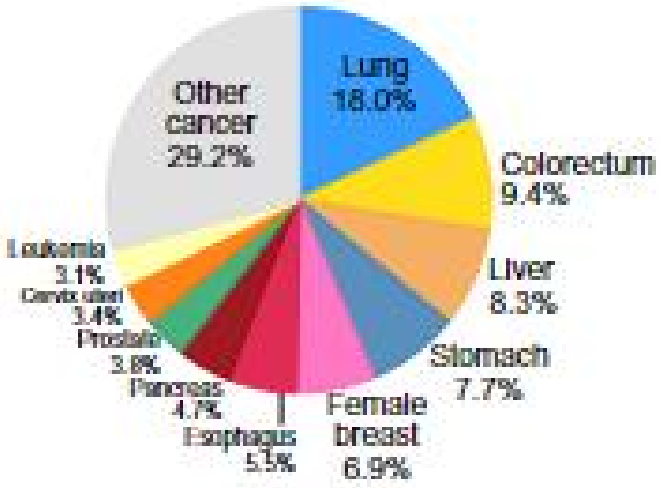
Serum KL-6 levels predict the occurrence and reflect the severity of treatment-related interstitial lung disease in lung cancer

2023.03.18

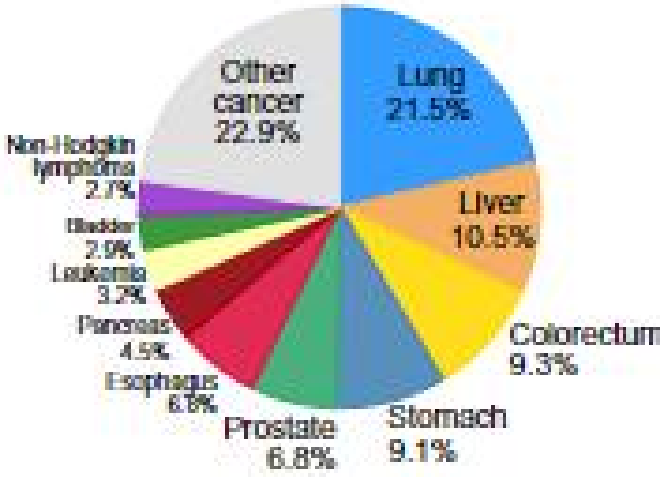
Park Hwa Kyung

High mortality of lung cancer



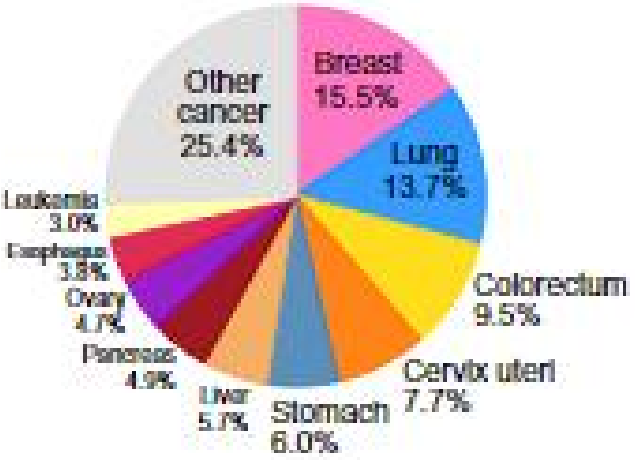
9.9 million deaths

Both sexes



5.5 million deaths

Male

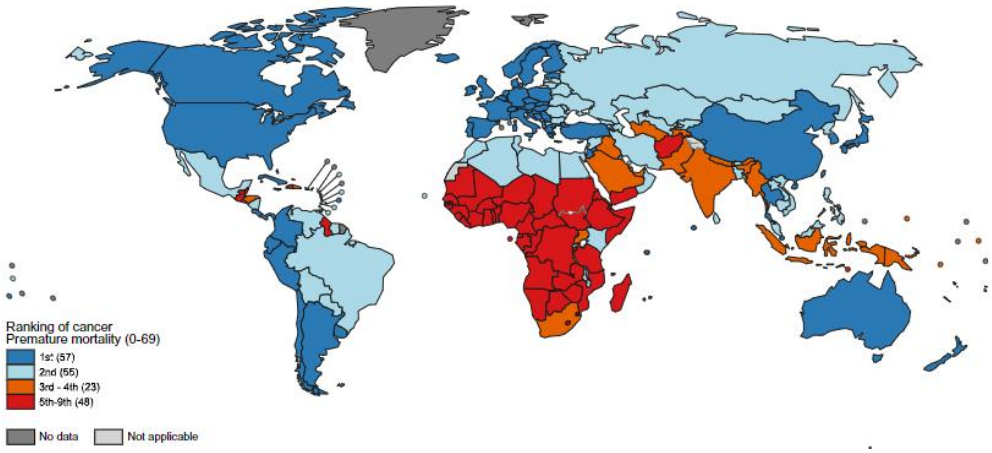


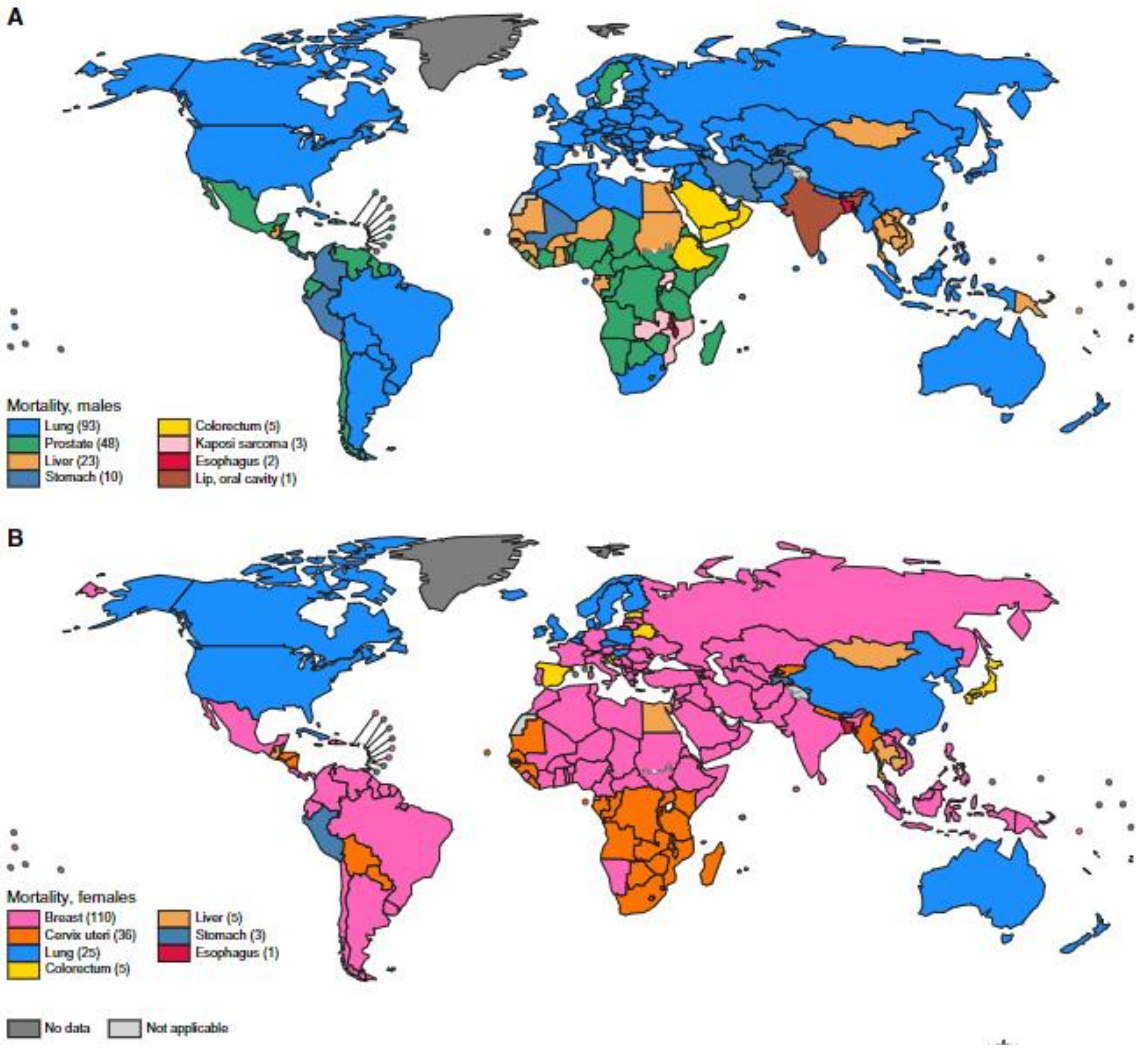
4.4 million deaths

Female

A Cancer Journal for Clinicians 71(3) (2021) 209-249.

High mortality of lung cancer





A Cancer Journal for Clinicians 71(3) (2021) 209-249.

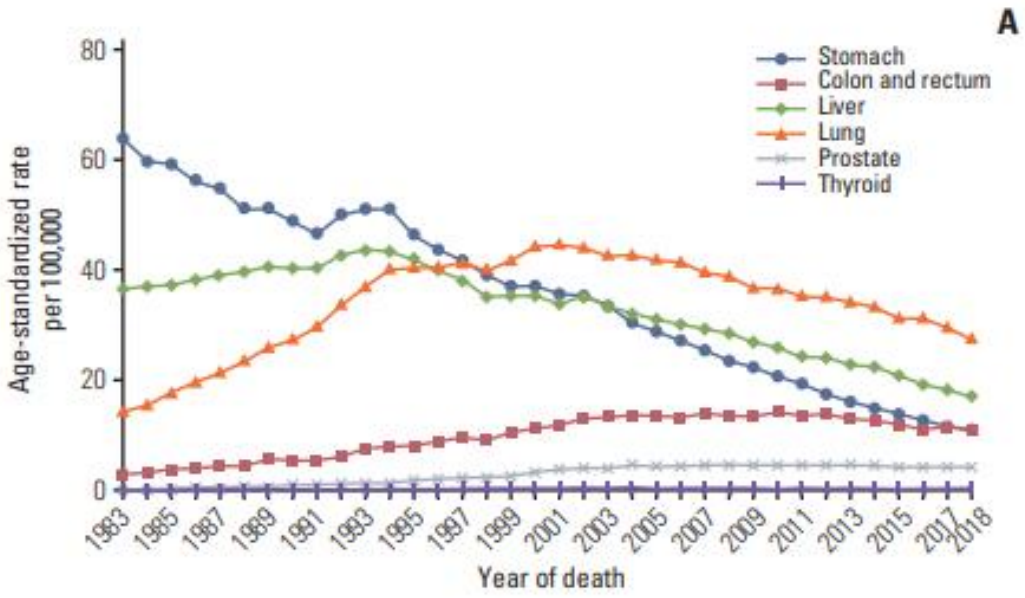
High mortality of lung cancer in Korea (2018)

