Supplementary

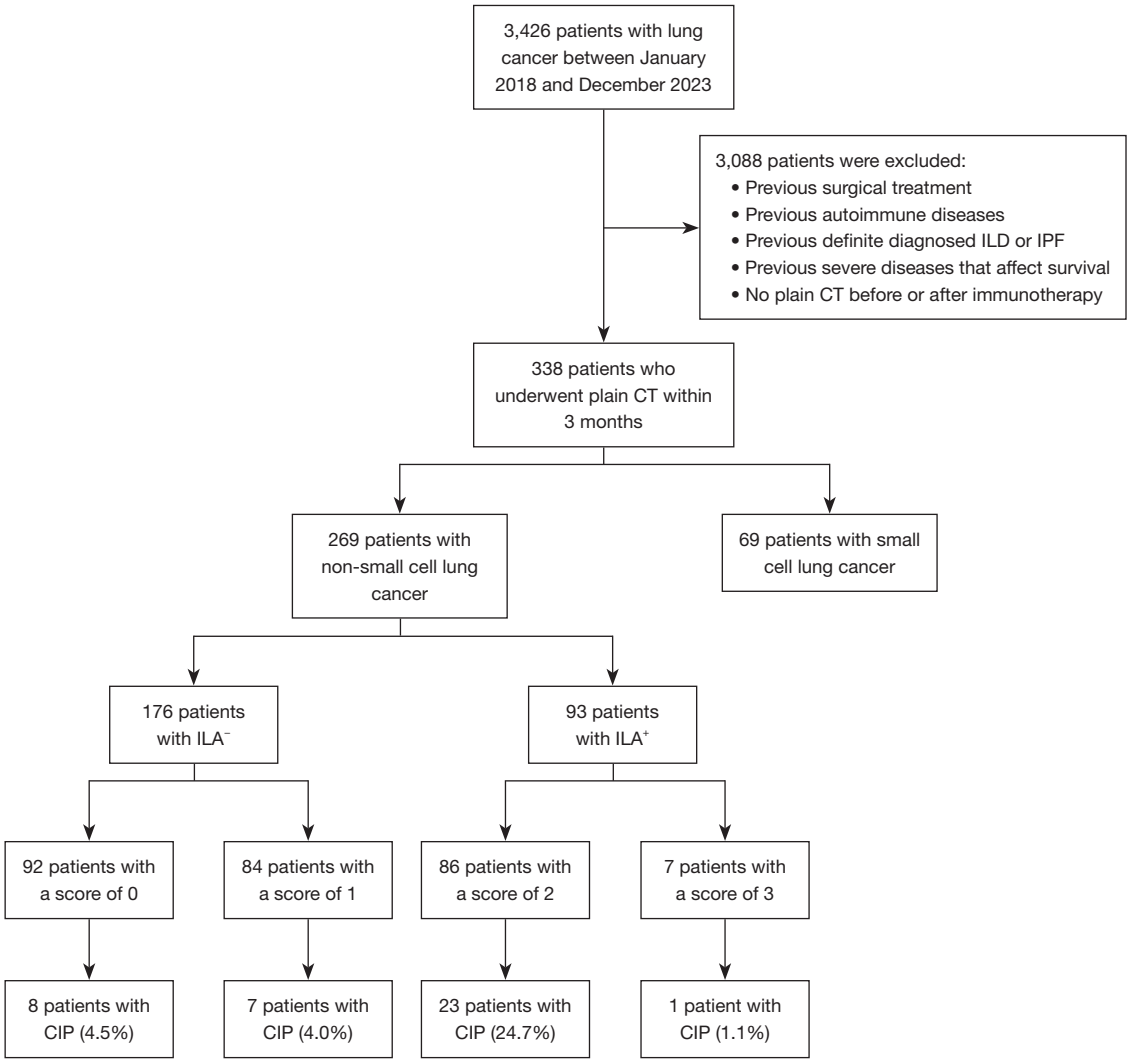

Figure S1 Flowchart of patient selection. 0 points, no ILA; 1 point, focal or unilateral GGA, focal or unilateral reticulation, or patchy GGA (affecting less than 5% of the lung); 2 points, non-dependent GGA affecting more than 5% of any lung zone, non-dependent reticular abnormality, diffuse centrilobular nodularity with GGA, honeycomb structure, traction bronchiectasis, non-emphysematous cysts, or architectural distortion; 3 points, bilateral fibrosis in multiple lobes associated with honeycomb structure or traction bronchiectasis with a subpleural distribution. CIP, checkpoint inhibitor-related pneumonitis; CT, computed tomography; GGA, ground glass attenuation; ILA, interstitial lung abnormality; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

