3.42 [0.13-6.71]
Gettinger S, 2015	3	129	2.33 [–0.28-4.93]
Gettinger S, 2016	1	52	1.92 [–1.81-5.66]
Garon EB, 2015	9	495	1.82 [0.64-3.00]
Herbst RS, 2016	14	682	2.05 [0.99-3.12]
Makoto N, 2015	0	76	0.00 [0.00-0.00]
Makoto N, 2015	0	35	0.00 [0.00-0.00]
Todd MB, 2015	2	807	0.25 [–0.10-0.59]
Reck M, 2016	4	154	2.60 [0.09-5.11]
Socinski MA, 2016	1	267	0.37 [–0.36-1.11]
RE Model			1.15 [0.57-1.73]



PD-L1

B

Author, year	3–4 Pneum	Total	Incidence [95%CI]
Besse B, 2015	0	659	0.00 [000-0.00]
Antonia S, 2016	1	59	1.69 [–1.60-4.99]
Spigel DR, 2015	1	137	0.73 [–0.70-2.16]
Herbst RS, 2014	0	53	0.00 [0.00-0.00]
Verschraegen CF, 2016	0	145	0.00 [0.00-0.00]
Fehrenbacher L, 2016	1	144	0.69 [–0.66-2.05]
Rittmeyer A, 2016	4	609	0.66 [0.02-1.30]
RE Model			0.41 [0.00-0.85]

Figure 4 – *Incidence of grade ≥ 3 pneumonitis in studies of programmed death 1 inhibitors (A) and programmed death-ligand 1 inhibitors (B). Pneu = pneumonitis.*

CHEST 2017; 152(2):271-281

Treatment-naive

A

Author, year	Pneumonitis	Total	Incidence [95%CI]
Gettinger S, 2016	3	52	5.77 [–0.57-12.11]
Reck M, 2016	9	154	5.84 [2.14-9.55]
Socinski MA, 2016	14	267	5.24 [2.57-7.92]
Antonia S, 2016	3	59	5.08 [–0.52-10.69]
Verschraegen CF, 2016	3	145	2.07 [–0.25-4.39]
RE Model			4.3 [2.4-6.3]

Previously treated

B

Author, year	Pneumonitis	Total	Incidence [95%CI]
Borghaei H, 2015	8	287	2.79 [0.88-4.69]
Brahmer J, 2015	6	131	4.58 [1.00-8.16]
Rizvi NA, 2015	6	117	5.13 [1.13-9.13]
Gettinger S, 2015	10	129	7.75 [3.14-12.37]
Garon EB, 2015	18	495	3.64 [1.99-5.29]
Herbst RS, 2016	31	682	4.55 [2.98-6.11]
Makoto N, 2015	0	76	0.00 [0.00-0.00]
Makoto N, 2015	1	35	2.86 [–2.66-8.38]
Todd MB, 2015	8	807	0.99 [0.31-1.67]
Fehrenbacher L, 2016	4	144	2.78 [0.09-5.46]
Rittmeyer A, 2016	6	609	0.99 [0.20-1.77]
RE Model			2.8 [1.7-4.0]

Figure 5 – *Incidence of all grade pneumonitis in studies evaluating treatment naive patients (A) and previously treated patients (B).*

CHEST 2017; 152(2):271-281

[Original Research **Lung Cancer**]

CHEST

Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer

A Systematic Review and Meta-Analysis of Trials

Monica Khunger, MD; Sagar Rakshit, MD; Vinay Pasupuleti, MD, PhD; Adrian V. Hernandez, MD, PhD; Peter Mazzone, MD, MPH, FCCP; James Stevenson, MD; Nathan A. Pennell, MD, PhD; and Vamsidhar Velcheti, MD

- PD-1 inhibitors were found to have statistically significant higher incidence of any grade pneumonitis compared with PD-L1 inhibitors (3.6%; 95% CI, 2.4%- 4.9% vs 1.3%; 95% CI, 0.8%-1.9%, respectively; P= .001).

