Supplementary material

Methods

Patient enrollment

We retrospectively enrolled 568 patients diagnosed with histologically or cytologically documented limited-stage small cell lung cancer (LS-SCLC) at 4 tertiary medical centers between January 2020 and December 2024. All enrolled patients were diagnosed with histologically or cytologically confirmed stage I–III LS-SCLC. Patients who were diagnosed with other pathologic types of lung cancer or extensive-stage small cell lung cancer (ES-SCLC) were excluded, as were patients who did not receive radiotherapy due to poor performance status. Patients with other malignancies, life-threatening underlying medical conditions, or immune system disorders were also excluded, as were patients with incomplete documentation of baseline clinical parameters, unavailable diagnostic imaging studies, or insufficient longitudinal clinical surveillance records. All enrolled patients had at least one measurable target lesion [per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)] for tumor response assessment. Based on the therapeutic strategy, the enrolled patients were classified into two groups: 1) immune-chemoradiotherapy (I-CRT) group, including patients who received induction immunochemotherapy followed by definitive radiotherapy (n = 101); and 2) CRT group, including patients who received standard chemoradiotherapy (n = 467; **Figure S1**). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Board of Shandong Cancer Hospital Affiliated to Shandong First Medical University (SDTHEC202508026).

Treatment

Patients received standard chemotherapy combined with concurrent or sequential thoracic radiotherapy (TRT) according to the Chinese Society of Clinical Oncology (CSCO) or National Comprehensive Cancer Network (NCCN) guidelines. The standard chemotherapeutic regimen consisted of etoposide in combination with cisplatin or carboplatin. Most enrolled patients were treated with standard dose/fractionation regimens of once-daily radiotherapy (60–70 Gy in 30–35 fractions) or twice-daily radiotherapy (45 Gy in 30 fractions). All enrolled patients in the CRT group received standard systemic chemotherapy combined with concurrent or sequential TRT. All of the enrolled patients in the I-CRT group received at least one cycle of intravenous anti-PD-(L)1 agents before definitive radiotherapy (**Table S4**). This retrospective study had no predefined criteria for assigning patients to induction immunochemotherapy because this approach was not a standard treatment for LS-SCLC. Treatment decisions were made by physicians based on clinical judgment and patient characteristics. All patients who received induction therapy underwent repeat simulation computed tomography (CT) before definitive radiotherapy to ensure target volumes reflected post-induction tumor extent. Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were delineated according to standard guidelines. Adaptive planning was not routinely used because adaptive planning was not uniformly available across participating centers during the study period.

Data collection and outcomes

Patient demographics and treatment details were retrieved from the digital medical archives, specifically including age, sex, smoking history, histological subtype, disease stage, and the specific systemic therapy regimens (drug names, dosages, and number of cycles). Prior to treatment, tumor size data were obtained as baseline measurements from evaluable chest CT scans; baseline tumor size was defined as the sum of the longest diameters of target lesions, as measured by a centralized radiology reviewer. Routine follow-up assessments, conducted at protocol-specified intervals (e.g., every 3 weeks during treatment and every 2 months following treatment discontinuation), included monitoring vital signs, performance status, tumor markers, and other hematologic parameters (comprising complete blood count, hepatic, and renal function panels), with comprehensive documentation of all adverse events (AEs), which were captured from the time of informed consent through 30 days after the last treatment dose and assessed according to version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE). Response assessments were performed every 6–8 weeks (±7 days) using CT or positron emission tomography (PET) according to the RECIST (version 1.1). Tumor response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The overall response rate (ORR) was defined as the proportion of patients who achieved a CR or PR. The disease control rate (DCR) was defined as the proportion of patients with a CR, PR, or SD. Progression-free survival (PFS) referred to the duration between the first anti-tumor treatment and the earliest occurrence of tumor progression (radiologically determined according to RECIST v1.1) or death from any cause. Overall survival (OS) was calculated from the date of first anti-tumor treatment until the last documented follow-up or all-cause mortality.