Table 4. Crude and age-standardized cancer mortality rates by sex in Korea, 2018

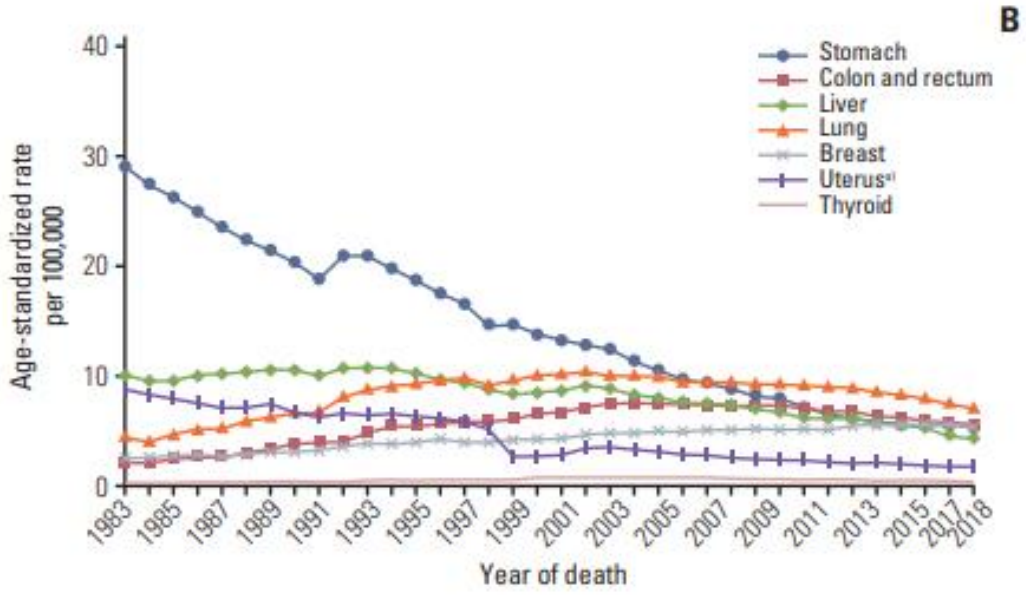
Site/Type	Crude mortality rates per 100,000			Age-standardized mortality rates per 100,000[a]		
	Both sexes	Men	Women	Both sexes	Men	Women
All sites	154.3	191.0	117.7	73.3	105.3	49.5
Lip, oral cavity, and pharynx	2.2	3.3	1.2	1.1	1.8	0.5
Esophagus	2.8	5.1	0.5	1.3	2.8	0.2
Stomach	15.1	19.9	10.4	7.1	11.0	4.1
Colon and rectum	17.0	19.1	14.8	7.7	10.6	5.5
Liver[b]	20.7	30.4	11.0	10.2	17.0	4.4
Gallbladder[c]	9.5	9.8	9.2	4.2	5.2	3.4
Pancreas	11.8	12.5	11.1	5.5	6.9	4.3
Larynx	0.6	1.1	0.1	0.3	0.6	0.0
Lung[d]	34.8	51.5	18.1	15.7	27.5	7.0
Breast	4.8	0.1	9.6	2.7	0.0	5.3
Cervix uteri	1.6	-	3.3	0.9	-	1.7
Corpus uteri	0.6	-	1.3	0.3	-	0.6
Ovary	2.4	-	4.8	1.3	-	2.4
Prostate	3.9	7.8	-	1.5	4.2	-
Testis	0.0	0.1	-	0.0	0.1	-
Kidney	1.9	2.6	1.2	0.9	1.5	0.5
Bladder	2.7	4.1	1.3	1.1	2.2	0.4
Brain and CNS	2.6	2.8	2.4	1.7	1.9	1.5
Thyroid	0.7	0.4	1.0	0.3	0.2	0.4
Hodgkin lymphoma	0.1	0.2	0.1	0.1	0.1	0.0
Non-Hodgkin lymphoma	3.7	4.2	3.1	1.8	2.4	1.3
Multiple myeloma	1.9	2.0	1.7	0.8	1.1	0.7
Leukemia	3.6	4.2	3.0	2.1	2.7	1.7
Other and ill-defined	9.2	9.9	8.5	4.5	5.7	3.6

Cancer Res Treat 53(2) (2021) 301-315.

High mortality of lung cancer in Korea



Male



Female

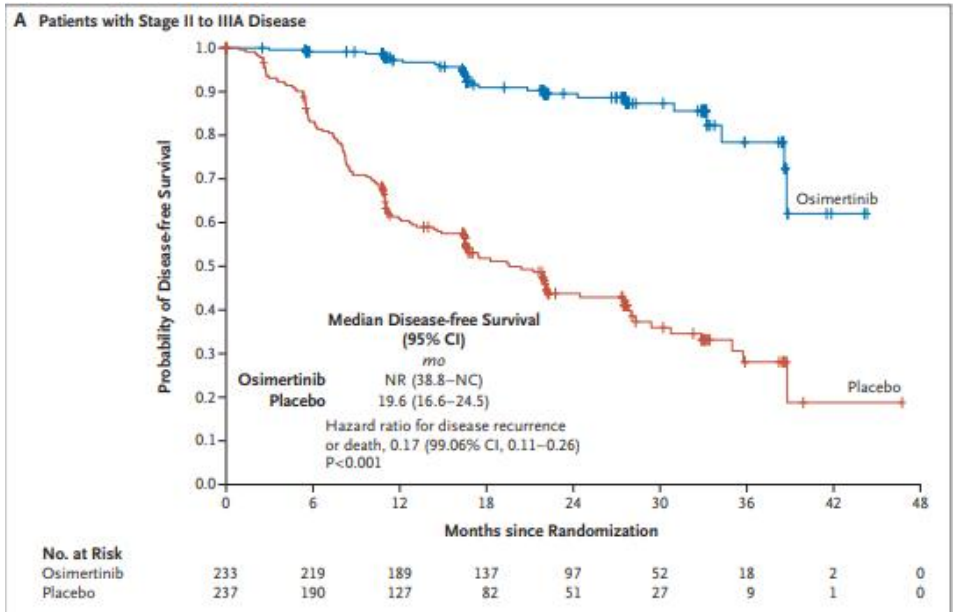
Cancer Res Treat 53(2) (2021) 301-315.

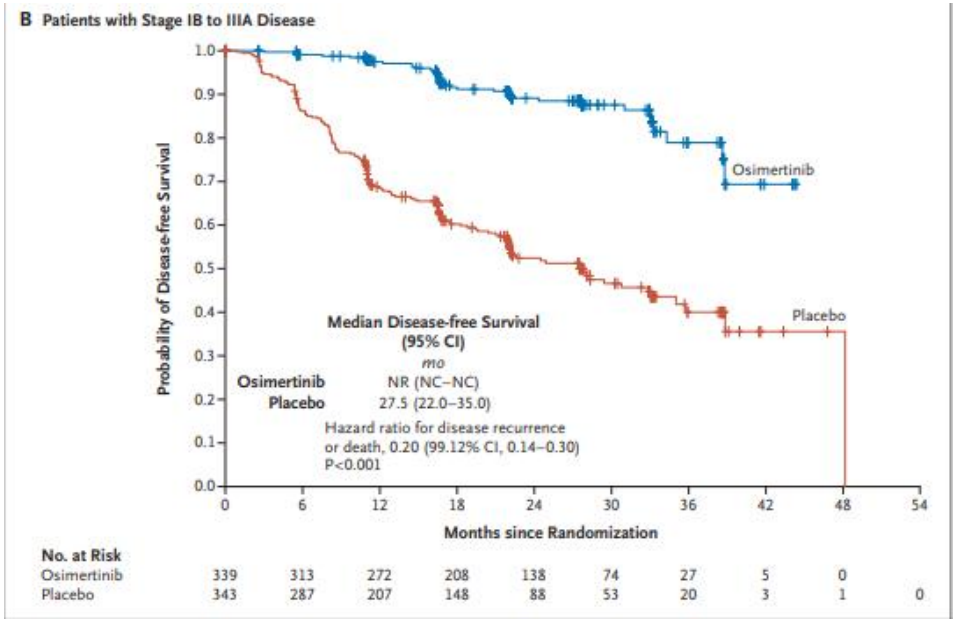
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

- Double-blind, 1:1 RCT, phase 3 trial
- Patients with completely resected EGFR mutation positive NSCLC
- Osimertinib vs Placebo for 3 years (339 vs 343)





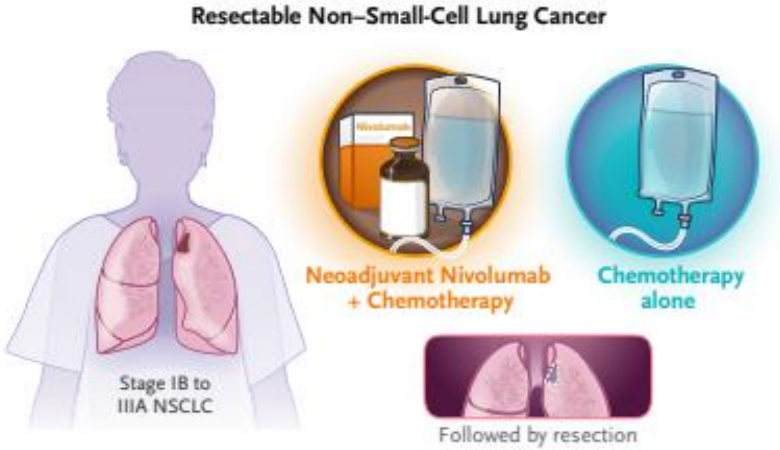
New England Journal of Medicine 383(18) (2020) 1711-1723.

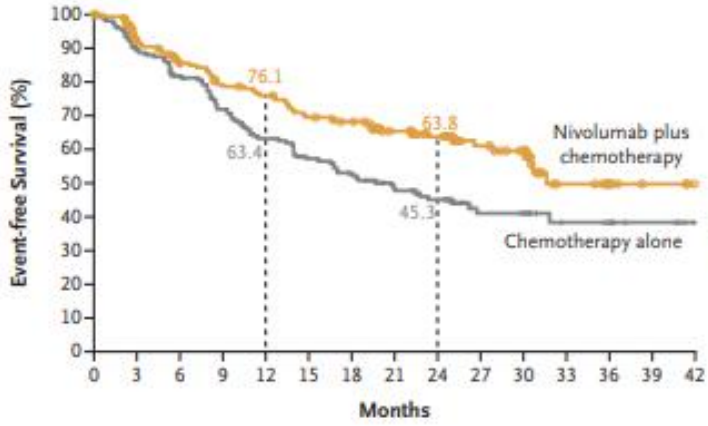
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

- Open-label, randomized, phase 3 trial

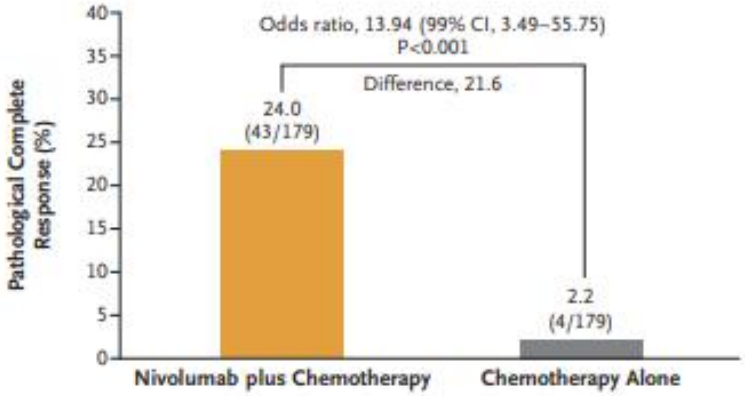




No. at Risk															
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

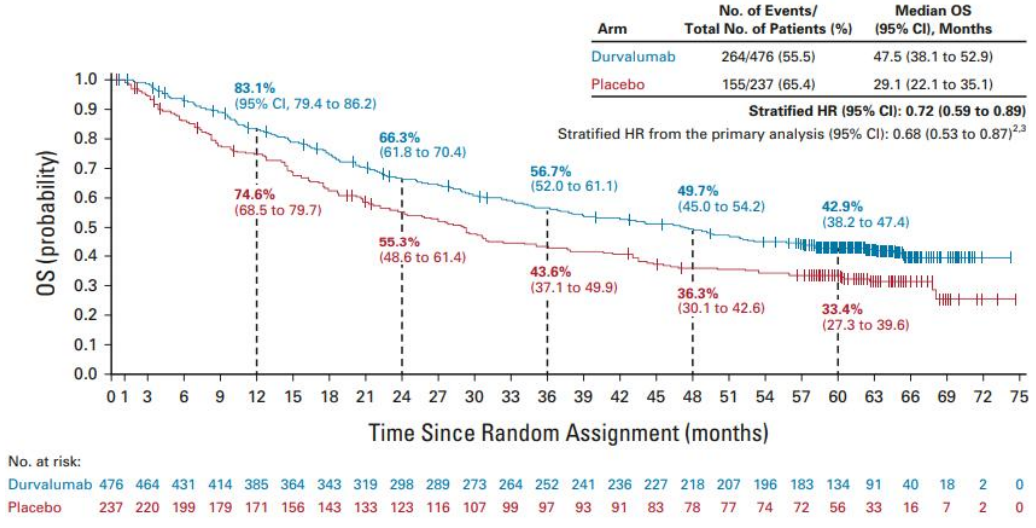
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

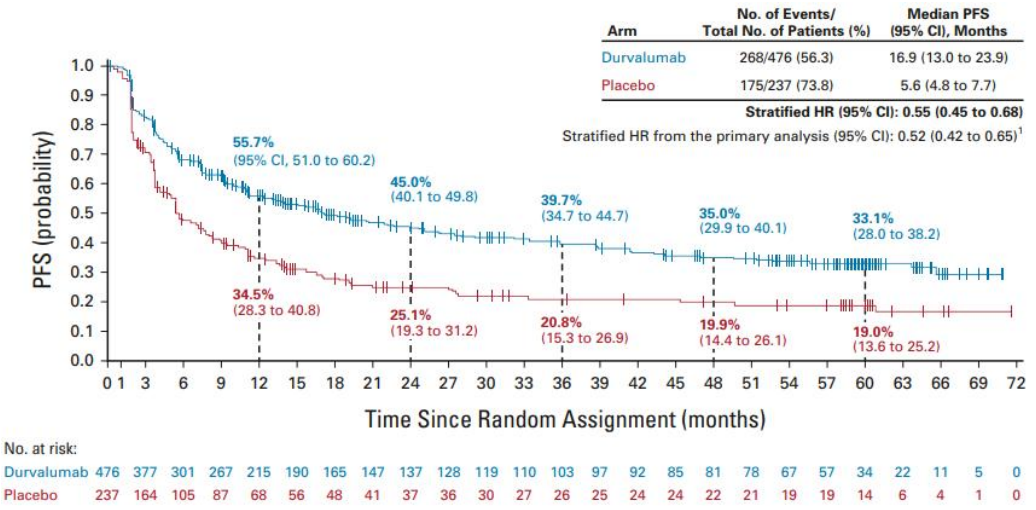


N Engl J Med 2022; 386:1973-1985

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

- 2:1 randomized, phase 3 trial
- Patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum based CCRT
- Durvalumab vs Placebo up to 12 months