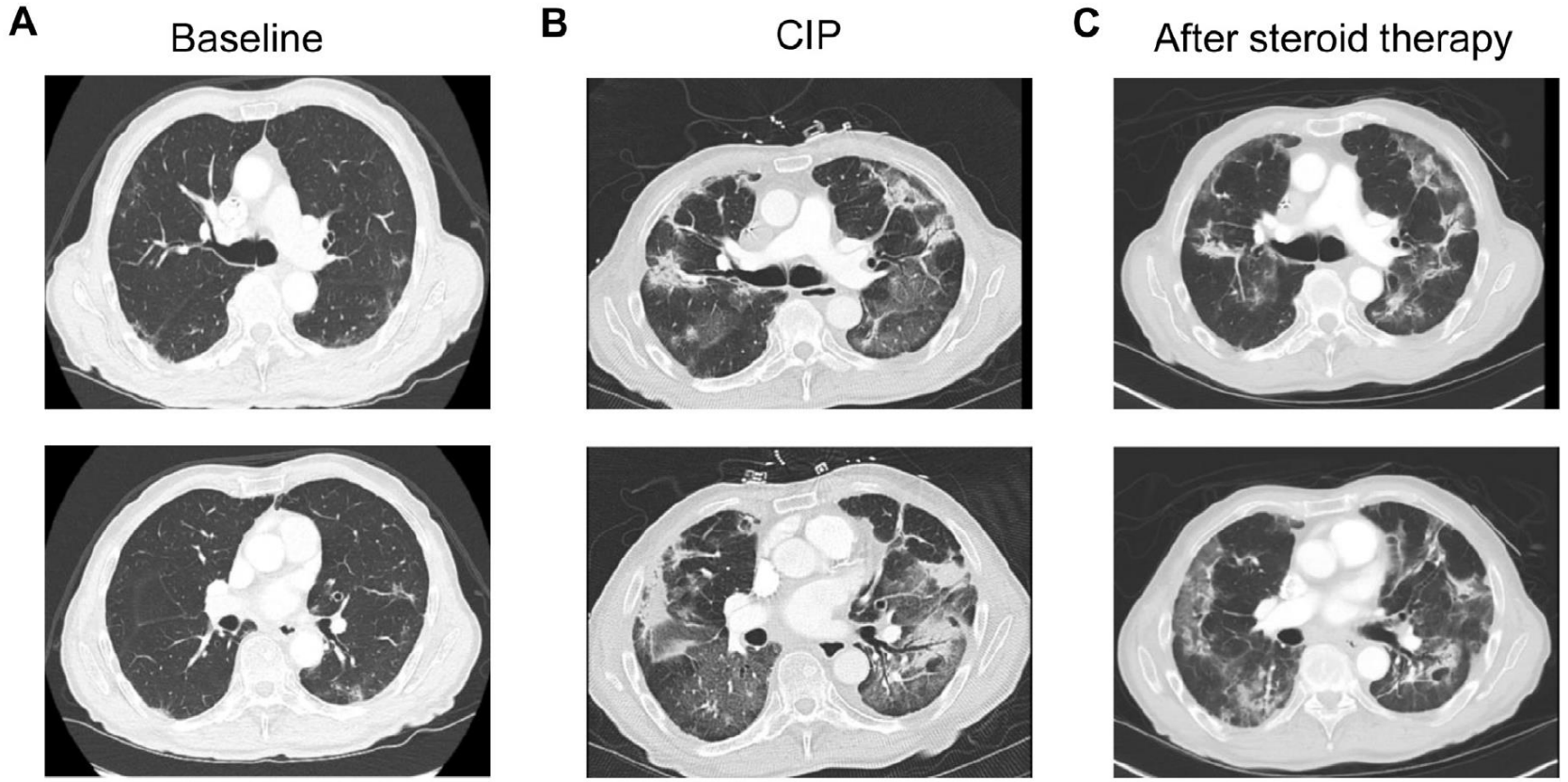
- PD-1 inhibitors were also associated with higher incidence of grade 3 or 4 pneumonitis (1.1%; 95% CI, 0.6%-1.7% vs 0.4%; 95% CI, 0%-0.8%; P=.02).

- Treatment naive patients had higher incidence of grade 1 through 4 pneumonitis compared with previously treated patients

IASLC

Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors

Check for updates



ved anti–programmed

n of therapy).

Figure 1. Representative computed tomography images from an immune checkpoint inhibitor–treated patient after initiation of immune checkpoint inhibitor therapy (*A*), at time of checkpoint inhibitor pneumonitis (CIP) diagnosis (*B*), and after 1 week of steroid therapy for CIP (*C*).

Thoracic Oncology Vol. 13 No. 12: 1930-1939

Table 1. Baseline Characteristics

Characteristic	CIP (n = 39)	No CIP (n = 166)	All Patients (N = 205)	*p* Value
Median age, y (IQR)	68 (10.5)	68 (14)	68 (14)	0.38
Female sex, n (%)	18 (47)	73 (44)	91 (44)	0.84
Race, n (%)				0.8
Caucasian	30 (76.9)	132 (79.5)	162 (79)	
African American	7 (17.9)	28 (16.8)	35 (17)	
Other	2 (5.1)	6 (3.6)	8 (3.9)	
Smoking, n (%)				0.72
Current	2 (5)	13 (7.8)	15 (7.3)	
Former	31 (79)	120 (72.2)	151 (73.6)	
Never	6 (15)	33 (19.8)	39 (19)	
Tumor histologic type, n (%)				0.005
Squamous	16 (41)	41 (24.6)	57 (27.8)	
Adenocarcinoma	18 (46)	114 (68.6)	132 (64.3)	
Other[a]	5 (13)	11 (6.6)	16 (7.8)	
Initial cancer stage, n (%)				0.396
I	1 (2.6)	17 (10)	18 (8.7)	
II	5 (12.8)	12 (7.2)	17 (8.3)	
III	13 (33.3)	44 (26.5)	57 (27.8)	
IV	19 (48.7)	90 (54.2)	109 (53.1)	
Unknown	1 (2.6)	3 (1.8)	4 (1.9)	
Prior chemotherapy, n (%)	26 (66)	125 (75)	151 (73.6)	0.52
Prior surgery, n (%)	7 (17.9)	41 (24.6)	48 (23.4)	0.27
ICI agent, n (%)				0.07
Nivolumab	36 (92.3)	124 (74.6)	160 (78.0)	
Pembrolizumab	2 (5.1)	21 (12.6)	23 (11.2)	
Durvalumab	1 (2.5)	10 (6.0)	11 (5.3)	
Combination therapy, n (%)				0.12
CTLA4 therapy	8 (20.5)	11 (6.6)	19 (9.2)	
Other ICI	1 (2.5)	6 (3.6)	7 (3.4)	
Investigational therapy	5 (12.8)	26 (15.6)	31 (15.1)	
Chemotherapy	2 (5.1)	4 (2.4)	6 (2.9)	

[a]Other includes large cell neuroendocrine carcinoma (2), mesothelioma (2), atypical carcinoid (2), and sarcomatoid carcinoma (1).