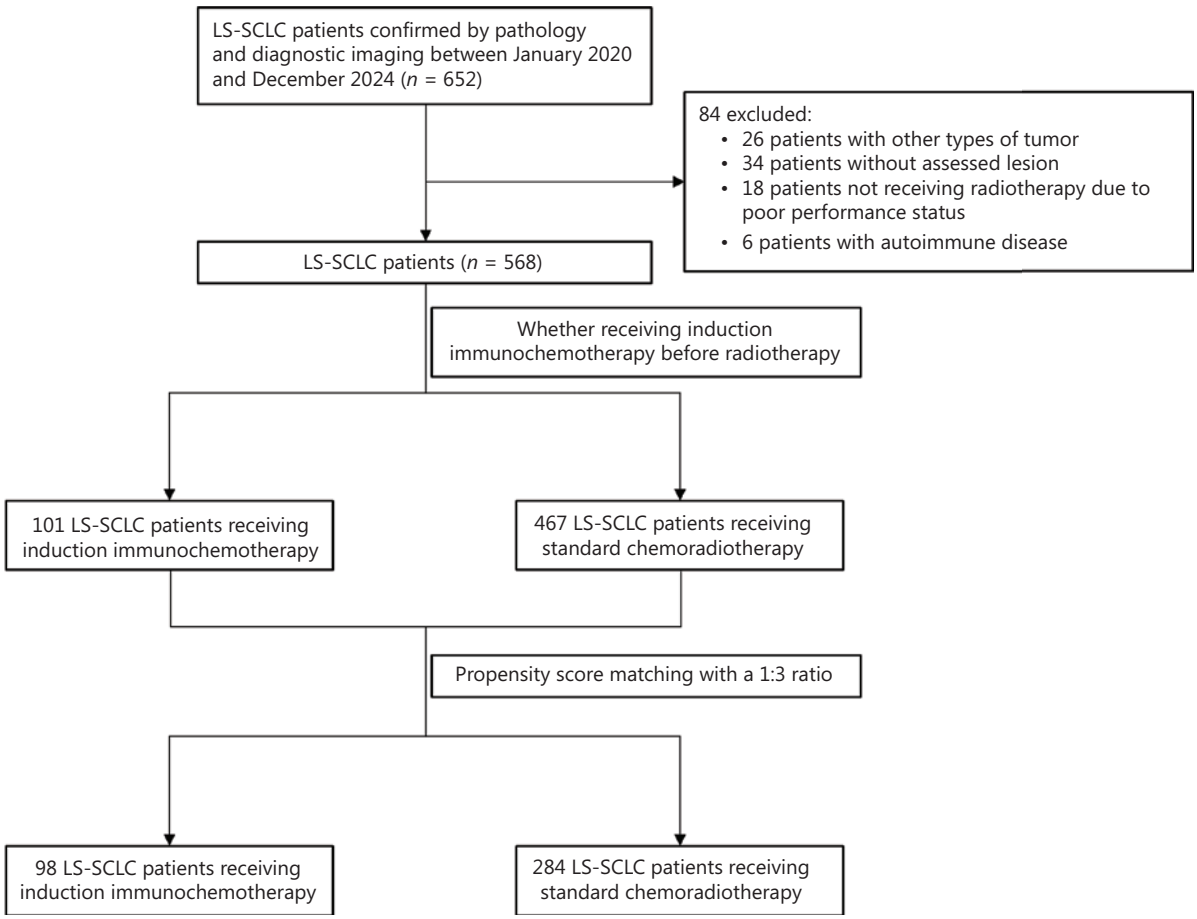

Figure S1 Enrollment flow diagram.

Statistical analysis

Only patients with complete electronic medical records and follow-up information were enrolled per the study inclusion criteria. Key covariates were extracted from the electronic medical record systems of the four participating centers, where completion of essential fields is mandatory. Consequently, no missing data were present for any of the variables analyzed. A chi-square or Fisher's exact test was used to analyze categorical variables. Propensity score matching (PSM) was performed using a 1:3 nearest-neighbor algorithm with a caliper of 0.2 to reduce selection bias based on key covariates including age, gender, a history of smoking, Eastern Cooperative Oncology Group (ECOG) performance status, T stage, N stage, TNM stage, sequential chemotherapy, prophylactic cranial irradiation (PCI), and radiotherapy fractionation. Standardized mean differences (SMDs) <0.1 were considered to indicate good balance between groups. As a complementary sensitivity analysis, inverse probability of treatment weighting (IPTW) was applied to the original cohort using the same propensity score model, and covariate balance was reassessed with SMDs. Kaplan–Meier (KM) survival curves and log-rank tests were used to determine the survival differences between the two groups. Survival outcomes were analyzed using univariate and multivariate Cox proportional hazards models, yielding hazard ratios (HRs) with 95% confidence intervals (CIs). For multivariable Cox regression analysis, variables with a P value < 0.10 in univariable analysis were entered into the multivariable model. A Fine-Gray competing-risk analysis was performed with cancer-specific death as the primary outcome and non-cancer death as the competing event. Cumulative incidence functions were estimated and compared using Gray's test. All statistical tests were two-sided, with a P-value < 0.05 considered statistically significant. All subgroup analyses were exploratory in nature and no adjustment for multiple comparisons was applied. Therefore, the results of subgroup analyses should be considered hypothesis-generating and the primary conclusions of this study are based on the overall population analysis. A *post-hoc* power analysis was performed for the negative comparison between the 1–3 and 4–6 cycles induction therapy groups. Based on clinically meaningful effect sizes from landmark LS-SCLC trials (e.g., ADRIATIC: OS HR = 0.73; NRG-LU005 design assumption: HR = 0.71), a target HR of 0.70 with a two-sided α of 0.05 was pre-specified. Power