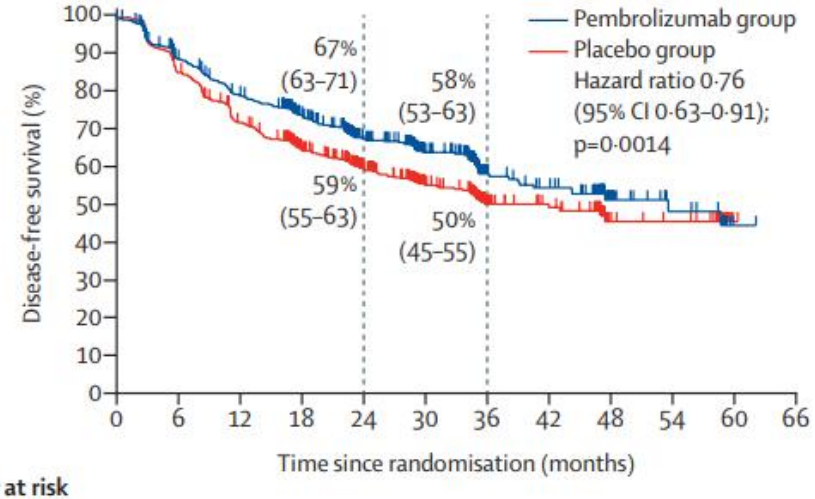


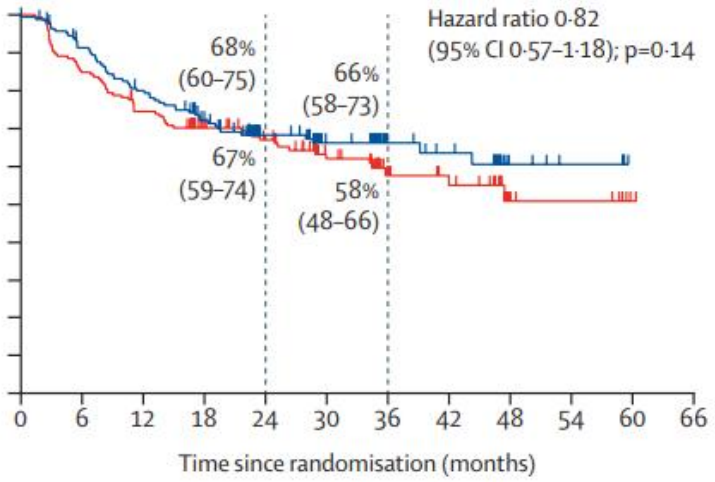
J Clin Oncol 40(12) (2022) 1301-1311.

Lancet Oncol 2022; 23: 1274–86

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

- Triple-blind, 1:1 randomized, phase 3 trial
- Patients with completely resected stage IB-IIIA NSCLC
- Pembrolizumab vs Placebo up to 18 cycles (590 vs 587)



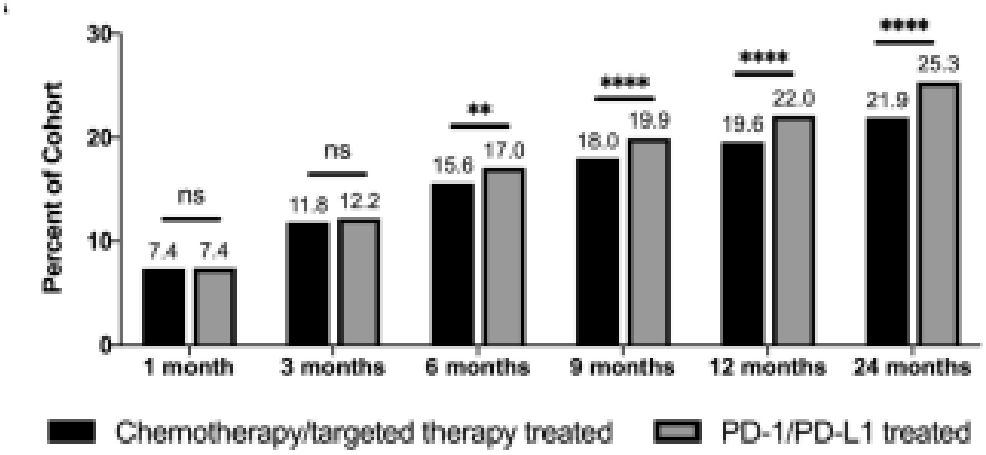


Number at risk (number censored)												
Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

168	145	126	99	69	50	26	22	7	4	0	0
(0)	(8)	(9)	(24)	(49)	(66)	(90)	(93)	(107)	(110)	(114)	(114)
165	140	121	100	75	54	28	22	8	6	1	0
(0)	(0)	(2)	(16)	(37)	(53)	(76)	(81)	(94)	(96)	(101)	(102)

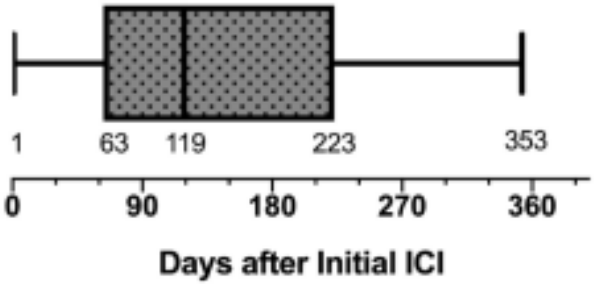
Lancet Oncol 23(10) (2022) 1274-1286

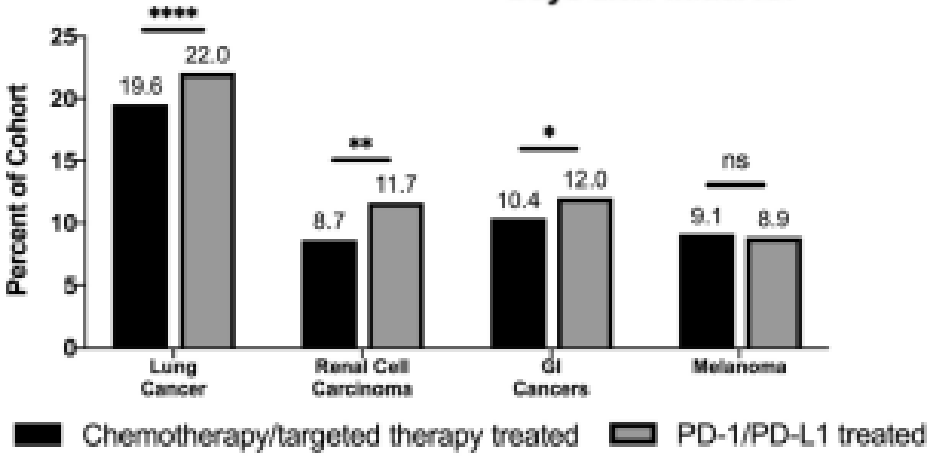
Real world incidence of ICI-related pneumonitis



	1 month	3 months	6 months	9 months	12 months	24 months
ICI attributable risk (95% CI)	0.04% (-0.59 – 0.67%)	0.37% (-0.42 – 1.15%)	1.45% (0.55 – 2.34%)	1.96% (1.01 – 2.91%)	2.49% (1.50 – 3.47%)	3.49% (2.46 – 4.51%)

Incidence of pneumonitis/pneumonia



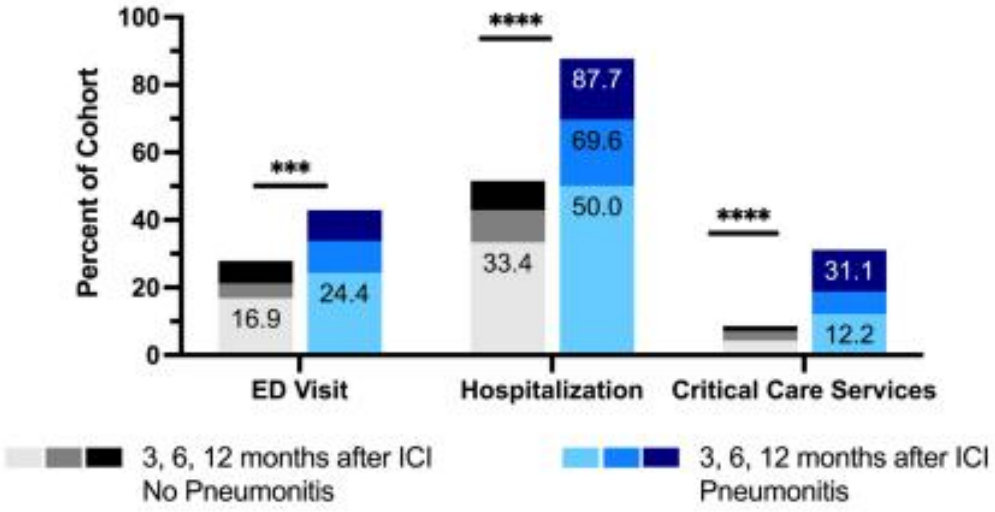


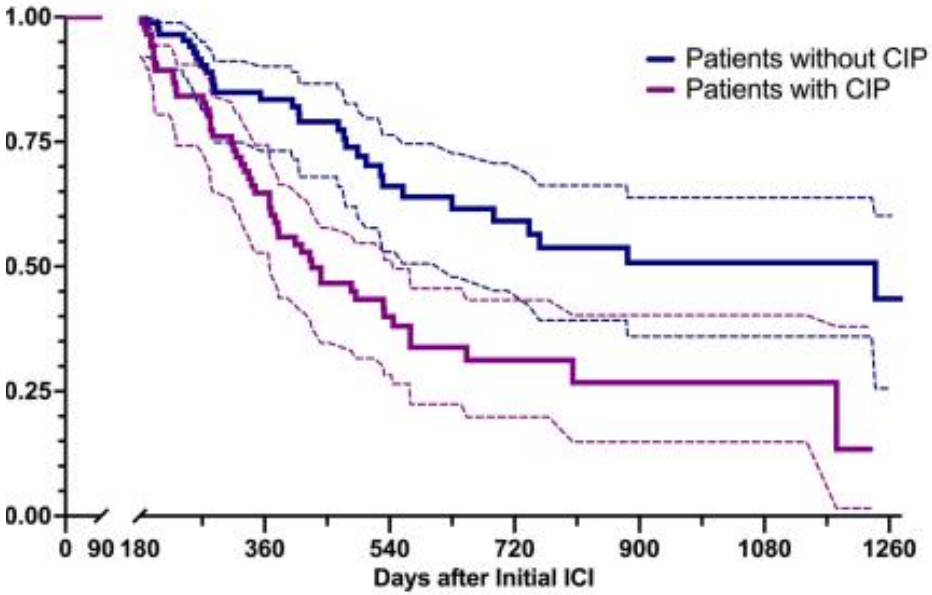
	Lung cancer N = 13,113	RCC N = 1,845	GI Cancers N = 4,813	Melanoma N = 2,427
ICI attributable risk (95% CI)	2.49% (1.50 – 3.47%)	2.98% (1.03 – 4.93%)	1.64% (0.38 – 2.90%)	-0.25% (-1.86 – 1.36%)

Incidence of pneumonitis/pneumonia in the first year

J Immunother Cancer. 2022 Jun;10(6):e004670.