CIP, checkpoint inhibitor pneumonitis; IQR, interquartile range; CTLA4, cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor.

Journal of Thoracic Oncology Vol. 13 No. 12: 1930-1939

ORIGINAL ARTICLE

Pneumonitis in Non–Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors

Karthik Suresh, MD,[a,*] Khinh Ranh Voong, MD,[b] Bairavi Shankar, BS,[c] Patrick M. Forde, MD,[c,d] David S. Ettinger, MD,[c] Kristen A. Marrone, MD,[c,d] Ronan J. Kelly, MD,[c,d] Christine L. Hann, MD,[c,d] Benjamin Levy, MD,[c,d] Josephine L. Feliciano, MD,[c,d] Julie R. Brahmer, MD,[c,d] David Feller-Kopman, MD,[a] Andrew D. Lerner, MD,[a] Hans Lee, MD,[a] Lonny Yarmus, DO,[a] Franco D'Alessio, MD,[a] Russell K. Hales, MD,[b] Cheng Ting Lin, MD,[e] Kevin J. Psoter, PhD,[f] Sonye K. Danoff, MD, PhD,[a] Jarushka Naidoo, MBBCh[c,d]

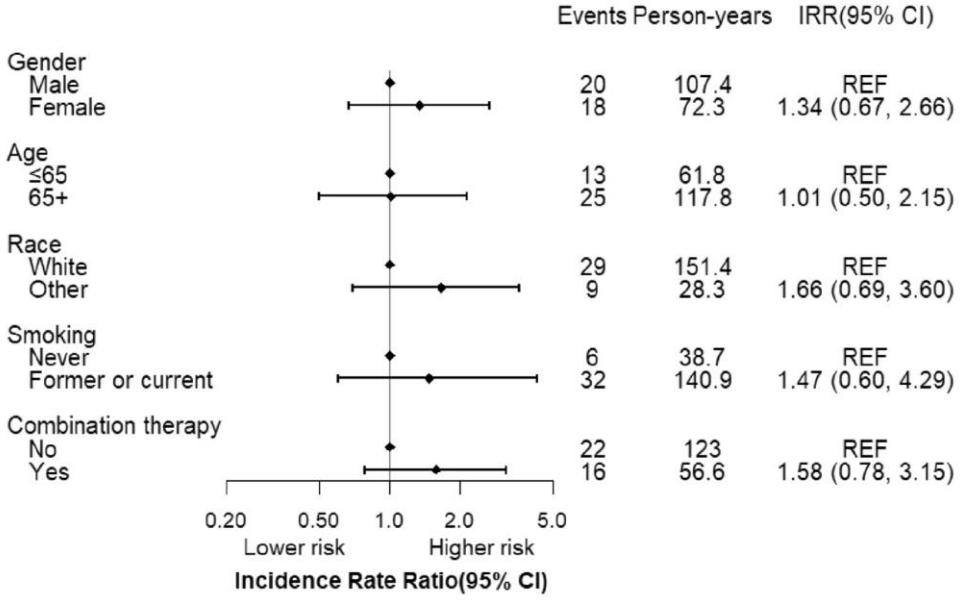


Figure 3. Forest plot showing incidence rate and incidence rate ratios (IRRs) for checkpoint inhibitor pneumoni demographic factors. CI, confidence interval; REF, reference.

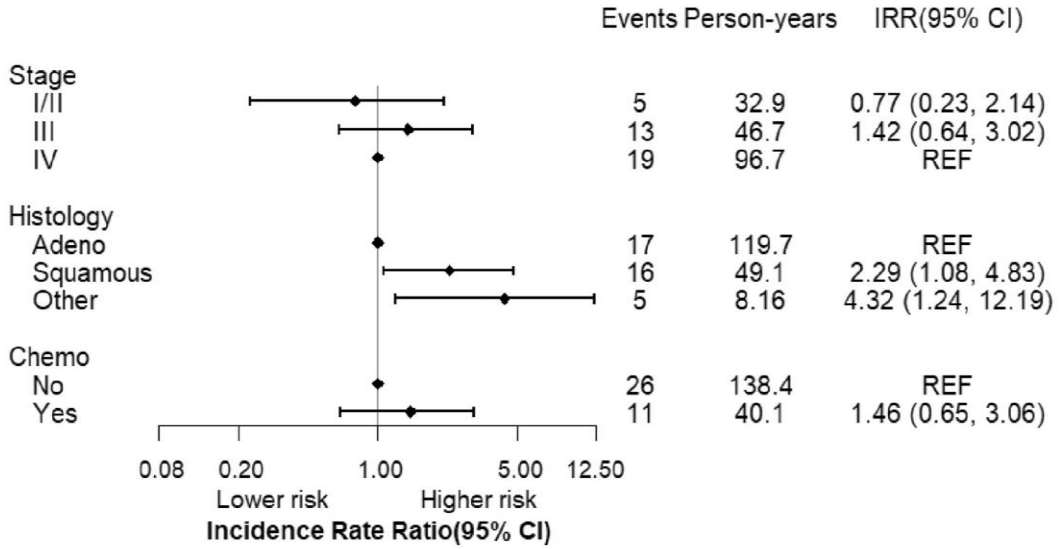


Figure 4. Forest plot showing checkpoint inhibitor pneumonitis (CIP) incidence rate/incidence rate ratio (IRR) by tumor characteristics (stage, histologic type, and antecedent chemotherapy). CI, confidence interval; REF, reference; Adeno, adenocarcinoma; Chemo, chemotherapy.