Table S1 Baseline characteristics of enrolled patients

	Before matching (%)				After matching (%)			
Variable	I-CRT (*n* = 101)	CRT (*n* = 467)	*P* value	SMD	I-CRT (*n* = 98)	CRT (*n* = 284)	*P* value	SMD
Age			0.40	−0.07			0.91	−0.02
<60	47 (46.5)	196 (42.0)			46 (46.9)	135 (47.5)		
≥60	54 (53.5)	271 (58.0)			52 (53.1)	149 (52.5)		
Gender			0.12	−0.07			0.56	0.02
Male	81 (80.2)	340 (72.8)			79 (80.6)	221 (77.8)		
Female	20 (19.8)	127 (27.2)			19 (19.4)	63 (22.2)		
ECOG PS			0.61	−0.02			0.43	0.04
0	19 (18.8)	78 (16.7)			18 (18.4)	63 (22.2)		
≥1	82 (81.2)	389 (83.3)			80 (81.6)	221 (77.8)		
Smoking history			0.32	0.05			0.51	0.04
Yes	63 (62.4)	266 (57.0)			63 (64.3)	172 (60.6)		
No	38 (37.6)	201 (43.0)			35 (35.7)	112 (39.4)		
T stage			0.17	0.08			0.98	−0.02
T1–2	46 (45.5)	248 (53.1)			45 (45.9)	130 (45.8)		
T3–4	55 (54.5)	219 (46.9)			53 (54.1)	154 (54.2)		
N stage			0.51	−0.03			0.88	<0.01
N0–1	21 (20.8)	84 (18.0)			20 (20.4)	56 (19.7)		
N2–3	80 (79.2)	383 (82.0)			78 (79.6)	228 (80.3)		
Stage			0.70	0.02			0.65	0.01
I–II	13 (12.9)	67 (14.3)			12 (12.2)	40 (14.1)		
III	88 (87.1)	400 (85.7)			86 (87.8)	244 (85.9)		
PCI			0.27	−0.06			0.90	0.04
Yes	51 (50.5)	208 (44.5)			50 (51.0)	147 (51.8)		
No	50 (49.5)	259 (55.5)			48 (49.0)	137 (48.2)		
Treatment sequence			0.50	0.04			0.63	0.03
CCRT	58 (57.4)	285 (61.0)			57 (58.2)	173 (60.9)		
SCRT	43 (42.6)	182 (39.0)			41 (41.8)	111 (39.1)		
Radiotherapy schedule			0.09	0.09			0.64	0.01
Once daily	56 (55.4)	301 (64.5)			55 (56.1)	167 (58.8)		
Twice daily	45 (44.6)	166 (35.5)			43 (43.9)	117 (41.2)		

CRT, chemoradiotherapy; CCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; I-CRT, immune-chemoradiotherapy; PCI, prophylactic cranial irradiation; SCRT, sequential chemoradiation therapy; SMD, standardized mean difference.

Table S2 SMD before and after IPTW

Variable	SMD before weighting	SMD after weighting
Age	−0.071	−0.004
Gender	−0.074	0.001
ECOG PS	−0.021	−0.006
Smoking history	0.054	−0.004
T stage	0.076	−0.007
N stage	−0.028	−0.005
Stage	0.015	−0.007
PCI	−0.060	−0.022
Treatment sequence	0.036	−0.008
Radiotherapy schedule	0.090	0.001

ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; SMD, standardized mean difference.

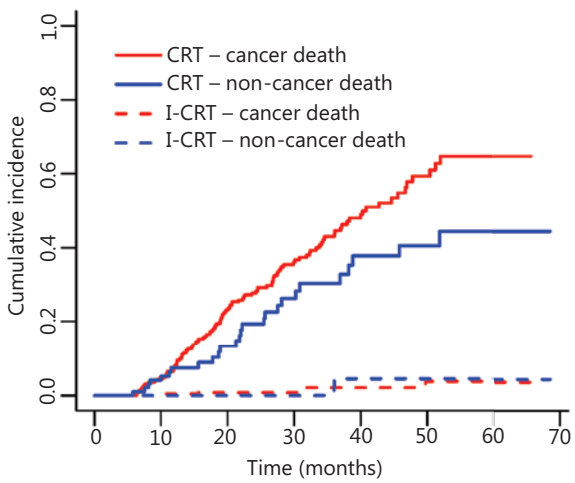

Figure S2 Cumulative Fine-Gray incidence curves.

was calculated using the Schoenfeld formula. Analyses were performed using GraphPad Prism (version 8.0.2; GraphPad Software, La Jolla, CA, USA) and SPSS (version 26.0; IBM Corp., Armonk, NY, USA).