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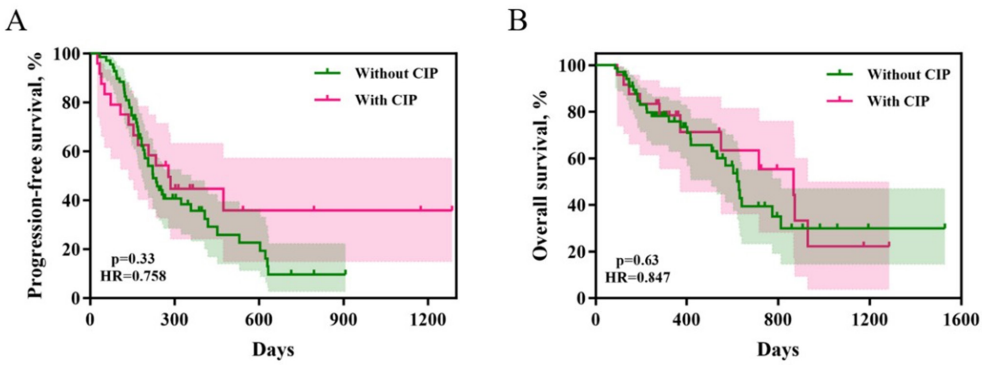

Figure S2 Analysis of PFS and OS in relation to the development of CIP in patients with ILA. (A) Kaplan-Meier analysis of PFS in patients with ILA who developed CIP or not. (B) Kaplan-Meier analysis of OS in patients with ILA who developed CIP or not. CIP, checkpoint inhibitor-related pneumonitis; HR, hazard ratio; ILA, interstitial lung abnormality; OS, overall survival; PFS, progression-free survival.

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Table S1 Baseline data and univariate analysis by ILA status