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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

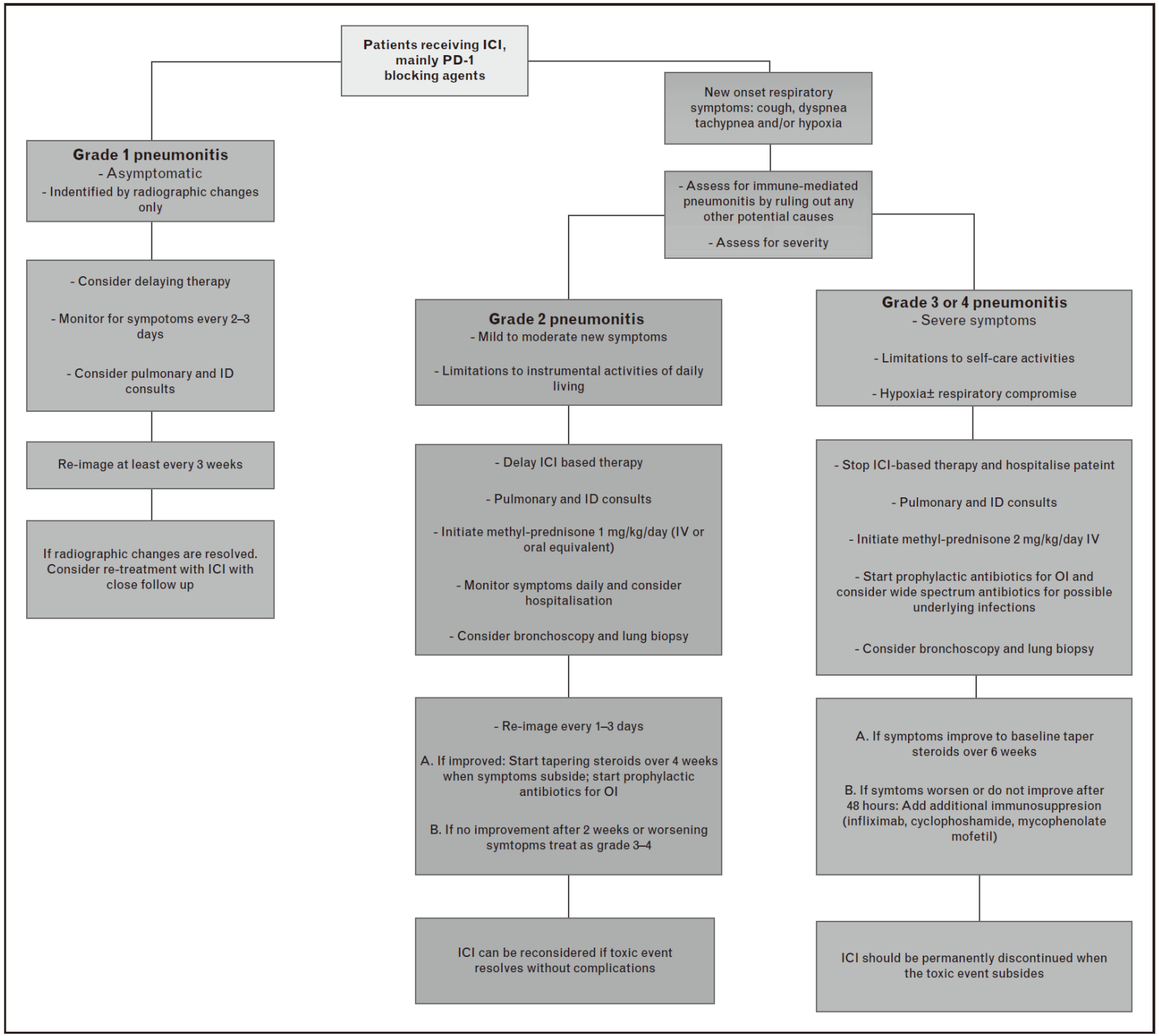
[a]Adjusted for prior chemotherapy and combination ICI therapy.
CIP, checkpoint inhibitor pneumonitis; OR, odds ratio; CI, confidence interval; ICI: immune checkpoint inhibitor.

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)

CIP, checkpoint inhibitor pneumonitis.

Journal of Thoracic Oncology Vol. 13 No. 12: 1930-1939



Curr Opin Oncol 2016, 28:269–277

Guideline of Pneumonitis Management

- **Mild to moderate cases**
  - Prednisone 1-2 mg/kg/d or Methylprednisolone 0.5-1 mg/kg/d
  - Assess response within 48~72hrs

- **Severe cases**
  - Hospitalization is necessary
  - High-dose corticosteroids, such as methylprednisolone 2-4 mg/kg/d
  - Assess response within 48hrs; additional immunosuppression: mycophenolate mofetil, cyclophosphamide, infliximab

JAMA Oncol. 2016;2(10):1346-1353.