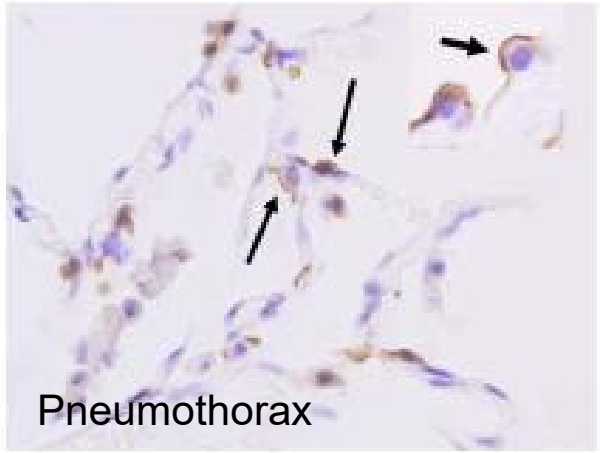
Real world incidence of ICI-related pneumonitis in lung cancer

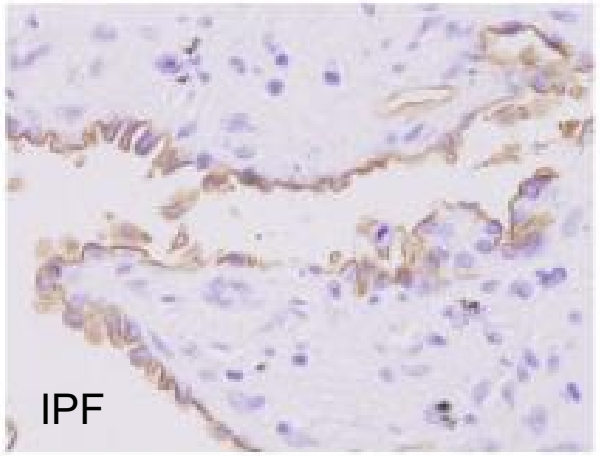


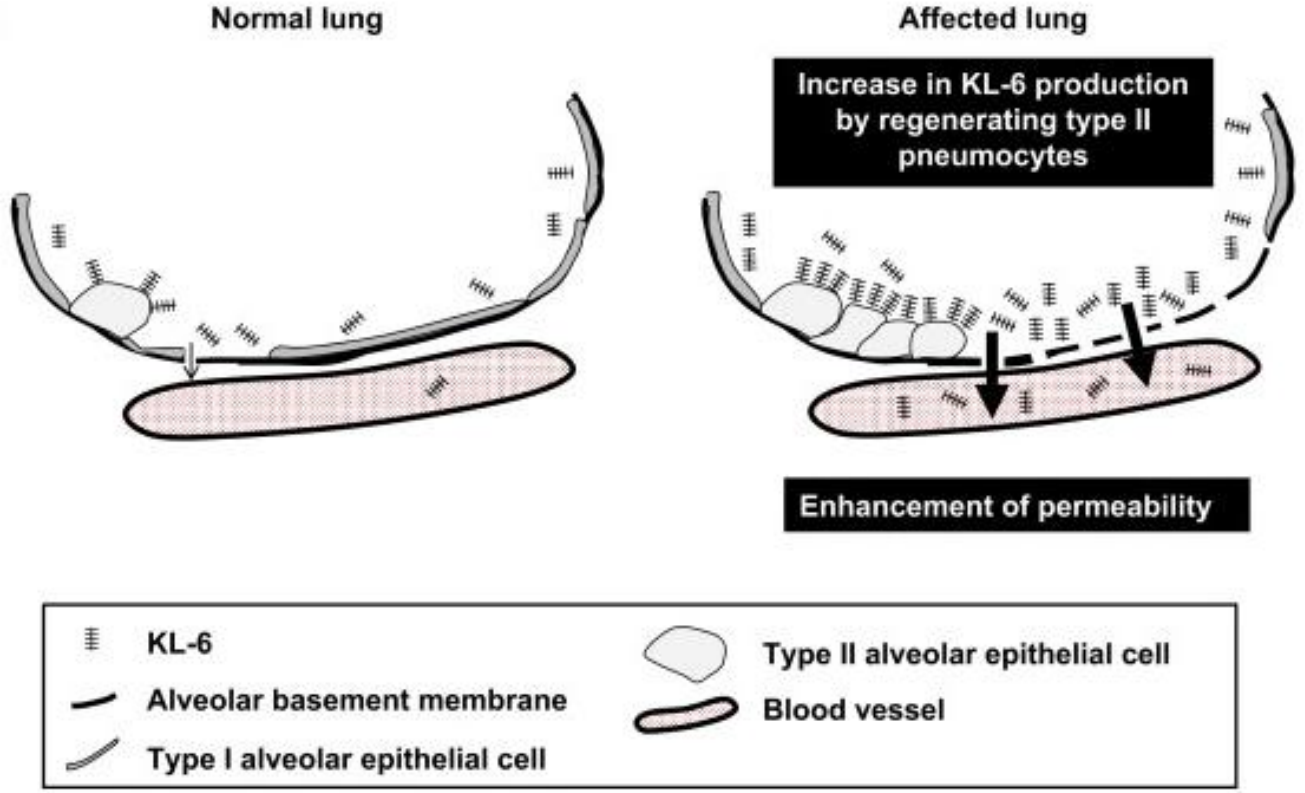


J Immunother Cancer. 2022 Jun;10(6):e004670.

KL-6 (



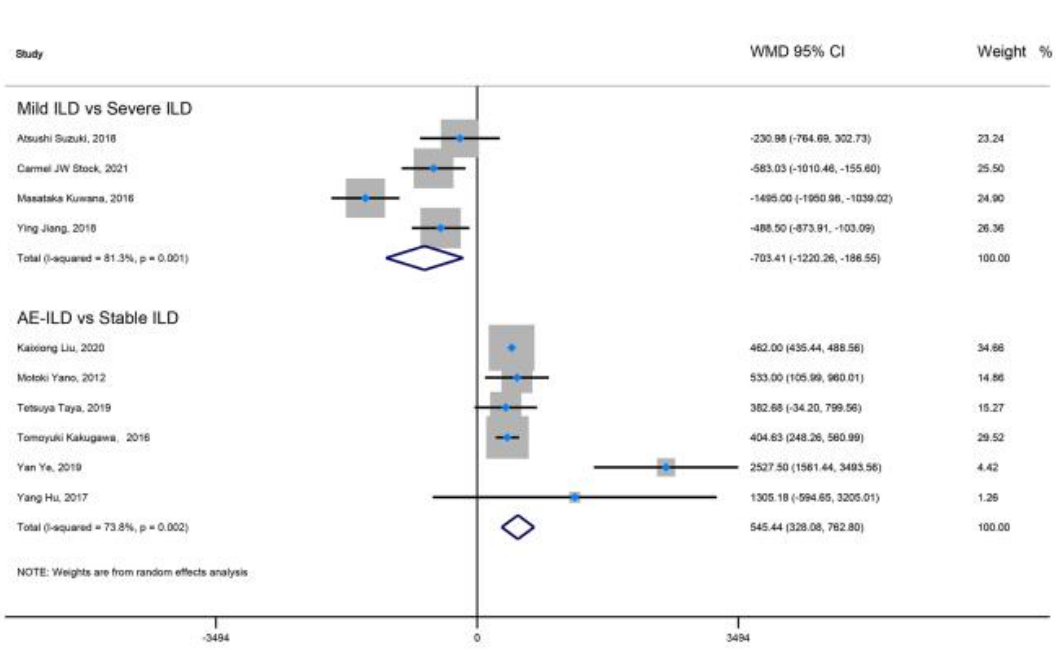


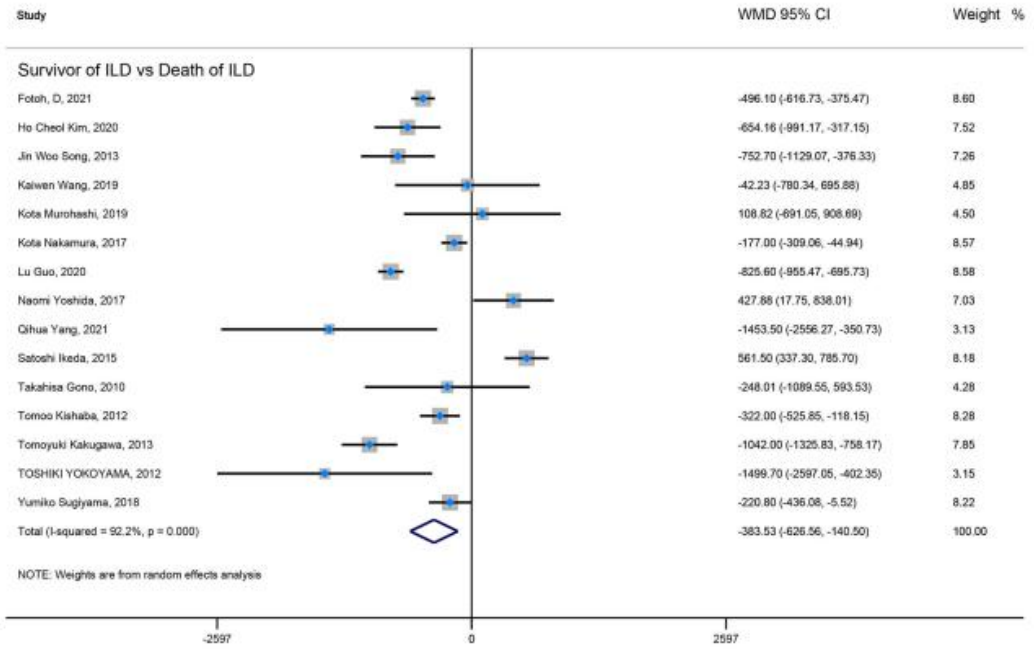


KL-6 expression on the surface of type II pneumocytes

Respir Investig, 2012. 50(1): p. 3-13

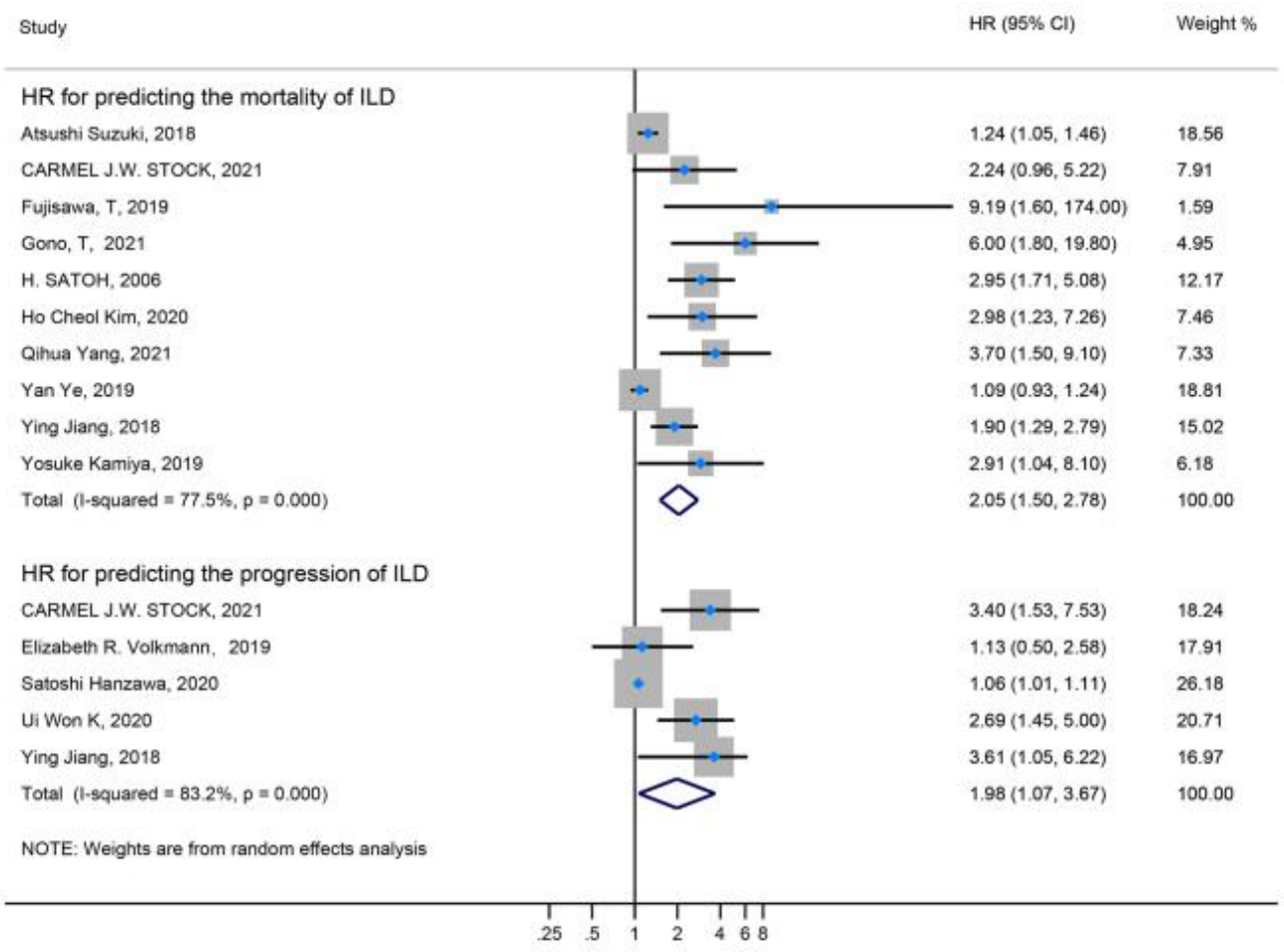
Comparison of serum KL-6 level





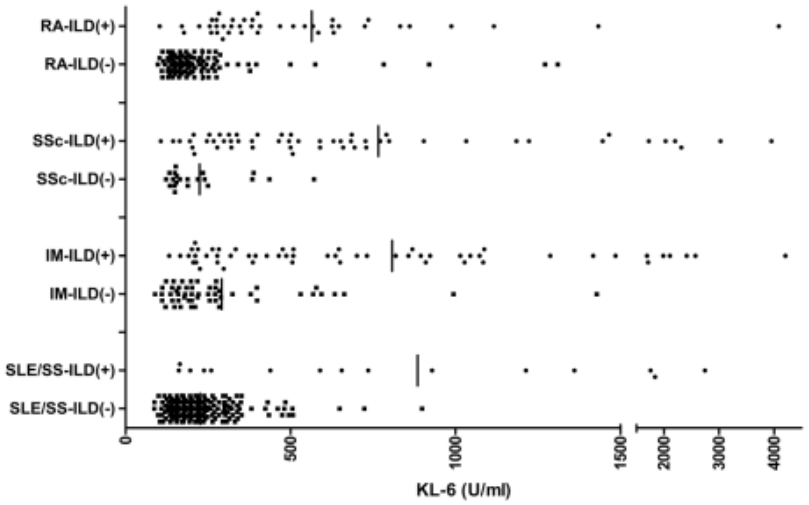
Front Immunol, 2021. 12: p. 745233.