Variables	Total	Group 1 (without ILA)	Group 2 (with ILA)	P value
Patient	269	176	93	–
Age (years)				<0.001
<65	122 (45.35)	95 (53.98)	27 (29.03)	
≥65	147 (54.65)	81 (46.02)	66 (70.97)	
Sex				0.10
Male	223 (82.90)	141 (80.11)	82 (88.17)	
Female	46 (17.10)	35 (19.89)	11 (11.83)	
Smoking history				0.41
Never	84 (31.23)	52 (29.55)	32 (34.41)	
Former/current	185 (68.77)	124 (70.45)	61 (65.59)	
ECOG PS				0.27
0–1	234 (86.99)	156 (88.64)	78 (83.87)	
≥2	35 (13.01)	20 (11.36)	15 (16.13)	
BMI (kg/m^2)	23.21 (21.58, 24.73)	23.27 (22.17, 25.00)	23.18 (20.76, 24.29)	0.02
Co-morbidities				
GERD	3 (1.12)	2 (1.14)	1 (1.08)	0.96
COPD	39 (14.50)	21 (11.93)	18 (19.35)	0.10
Histology				>0.99
LUSC	136 (50.56)	89 (50.57)	47 (50.54)	
LUAD	124 (46.10)	81 (46.02)	43 (46.24)	
Other NSCLC	9 (3.35)	6 (3.41)	3 (3.23)	
Clinical stage				0.18
III	122 (45.35)	85 (48.30)	37 (39.78)	
IV	147 (54.65)	91 (51.70)	56 (60.22)	
PD-L1 tumor proportion score				0.87
≥50	16 (5.95)	12 (6.82)	4 (4.30)	
1–49	29 (10.78)	19 (10.80)	10 (10.75)	
<1	39 (14.50)	25 (14.20)	14 (15.05)	
Not tested	185 (68.77)	120 (68.18)	65 (69.89)	
Prior chest radiation therapy	57 (21.19)	42 (23.86)	15 (16.13)	0.14
Laboratory examination				
Cyfra21-1 (ng/mL)	8.31 (4.02, 14.29)	7.64 (3.81, 14.29)	10.11 (4.56, 15.00)	0.09
NSE (μg/L)	13.60 (11.36, 17.94)	13.44 (11.21, 17.57)	13.90 (11.54, 18.62)	0.40
CEA (μg/L)	4.00 (2.06, 15.67)	3.85 (1.89, 16.59)	4.29 (2.47, 12.85)	0.42
CA125 (U/mL)	48.40 (17.73, 95.13)	37.80 (14.23, 95.13)	73.90 (27.20, 95.13)	0.003
FIB (g/L)	4.29 (3.31, 5.10)	4.16 (3.23, 5.03)	4.45 (3.63, 5.27)	0.16
IL-6 (ng/L)	18.32 (10.14, 18.32)	18.32 (9.92, 18.32)	18.32 (10.49, 18.32)	0.88
LDH (U/L)	208 (167, 252)	209 (168, 248.50)	206 (162.50, 263)	0.95
ALB (g/L)	36.80 (34.50, 39.25)	36.95 (34.75, 39.08)	36.60 (33.75, 39.60)	0.60
NE (×10^9/L)	4.14 (3.19, 5.43)	3.98 (3.28, 5.38)	4.59 (3.00, 6.01)	0.045
Lym (×10^9/L)	0.56±0.30	1.57±0.58	1.42±0.42	0.46
Mono (×10^9/L)	0.48 (0.39, 0.62)	0.52 (0.39, 0.65)	0.47 (0.34, 0.51)	0.60
Eos (×10^9/L)	0.15 (0.10, 0.21)	0.17 (0.09, 0.25)	0.14 (0.10, 0.18)	0.19
NLR	2.79 (2.18, 4.11)	2.65 (2.21, 4.05)	3.27 (2.15, 4.36)	0.03
MLR	0.35 (0.24, 0.47)	0.35 (0.24, 0.55)	0.32 (0.22, 0.41)	0.38
Autoantibody				0.68
Positive	91 (33.83)	58 (32.95)	33 (35.48)	
Not tested or negative	178 (66.17)	118 (67.05)	60 (64.52)	

Data are presented as n, n (%), median (interquartile), or mean ± SD. ALB, albumin; BMI, body mass index; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; ECOG PS, eastern cooperative oncology group performance status; Eos, eosinophil; FIB, fibrinogen; GERD, gastroesophageal reflux disease; ILA, interstitial lung abnormality; IL-6, interleukin-6; LDH, lactate dehydrogenase; LUAD, adenocarcinoma; LUSC, squamous cell carcinoma; Lym, lymphocyte; MLR, monocyte-to-lymphocyte ratio; Mono, monocyte; NE, neutrophil; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron-specific enolase; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; SD, standard deviation.

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Table S2 Baseline data and univariate analysis by CIP status in patients with ILA

Variables	Total	Group 1 (without CIP)	Group 2 (with CIP)	P value
Patient	93	69	24	–
Age (years)				0.11
<65	27 (29.03)	17 (24.64)	10 (41.67)	
≥65	66 (70.97)	52 (75.36)	14 (58.33)	
Sex				0.91
Male	82 (88.17)	61 (88.41)	21 (87.50)	
Female	11 (11.83)	8 (11.59)	3 (12.50)	
Smoking history				0.90
Never	32 (34.41)	24 (34.78)	8 (33.33)	
Former/current	61 (65.59)	45 (65.22)	16 (66.67)	
ECOG PS				0.58
0–1	78 (83.87)	57 (82.61)	21 (87.50)	
≥2	15 (16.13)	12 (17.39)	3 (12.50)	
BMI (kg/m^2)	22.41 (20.20, 24.51)	22.06 (20.06, 24.22)	23.89 (20.63, 26.60)	0.050
Co-morbidities				
GERD	1 (1.08)	1 (1.45)	0 (0.00)	0.55
COPD	18 (19.35)	15 (21.74)	3 (12.50)	0.32
Histology				0.85
LUSC	47 (50.54)	36 (52.17)	11 (45.83)	
LUAD	43 (46.24)	31 (44.93)	12 (50.00)	
Other NSCLC	3 (3.23)	2 (2.90)	1 (4.17)	
Clinical stage				0.24
III	37 (39.78)	25 (36.23)	12 (50.00)	
IV	56 (60.22)	44 (63.77)	12 (50.00)	
PD-L1 tumor proportion score				0.63
≥50	4 (4.30)	4 (5.80)	0 (0.00)	
1–49	10 (10.75)	7 (10.14)	3 (12.50)	
<1	14 (15.05)	11 (15.94)	3 (12.50)	
Not tested	65 (69.89)	47 (68.12)	18 (75.00)	
Prior chest radiation therapy	15 (16.13)	13 (18.84)	2 (8.33)	0.23