Combination Tx

Chemo-immunoTx

Study	Cancer	Drug	Chemo-immunoTx		Placebo combination	
			Any grade pneumonitis	Grade 3,4,5 pneumonitis	Any grade pneumonitis	Grade 3,4,5 pneumonitis
KEYNOTE 021	NSCLC	Pemetrexed/platinum ± Pembrolizumab	3%	2%	0%	0%
KEYNOTE 189	NSCLC (non-SqCC)	Pemetrexed/platinum ± Pembrolizumab	4.4%	2.7%	2.5%	2.0%
KEYNOTE 407	NSCLC(SqCC)	Paclitaxel/platinum ± Pembrolizumab	6.5%	2.5%	2.1%	1.1%
IMPOWER 132	NSCLC	Pemetrexed/platinum ± Atezolizumab	6%	2%	2%	1%
IMPOWER 131	NSCLC	Paclitaxel/platinum ± Atezolizumab	3.2%	1.8%	0.6%	0.6%
CHECKMATE 026	NSCLC	Platinum doublet ± Nivolumab	N/A	N/A	N/A	N/A
IMPOWER 133	SCLC	Etoposide/platinum ± Atezolizumab	N/A	N/A	N/A	N/A
CASPIAN	SCLC	Etoposide/platinum ± Durvalumab	N/A	N/A	N/A	N/A

Dual immunoTx

Study	Cancer	Drug	Dual-immunoTx		Single-immuno	
			Any grade pneumonitis	Grade 3,4,5 pneumonitis	Any grade pneumonitis	Grade 3,4,5 pneumonitis
Checkmate 227	NSCLC	Nivolumab ± ipilimumab	N/A	N/A	N/A	N/A
Checkmate 012	NSCLC	Nivolumab + ipilimumab (12 weeks vs. 6 weeks)	6%	3%	6%	3%
KEYNOTE 021	NSCLC	Pembrolizumab + ipilimumab	5.1%	2%	0%	0%
Checkmate 032	SCLC	Nivolumab ± ipilimumab	4~6%	2%	3.1%	1%

Target Tx + immunoTx

- A recent observation trial
  - In a multi-arm phase Ib trial
  - PD-L1 inhibitor(durvalumab), plus EGFR-TKI(osimertinib) in EGFR-mutant NSCLC

  - A significantly high rate of lung toxicity
    - an overall incidence of 38% (13 of 34 patients) and a rate of grade 3 to 4 events of 15% (5 of 34 patients)

CCRTx -> immunoTx

Table 2. Incidence of Treatment-related Pneumonitis in Patients Receiving Anti-PD-1/PD-L1 Therapy

Study	Study Type	Indication	Prior Therapy	Treatment	Any Grade, n/N (%)	Grade 3/4, n/N (%)	Grade 5, n/N (%)
Antonia et al.[12]	Phase III	Stage III	Platinum-based doublet CT* with concurrent RT (≥2 cycles)	Durvalumab (anti-PD-L1) monotherapy versus placebo	Durvalumab: 43/475 (9.1) Placebo: 8/234 (3.4)	Durvalumab: 6/475 (1.3) Placebo: 2/234 (0.9)	Durvalumab: 4/475 (0.8) Placebo: 2/234 (0.9)