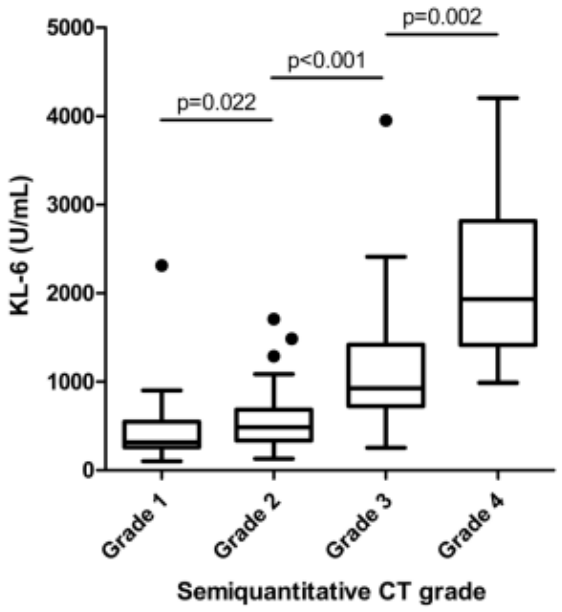
Serum KL-6 predicting prognosis of ILD

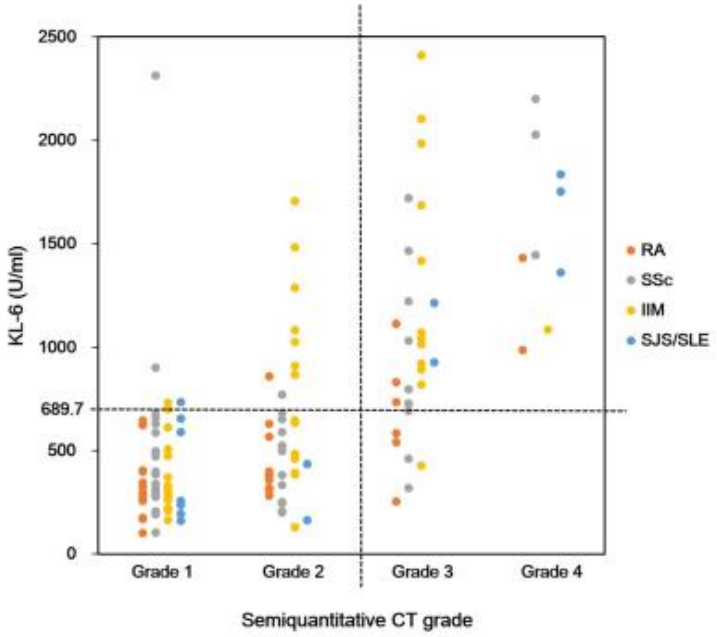


Front Immunol, 2021. 12: p. 745233.

Comparison of serum KL-6 level

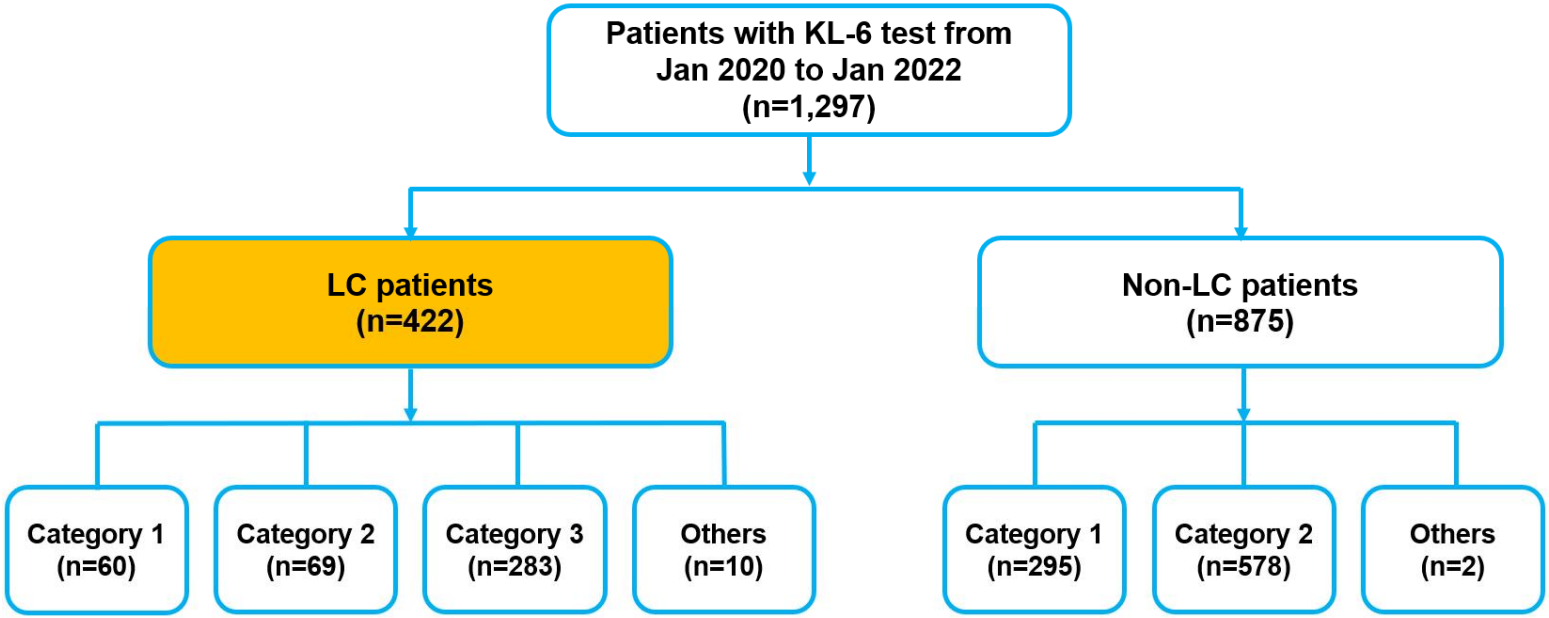






Arthritis Research & Therapy (2019) 21:58

Data collection



- Category 1 : For the differentiation between pneumonia and ILD
- Category 2 : For diagnosis and assessing the severity of suspicious ILD
- Category 3 : For evaluation of the baseline level before initiation of cancer treatment (immunotherapy or radiotherapy)

Baseline characteristics

Characteristics, n (%)	Total (*n*=1,297)	Non-LC (*n*=875)	LC (*n*=422)	*P*-value
Age	71.0 (69.5-70.7)	73.0 (69.8-71.4)	70.0 (68.2-69.8)	0.005
Sex				<0.001
Female	321 (24.7)	273 (31.2)	48 (11.4)	
Male	976 (75.3)	602 (68.8)	374 (88.6)	
Smoking				<0.001
Never smoker	544 (41.9)	482 (55.1%)	62 (14.7)	
Current smoker	279 (21.5)	126 (14.4%)	153 (36.3)	
Ex-smoker	474 (36.5)	267 (30.5%)	207 (49.0)	
Comorbidity				
ILD	718 (55.4)	674 (77.0)	44 (10.4)	<0.001
COPD	433 (33.4)	219 (25.0)	214 (50.7)	<0.001
ECOG PS score				<0.001
0	220 (17.0)	205 (23.4)	15 (3.5)	
1	690 (53.2)	392 (44.8)	298 (70.6)	
2	175 (13.5)	78 (8.9)	97 (23.0)	
3	93 (7.1)	85 (9.7)	8 (1.9)	
4	119 (9.2)	115 (13.1)	4 (1.0)	

Characteristics, n (%)	Total (*n*=1,297)	Non-LC (*n*=875)	LC (*n*=422)	*P*-value
Pulmonary function				
FEV1, L	2.16 (2.10-2.19)	2.30 (2.15-2.28)	1.80 (1.62-2.10)	0.008
FEV1, %	76.0 (74.79-77.74)	80.0 (78.87-82.82)	69.68 (58.68-73.55)	<0.001
FVC, L	2.89 (2.85-2.97)	2.87 (2.79-2.96)	2.77 (2.46-2.96)	0.085
FVC, %	73.06 (71.32-73.74)	75.0 (71.89-75.35)	66.41 (60.86-71.36)	0.132
DLCO, %	65.0 (64.61-67.57)	62.0 (62.03-66.25)	73.88 (65.27-79.37)	0.005
Serum CEA	6.60 (8.64-73.40)		6.60 (8.64-73.40)	
Serum CRP	7.76 (7.97-13.80)	8.71 (8.97-11.08)	6.83 (6.40-13.84)	0.602
Serum PCT	0.18 (0.23-0.47)	0.20 (1.05-3.39)	0.21 (0.22-0.51)	0.003

Baseline characteristics

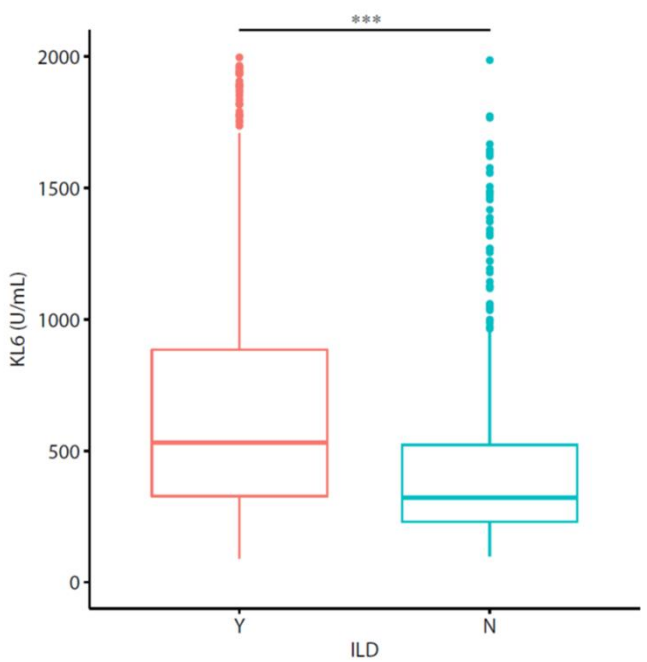
Characteristics, n (%)	Total (*n*=1,297)	Non-LC (*n*=875)	LC (*n*=422)	*P*-value
Initial diagnosis				-
Lung cancer	-	-	422 (100.0)	
ILD	-	670 (76.6)	-	
Pneumonia	-	154 (17.6)	-	
Others	-	51 (5.8)	-	
Histology				-
ADC	-	-	156 (37.0)	
SQC	-	-	174 (41.2)	
NSCLC, NOS	-	-	17 (4.0)	
SCLC	-	-	75 (17.8)	
Stage (TNM 8th)				-
Early (I-III, LD)	-	-	178 (42.2)	
Advanced (IV, ED)	-	-	244 (57.8)	
Driver mutation				-
EGFR (*n*=191)	-	-	34 (17.8)	
ALK (*n*=186)	-	-	14 (7.5)	
ROS1 (*n*=166)	-	-	2 (1.2)	