Data are presented as n, n (%) or median (interquartile). BMI, body mass index; CIP, checkpoint inhibitor-related pneumonitis; COPD, chronic obstructive pulmonary disease; ECOG PS, eastern cooperative oncology group performance status; GERD, gastroesophageal reflux disease; ILA, interstitial lung abnormality; LUAD, adenocarcinoma; LUSC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1.

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Table S3 Univariate logistic regression model assessing the association between specific imaging features on chest CT and CIP

Variables	Univariate analysis	
	OR (95% CI)	P value
(A)		
Ground glass attenuation	2.229 (0.980, 5.074)	0.056
Reticular shadow	1.155 (0.496, 2.692)	0.74
Honeycombing	1.327 (0.276, 6.388)	0.72
Traction bronchiectasis	2.018 (0.392, 10.379)	0.40
Nonemphysematous cysts	1.487 (0.162, 13.664)	0.73
(B)		
Non-subpleural	1.934 (0.746, 5.015)	0.18
Subpleural nonfibrotic	0.732 (0.288, 1.858)	0.51
Subpleural fibrotic	0.479 (0.098, 2.338)	0.36

(A) Univariate analysis based on specific imaging features. (B) Univariate analysis based on subcategories of ILAs. CI, confidence interval; CIP, checkpoint inhibitor-related pneumonitis; CT, computed tomography; OR, odds ratio.

Table S4 Results for the risk factors associated with PFS in the multivariate Cox proportional hazards model

Variables	PFS	
	HR (95% CI)	P value
ILA	1.621 (1.165, 2.255)	0.004
Cyfra21-1 (≥7.40 ng/mL)	1.462 (1.063, 2.013)	0.02
CEA (≥131.34 μg/L)	1.936 (1.130, 3.315)	0.02
CA125 (≥96.35 U/mL)	1.321 (0.878, 1.989)	0.18
NE (≥6.19×10^9/L)	1.468 (1.011, 2.130)	0.044

CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CI, confidence interval; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; HR, hazard ratio; ILA, interstitial lung abnormality; NE, neutrophil; PFS, progression-free survival.

Table S5 Results for the risk factors associated with OS in the multivariate Cox proportional hazards model

Variables	OS	
	HR (95% CI)	P value
ILA	1.899 (1.253, 2.878)	0.002
Cyfra21-1 (≥7.40 ng/mL)	1.404 (0.918, 2.147)	0.12
CEA (≥131.34 μg/L)	3.187 (1.787, 5.687)	<0.001
CA125 (≥96.35 U/mL)	1.122 (0.693, 1.817)	0.64
FIB (≥4.31 g/L)	1.388 (0.904, 2.131)	0.13
IL-6 (≥14.86 ng/L)	1.707 (1.047, 2.783)	0.03
LDH (≥169.50 U/L)	2.141 (1.270, 3.609)	0.004
Mono (≥0.39×10^9/L)	1.112 (0.579, 2.135)	0.75
NLR (≥2.63)	1.049 (0.656, 1.679)	0.84
MLR (≥0.29)	1.198 (0.693, 2.071)	0.52

CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CI, confidence interval; Cyfra21-1, cytokeratin 19 fragment antigen 21-1; FIB, fibrinogen; HR, hazard ratio; IL-6, interleukin-6; ILA, interstitial lung abnormality; LDH, lactate dehydrogenase; MLR, monocyte-to-lymphocyte ratio; Mono, monocyte; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

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