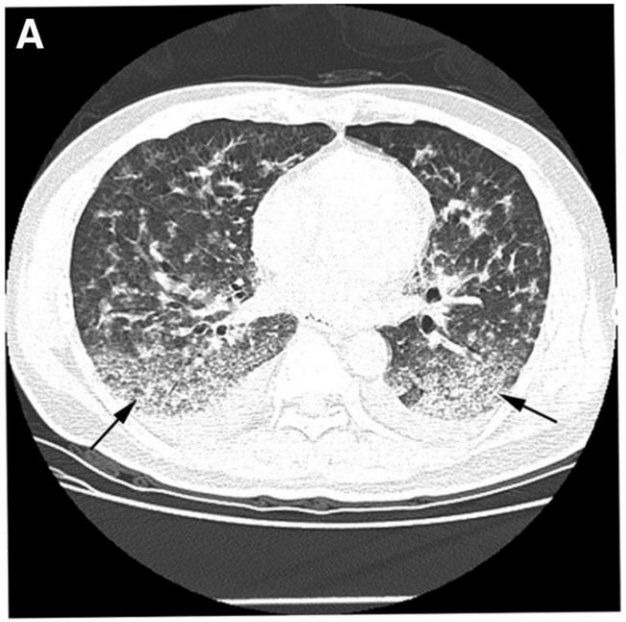
Retreatment

Succ

Induced

S

en Yu‡



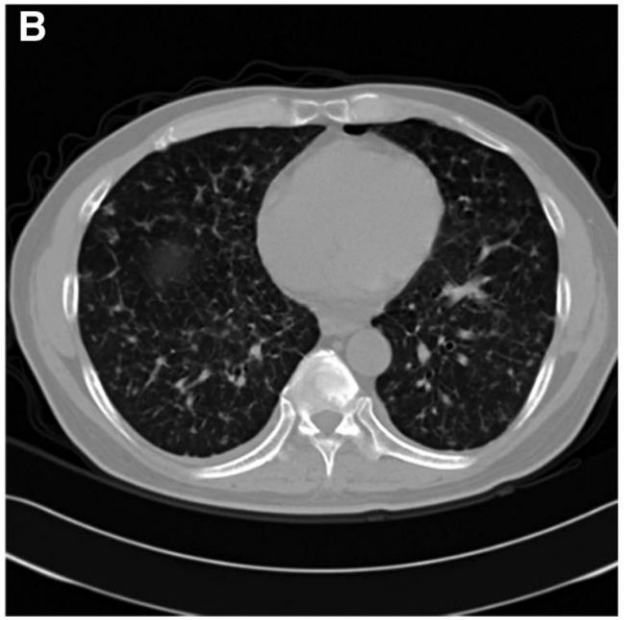
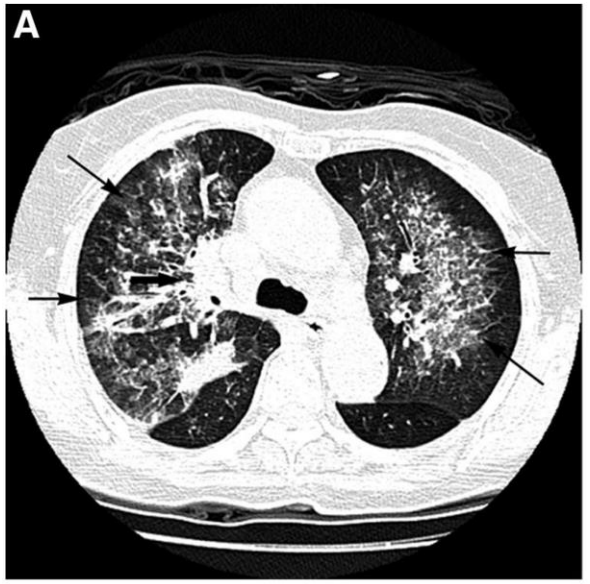


FIGURE 1. *A*, Chest computed tomography (CT) showed diffuse ground-glass opacity over lower lung zones (arrows) and pleural effusion on the sixth week of gefitinib therapy. *B*, Chest CT performed on 48th day of erlotinib therapy showed multiple small residual lung tumors.



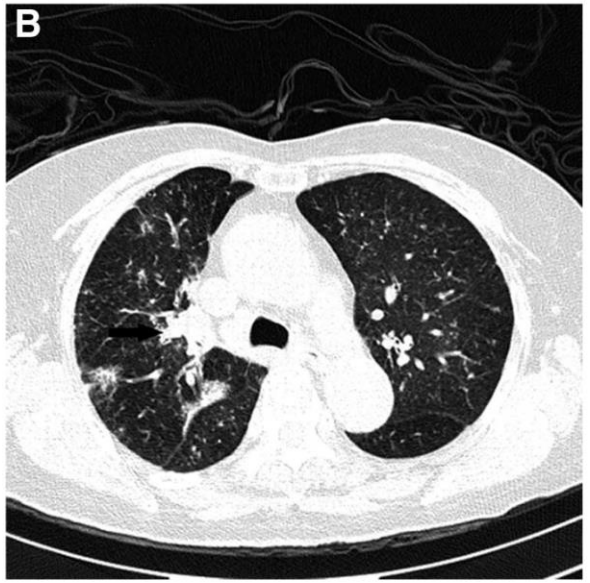
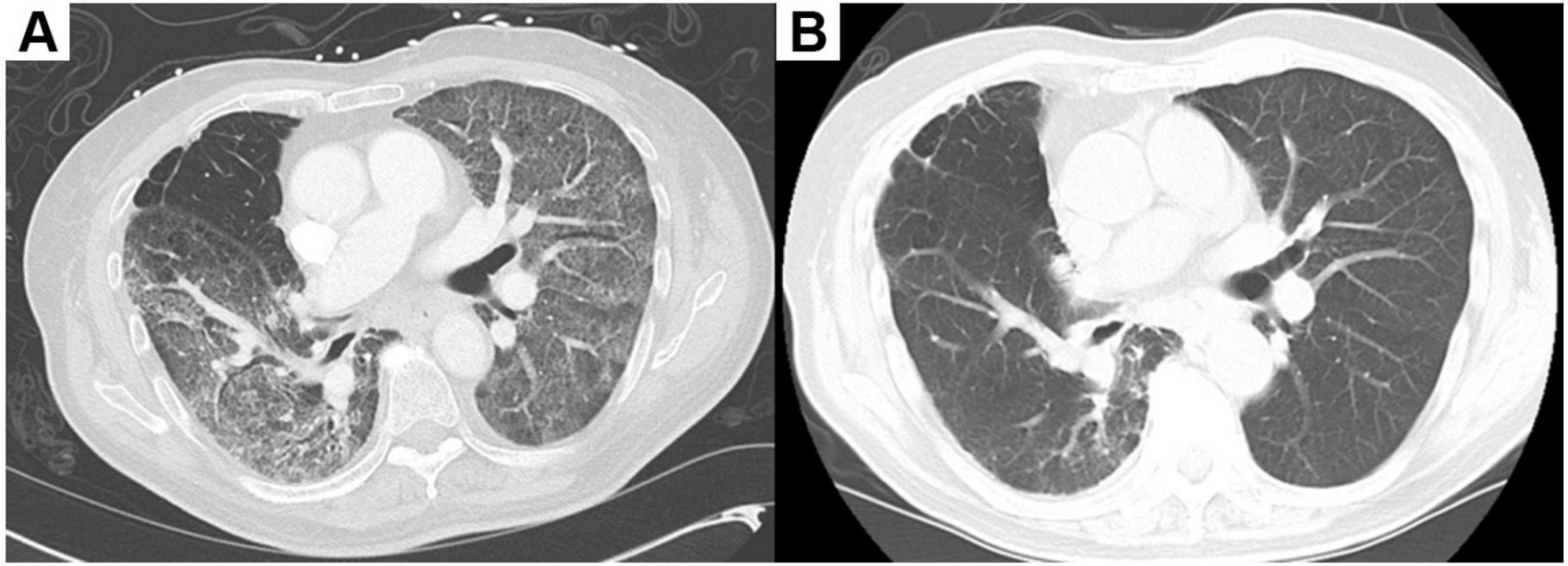