Characteristics, n (%)	Total (*n*=1,297)	Non-LC (*n*=875)	LC (*n*=422)	*P*-value
PD-L1 IHC (SP263) (*n*=312)				-
TPS <1%	-	-	120 (38.6)	
TPS ≥1%, <50%	-	-	90 (28.8)	
TPS ≥50%	-	-	102 (32.6)	
PD-L1 IHC (22C3) (*n*=157)				-
TPS <1%	-	-	39 (24.8)	
TPS ≥1%, <50%	-	-	56 (35.7)	
TPS ≥50%	-	-	62 (39.5)	
Initial therapy of LC				-
Operation	-	-	59 (14.0)	
CCRT	-	-	162 (38.4)	
Systemic chemotherapy	-	-	180 (42.6)	
SBRT or RT alone	-	-	12 (2.8)	
Palliative treatment	-	-	3 (0.7)	
Supportive care	-	-	6 (1.4)	

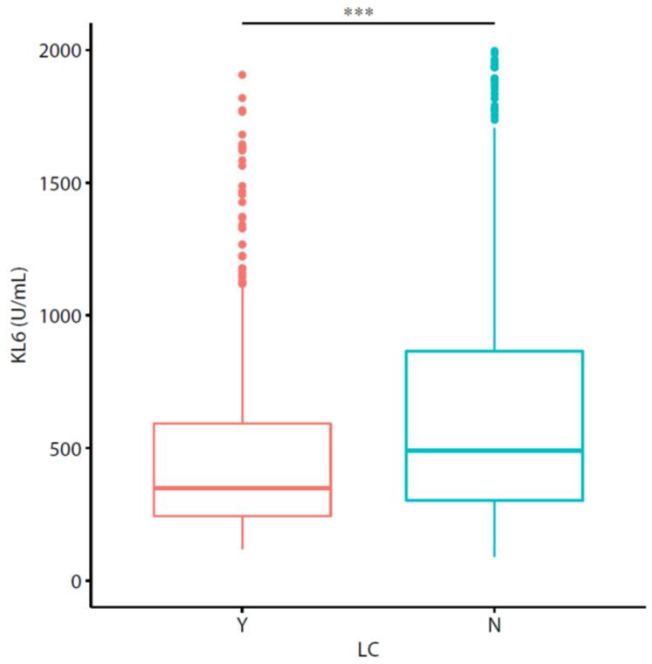
Baseline characteristics

Characteristics, n (%)	Total (*n*=1,297)	Non-LC (*n*=875)	LC (*n*=422)	*P*-value
IrAE (*n*=270)			53 (19.6)	
KL-6 test category				<0.001
1	355 (27.4)	295 (33.7)	60 (14.2)	
2	647 (49.9)	578 (66.1)	69 (16.3)	
3	283 (21.8)	0 (0.0)	283 (67.1)	
Unknown	12 (0.9)	2 (0.2)	10 (2.4)	
ILD type	864 (66.6)	670 (76.6)	194 (46.0)	<0.001
Drug-induced	59 (6.8)	9 (1.3)	50 (11.8)	
Radiation-induced	120 (13.9)	1 (0.2)	119 (28.2)	
AE of idiopathic ILD	685 (79.3)	660 (98.5)	25 (5.9)	
Survival				0.001
Live	730 (56.3)	486 (55.5)	244 (57.8)	
Death	172 (13.3)	99 (11.3)	73 (17.3)	
F/U loss or Hopeless discharge	395 (30.4)	290 (33.2)	105 (24.9)	

Comparison of serum KL-6 in all patients

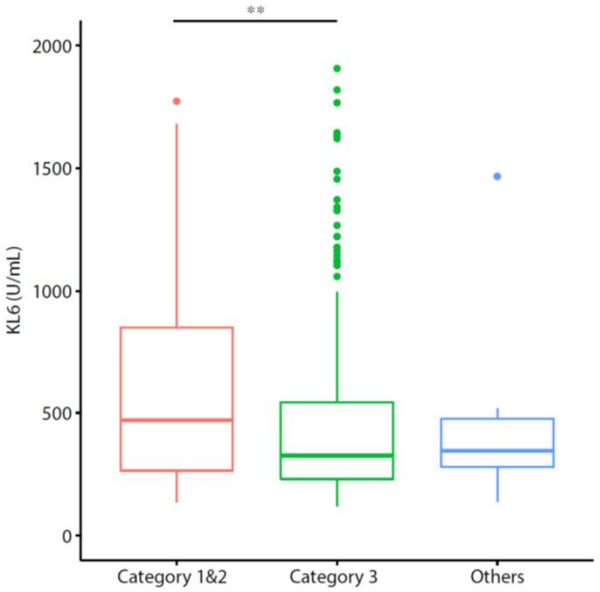


ILD vs No ILD
600.7 vs 326.7 (U/mL)
(*p<0.001*)

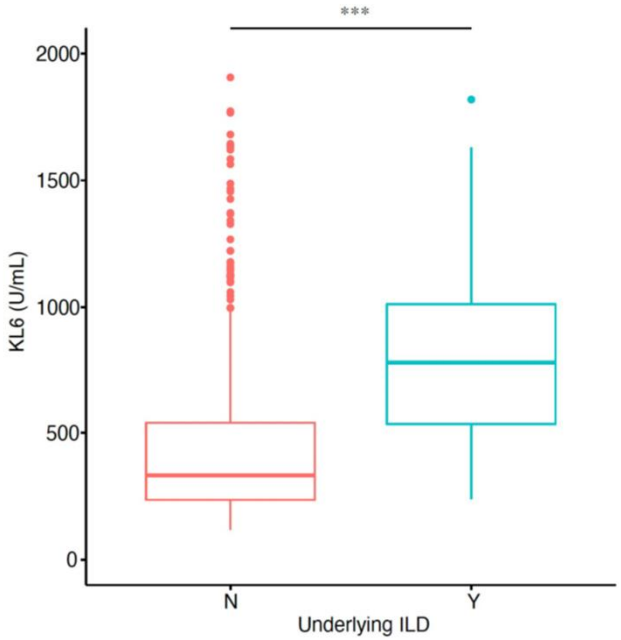


LC vs No LC
369.3 vs 556.5 (U/mL)
(*p<0.001*)

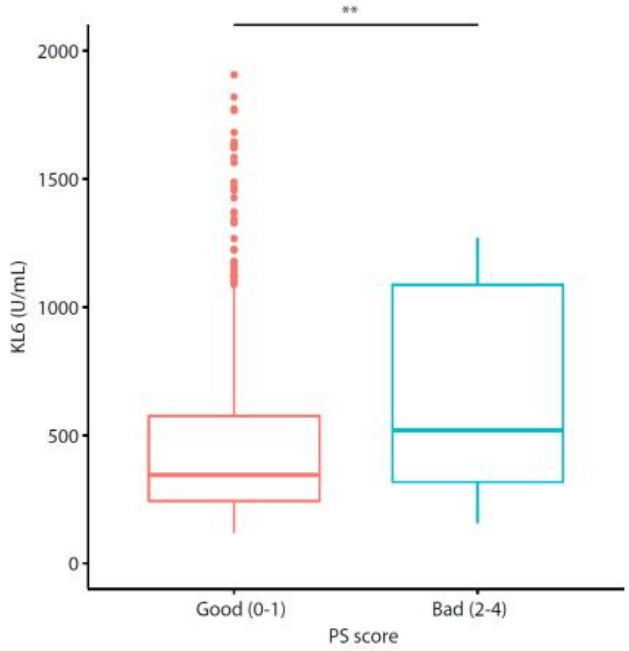
Comparison of serum KL-6 in lung cancer



Cat 1&2 vs Cat 3
492.2 vs 333.0 (U/mL)
(*p=0.019*)

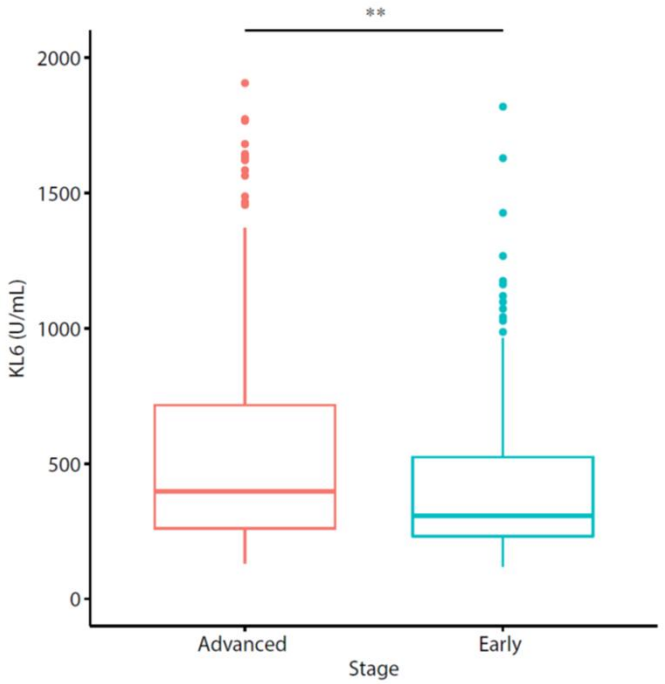


No Und ILD vs Und ILD
335.8 vs 821.3 (U/mL)
(*p<0.001*)

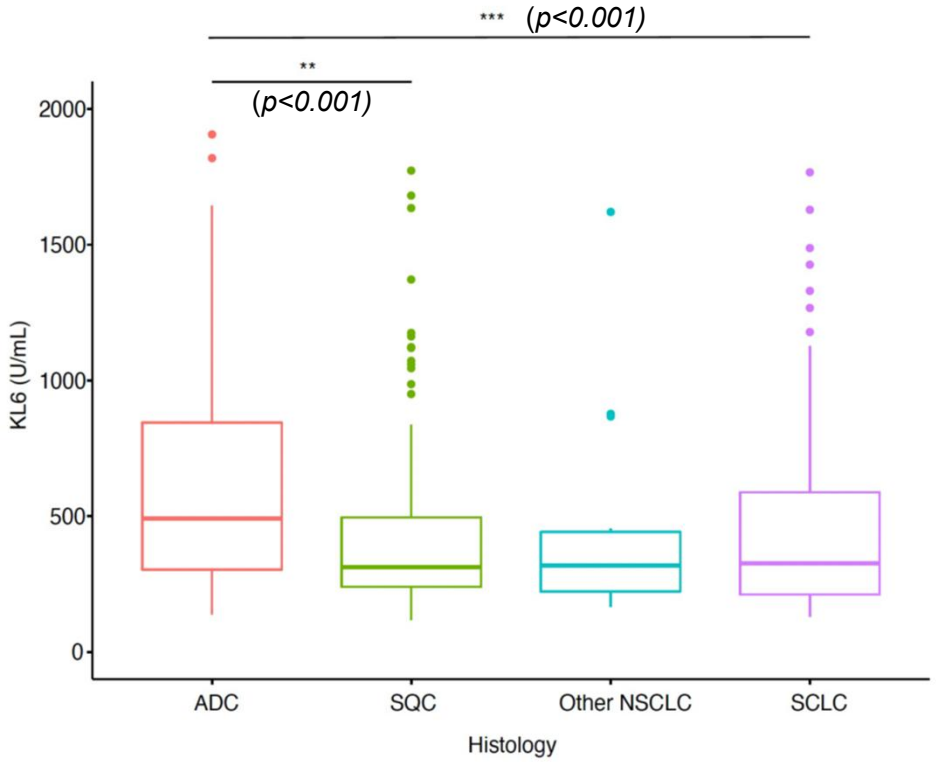


Good PS vs Bad PS
330.7 vs 506.8 (U/mL)
(*p<0.001*)