FIGURE 2. *A*, The chest computed tomography (CT) showed decreased size of the main tumor (*thick arrow*) and diffuse ground-glass opacity over upper lung zones (*thin arrows*) on the seventh week of gefitinib therapy. *B*, The chest CT performed on the 131th day of erlotinib therapy showed partial remission of right upper lung tumor (*arrow*).

5, Number 7, July 2010

Retreatment With Osimertinib Following Pneumonitis

Figure 1 Grade 4 Pneumonitis on Initial Osimertinib Use (A), Which Resolved in 7 Weeks After Intensive Care Unit Stay, Ventilator Support, and Systemic Dose Steroids (B)

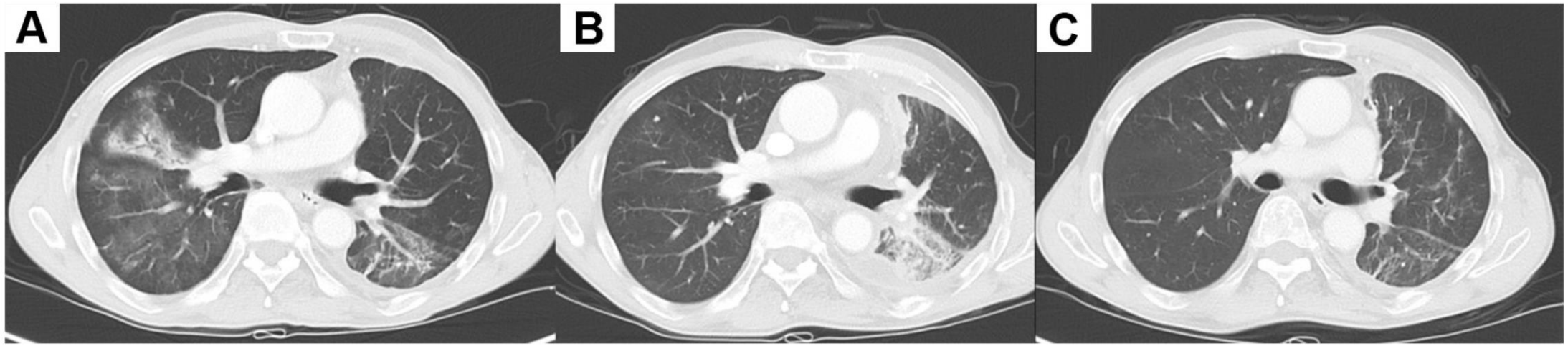


Case Report

Retreatment With Osimertinib Following Pneumonitis

Misako Nagasaka,[1] Shirish M. Gadgeel[2]

Figure 3 Grade 3 Pneumonitis on Initial Osimertinib Use (A), Which Resolved Upon Discontinuation But Resulted in Progression of Disease in the Left Lower Lobe (B). Three Weeks Post-Reintroduction of Osimertinib With Steroid Coverage, the Left Lower Lobe Lesion Had Partial Response, and There Was No Evidence of Recurrence of Pneumonitis (C)



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Research Article

Pneumonitis in advanced non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitor: Meta-analysis of 153 cohorts with 15,713 patients

Meta-analysis of incidence and risk factors of EGFR-TKI pneumonitis in NSCLC

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Table 5
Incidence of pneumonitis in EGFR-TKI retreatment group.

	All-grade pneumonitis		High-grade pneumonitis		Grade 5 pneumonitis	
	No. of studies	Incidence (%) (95% CI)	No. of studies	Incidence (%) (95% CI)	No. of studies	Incidence (%) (95% CI)
All agents	n = 17	1.13% (0.40-3.15%)	17	0.49% (0.21-1.11%)	17	0.16% (0.04-0.65%)
Erlotinib	n=6	1.54% (0.39-5.94%)	6	0.77% (0.11-5.25%)	6	0.77% (0.11-5.25%)
Gefitinib	n=4	1.33% (0.19-8.86%)	4	1.33% (0.19-8.86%)	4	No event
Afatinib	n=5	0.17% (0.00-13.64%)[a]	5	0.16% (0.01-3.89%)	5	No event
Osimertinib	n=2	3.01% (1.85-4.85%)	2	0.56% (0.18-1.73%)	2	0.19% (0.03-1.32%)

EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.
[a] $I^2 > 50\%$ indicating substantial heterogeneity.

Lung Cancer 123 (2018) 60–69

ICI retreatment after immune mediated pneumonitis

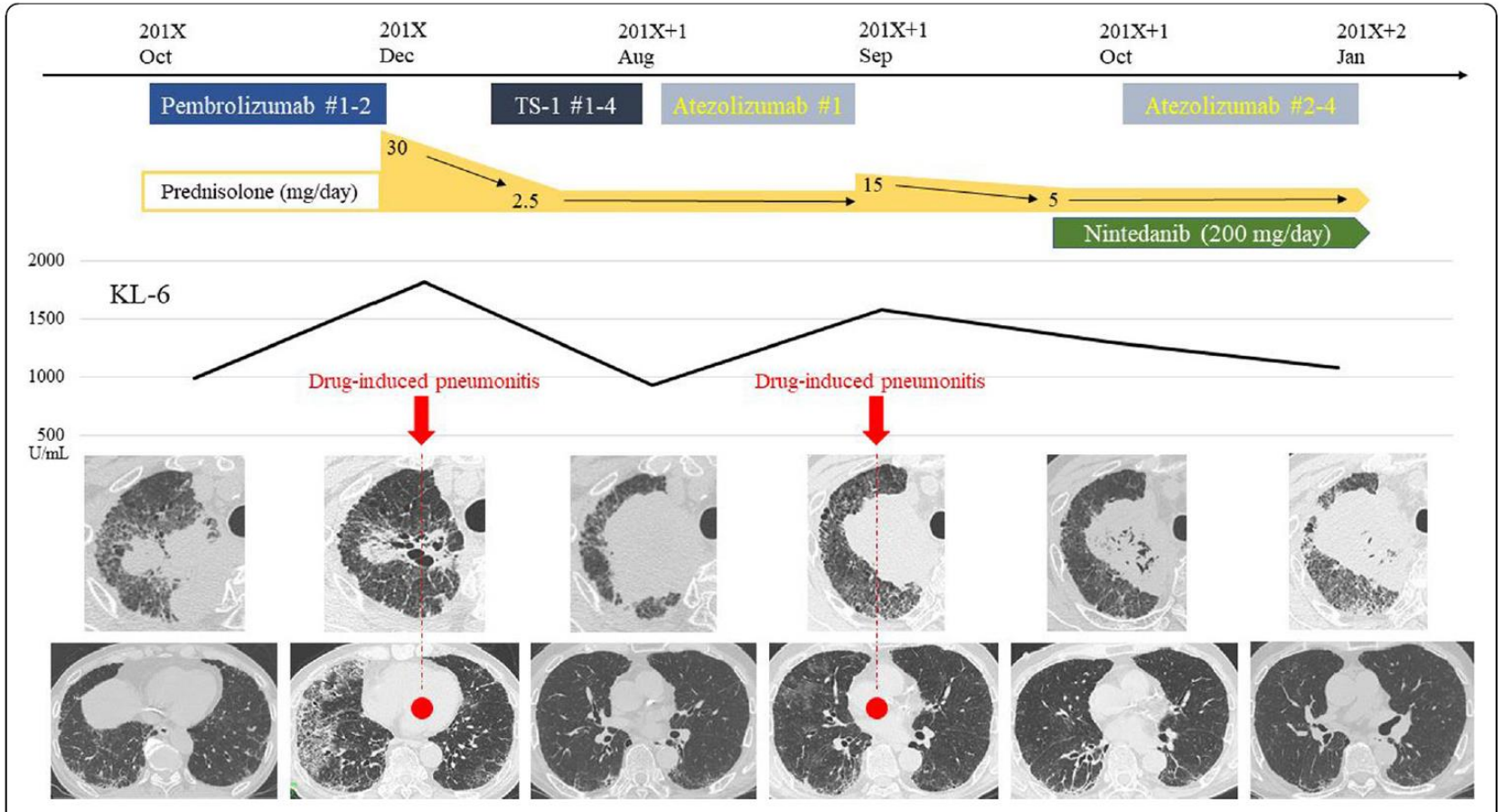
Drugs	Cancer	No. of pneumonitis	No. of Re-administration	No. of pneumonitis recurrence
Pembrolizumab	NSCLC	21	4(19%)	1(25%)
Anti-PD-1/PD-L1 antibody or combination with Anti-CTLA-4 antibody	Melanoma NSCLC etc.	43	12(28%)	3(25%)
Anti-PD-1/PD-L1 antibody or combination with other drugs	NSCLC	25	9(36%)	5(56%)
Nivolumab or combination with other immune checkpoint inhibitors	Melanoma Lung cancer, etc.	20	7(35%)	2(29%)

Ahn MJ:ESMO Asia 2015, Naidoo J:JCO 2016, Gettinger S: ASCO2016, Nishino M: CCR 2016

CASE REPORT Open Access

Nintedanib allows retreatment with atezolizumab of combined non-small cell lung cancer/idiopathic pulmonary fibrosis after atezolizumab-induced pneumonitis: a case report

Yamakawa et al. BMC Pulmonary Medicine (2019) 19:156



Summary

- Drug-related pneumonitis is one of the major categories of adverse events during cancer therapy.
- Clinical courses; Variable, Non-specific
  - between weeks to months
- Exclusion diagnosis
- No specific treatments
  - Drug discontinuation, Systemic glucocorticoids, and Supportive care

- Chemotherapy-Induced Pneumonitis
- Target-therapy-Induced Pneumonitis
- Immunotherapy-Induced Pneumonitis

- Combination; more frequently
- Retreatment or Rechallenge; debate… negative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