Comparison of serum KL-6 in lung cancer

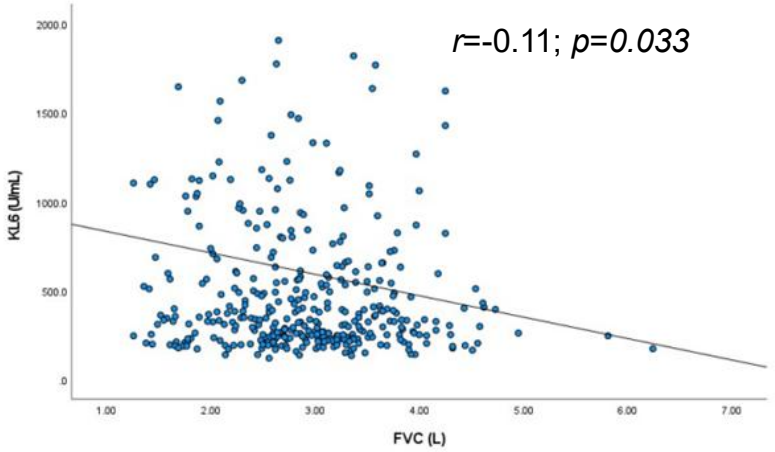


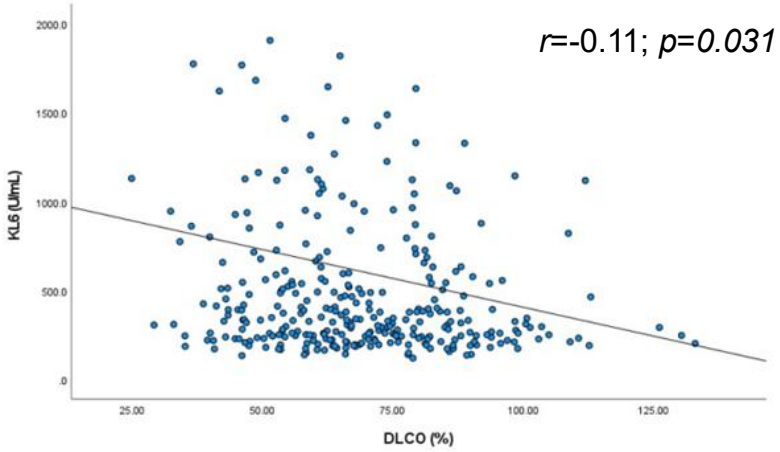
Advanced stage vs Early stage
409.1 vs 321.0 (U/mL)
(*p=0.007*)

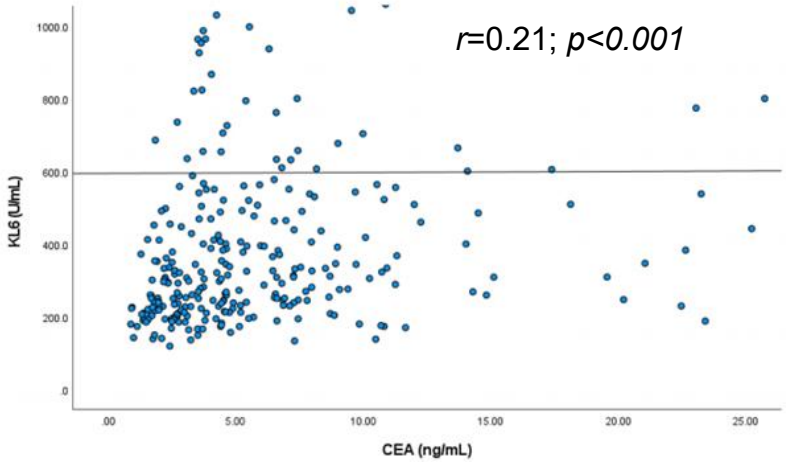


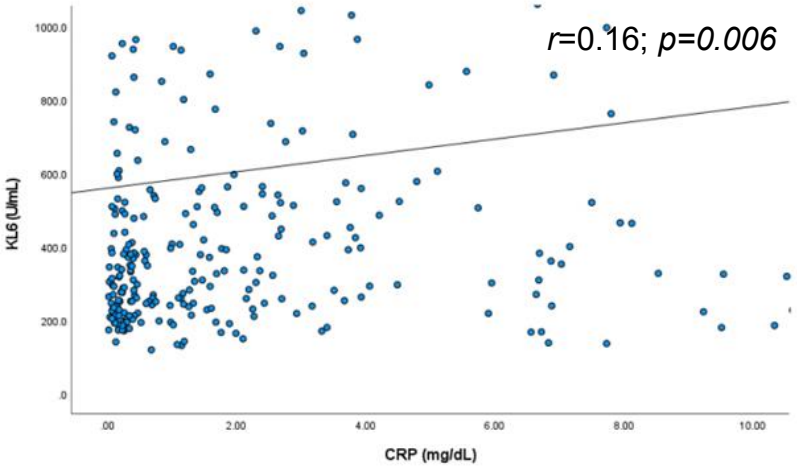
ADC vs SQC vs SCLC
519.4 vs 317.8 vs 322.4 (U/mL)

Comparison of serum KL-6 in lung cancer

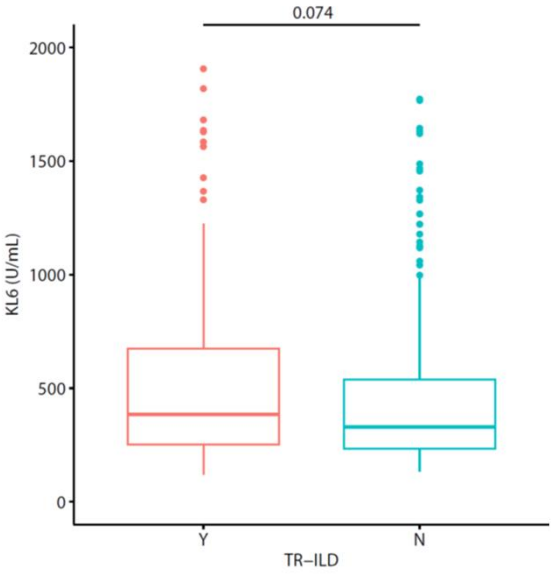




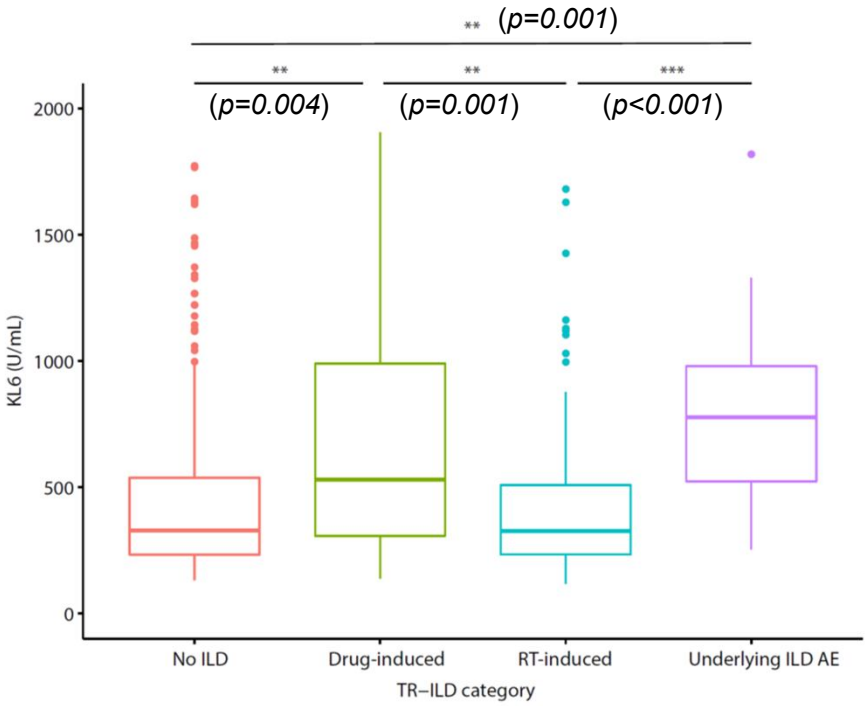




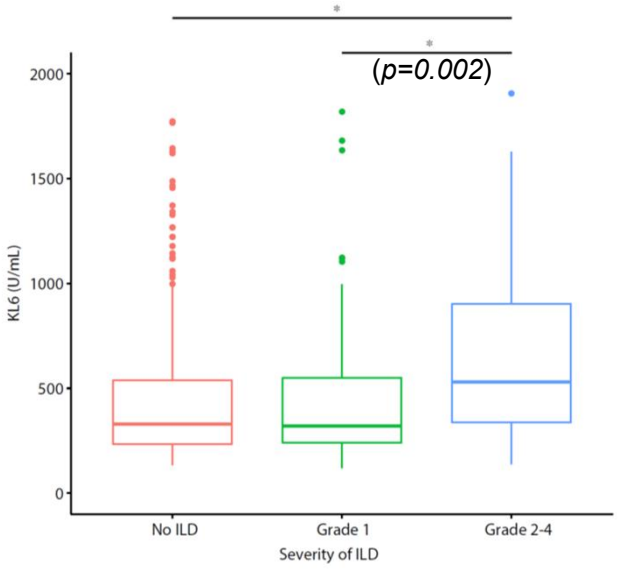
Comparison of serum KL-6 in lung cancer



TR-ILD vs No TR-ILD
394.4 vs 333.5 (U/mL)
(*p=0.079*)

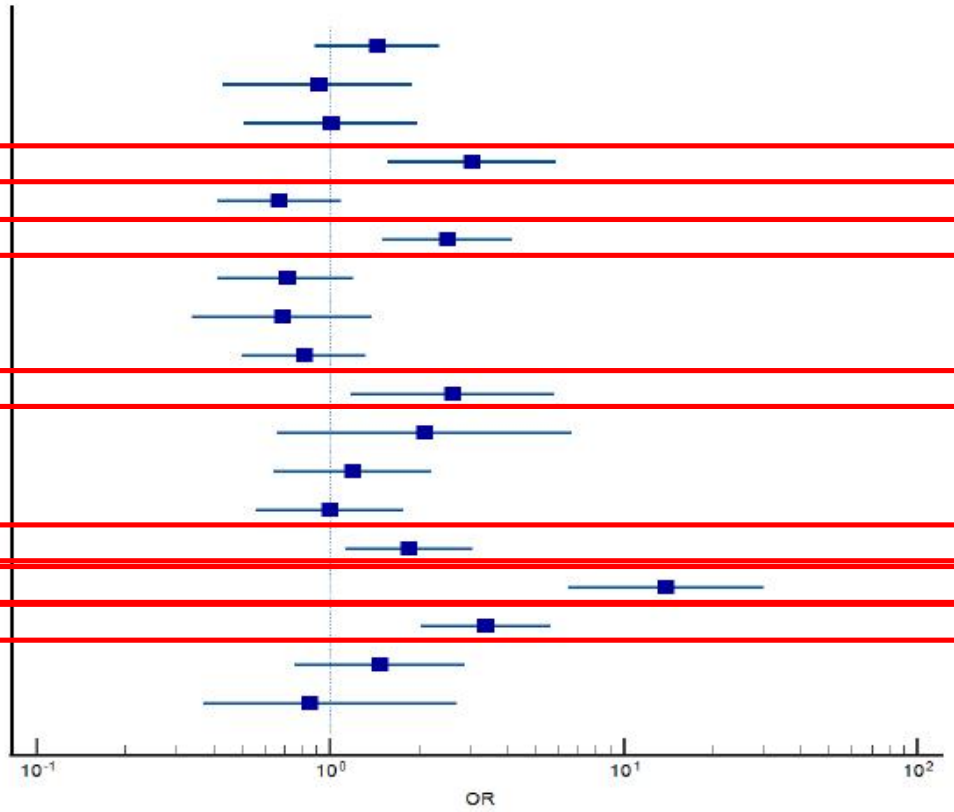


No TR-ILD vs DILD vs Rp vs ILD AE
333.5 vs 575.9 vs 330.7 vs 937.1(U/mL)



No TR-ILD vs Gr 1 vs Gr 2-4
333.5 vs 323.5 vs 561.1(U/mL)

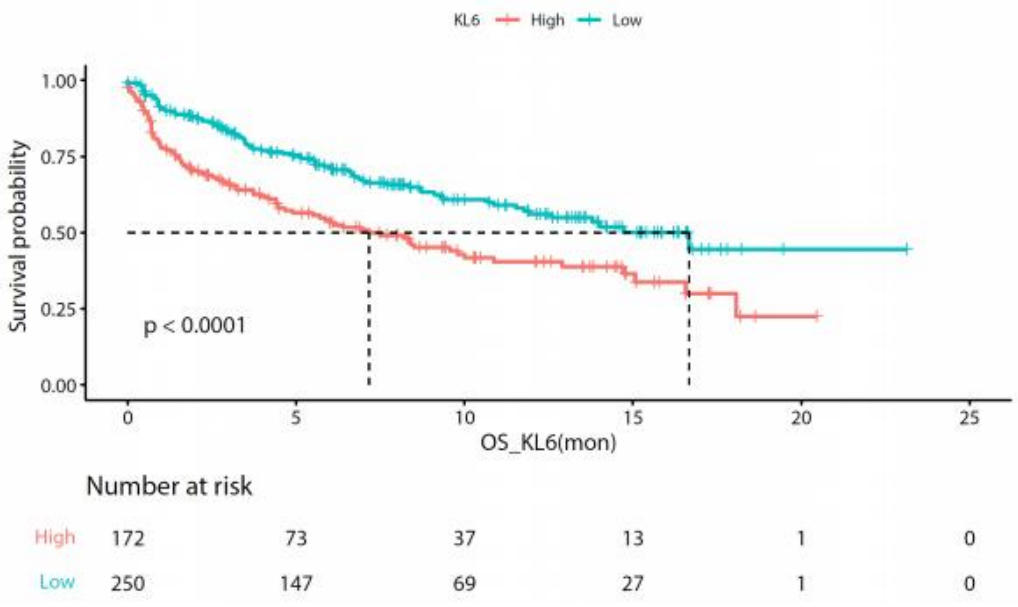
Risk factor for developing severe TR-ILD in lung cancer



	OR	Low	High	*P*-value
Age >=70 [vs.<70]	1.45	0.89	2.35	0.133
Male [vs. Female]	0.91	0.43	1.90	0.794
Smoker [vs. Never smoker]	1.01	0.51	1.99	0.987
Underlying ILD, Yes [vs. No]	3.03	1.56	5.88	0.001
Underlying COPD, Yes [vs. No]	0.67	0.41	1.09	0.106
ECOG PS 2-4 [vs. 0-1]	2.50	1.51	4.16	<0.001
SQC [vs. Non-SQC]	0.71	0.41	1.20	0.353
SCLC [vs. Non-SQC]	0.69	0.34	1.38	0.353
Stage IV or ED [vs. I-III or LD]	0.81	0.50	1.32	0.403
EGFR, Yes [vs. No]	2.62	1.18	5.82	0.018
ALK, Yes [vs. No]	2.10	0.66	6.65	0.208
PD-L1 >=1% [vs. <1%]	1.19	0.64	2.21	0.582
PD-L1 >=50% [vs. <50%]	1.00	0.56	1.77	0.997
Prior RT or ICI within 90d, Yes [vs. No]	1.86	1.13	3.06	0.014
IrAE, Yes [vs. No]	13.96	6.51	29.97	<0.001
Serum KL-6, High [vs. Low]	3.39	2.05	5.62	<0.001
CRP, High [vs. Normal]	1.47	0.76	2.87	0.257
PCT, High [vs. Normal]	0.85	0.37	2.72	0.788

Serum KL-6 as prognostic factor in lung cancer

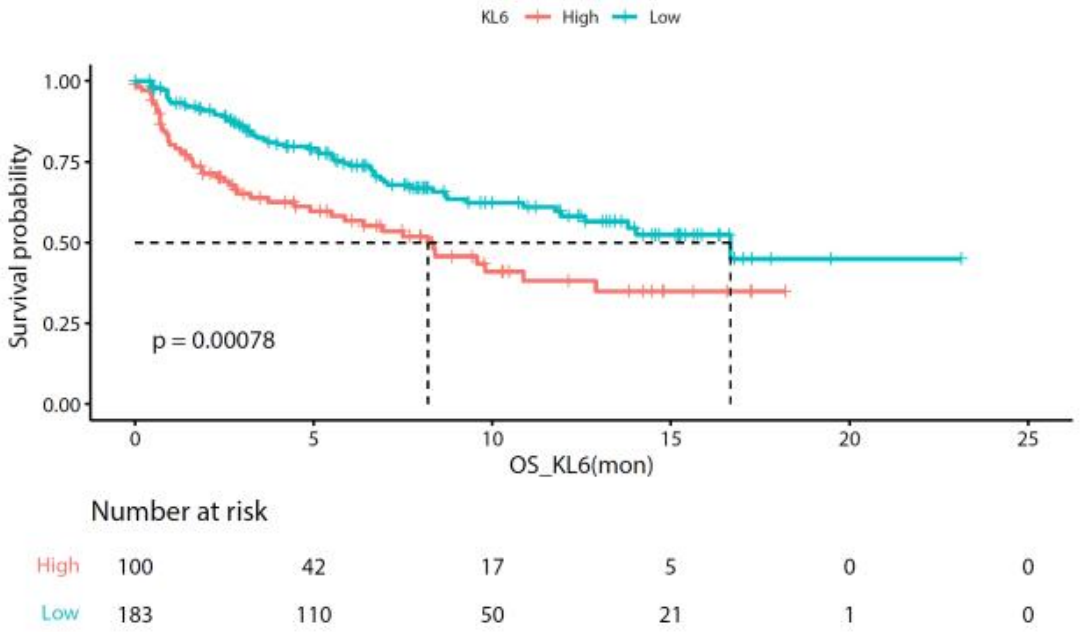
Overall



	No. of Events/ Total No. of patients (%)	Median OS (95% CI), Months
High KL-6 (≥ 449.9U/mL)	88/250 (35.2)	16.4 (11.2-21.7)
Low KL-6 (< 449.9U/mL)	90/172 (52.3)	7.1 (4.2-9-9)

HR 1.78 (95% CI : 1.33-2.39, *p<0.001*)

Category 3



	No. of Events/ Total No. of patients (%)	Median OS (95% CI), Months
High KL-6 (≥ 449.9U/mL)	48/100 (48)	16.4 (10.8-22.0)
Low KL-6 (< 449.9U/mL)	60/183 (32.8)	8.1 (5.1-11.1)

HR 1.90 (95% CI : 1.30-2.78, *p<0.001*)

Case 1. PMW 75/M SQC,RLL IIIC(T3N3M0)

1-CCRT(TC)6 (21.6.8~7.19)
Imfinzi (21.8.17~9.30)
* GKS (21.12.7)
2-GP (21.12.21~22.3.4)
* WBRT (22.6.13~6.24)

CCRT

Imfinzi

Imfinzi hold

Imfinzi restart

Imfinzi hold

405

216

1012

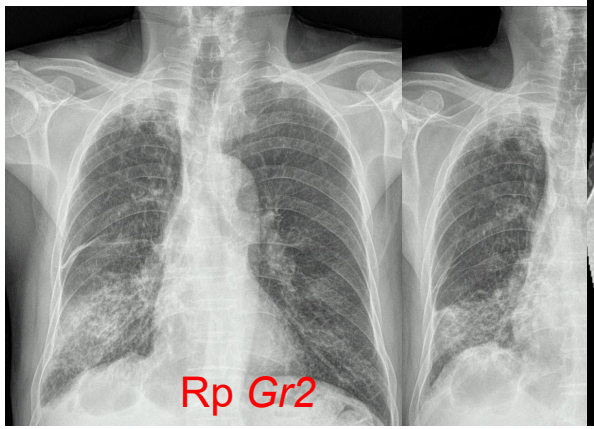
678

21.8.17

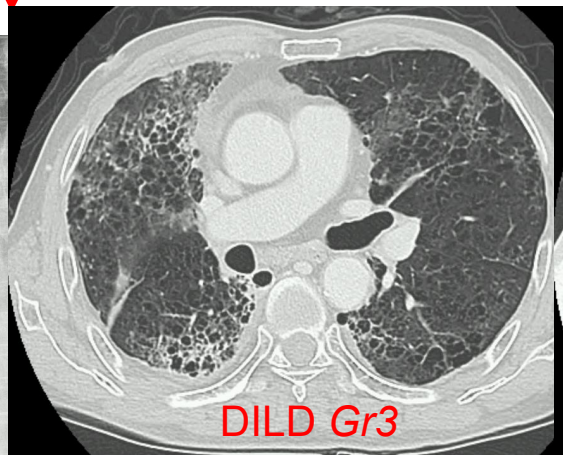
21.9.30

21.10.15

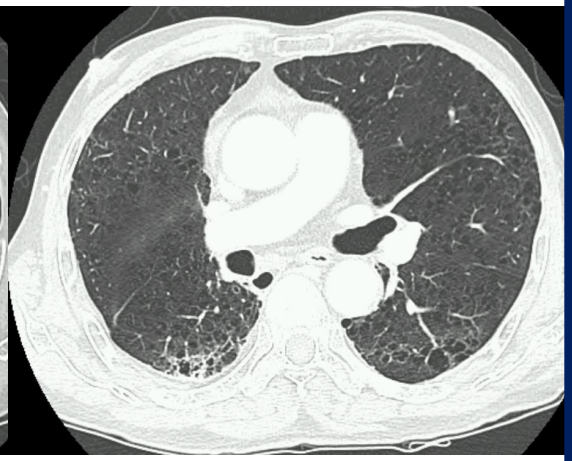
21.12.14



Rp *Gr2*

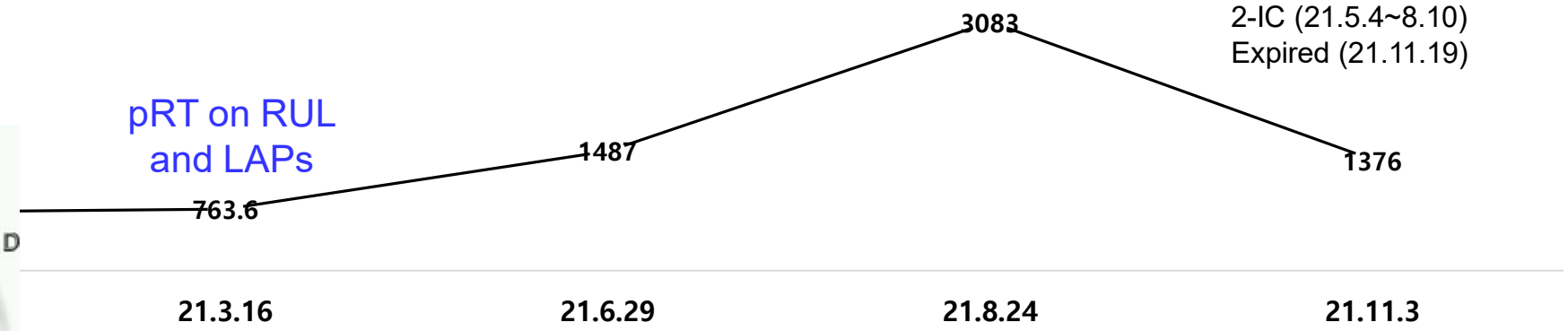


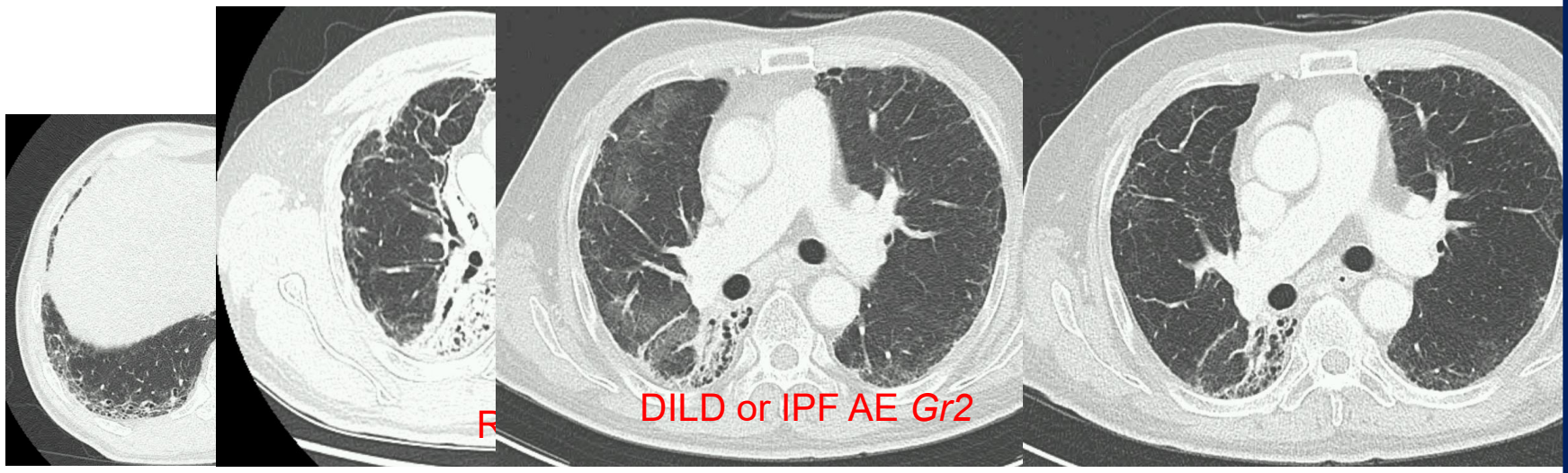
DILD *Gr3*



Case 2. LEJ 62/F SCLC,RUL ED (T4N3M1b : Rt cerebellum)

1-ACE (20.10.28~12.31)
mAtz (21.1.19~3.2)
pRT on RUL with LAPs (21.3.30~4.26)
2-IC (21.5.4~8.10)
Expired (21.11.19)





Summary

- Serum KL-6 can be considered when an event of ILD was suspected or before treatment of lung cancer started.
- High serum KL-6 level was an independent risk factor of severe TR-ILD.
- Patients with high serum KL-6 level had worse overall survival than those with low serum KL-6 level.

  The trend was same regardless of the timing of the test.
- Serum KL-6 can be a potential biomarker for the diagnosis, management and prognosis of TR-ILD in lung cancer.