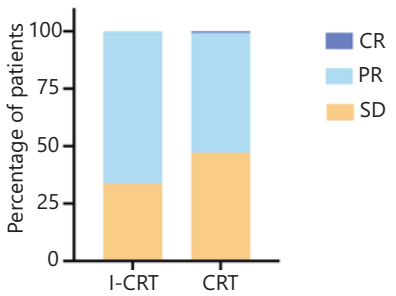

Figure S3 Tumor response before definitive radiotherapy. CR, complete response; PR, partial response; SD, stable disease.

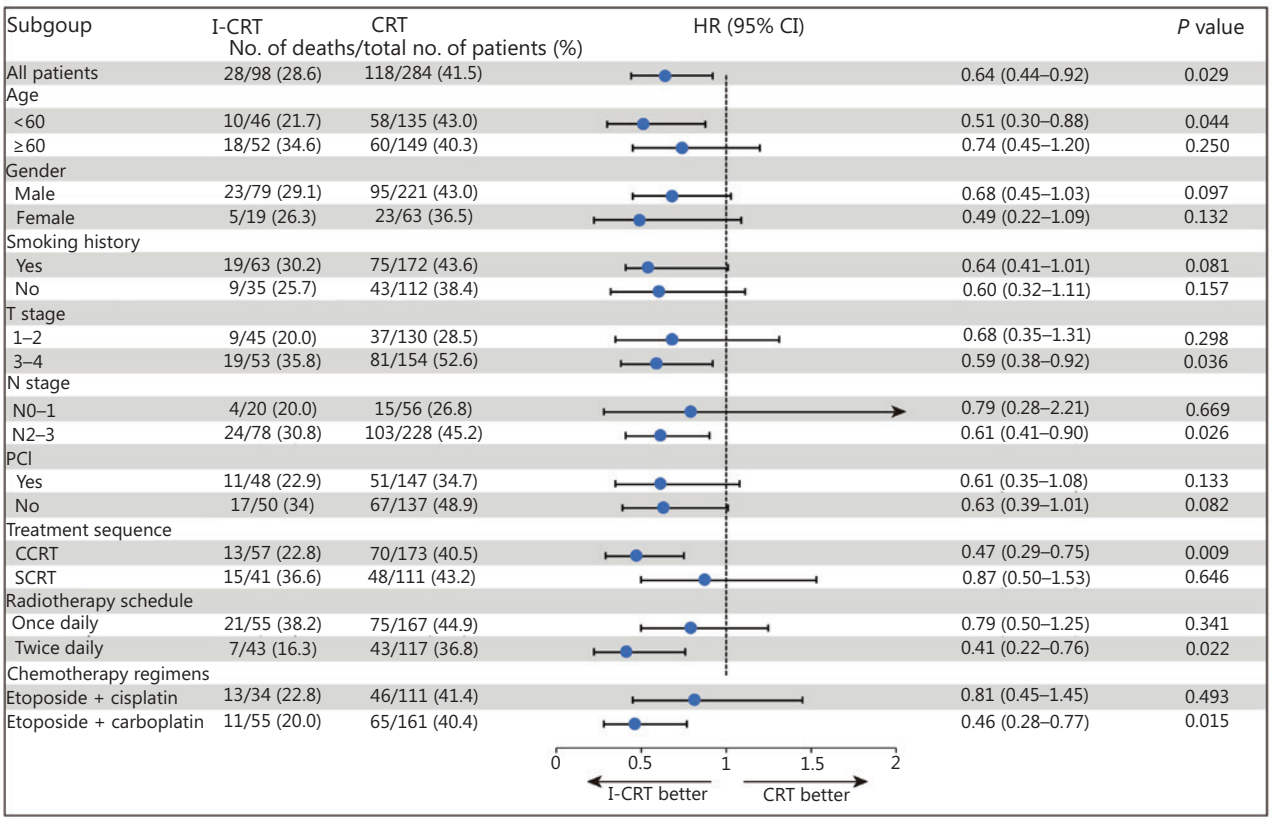

Figure S4 Exploratory subgroup analysis of overall survival (OS).

Table S3 Univariate and multivariable analyses of PFS and OS

	PFS				OS			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age								
≥60 *vs.* <60	1.076 (0.641–1.808)	0.781			1.421 (0.656–3.079)	0.374		
Gender								
Female *vs.* male	0.689 (0.347–1.365)	0.285			0.580 (0.219–1.535)	0.272		
Smoking history								
No *vs.* Yes	1.255 (0.725–2.173)	0.418			1.532 (0.690–3.401)	0.294		
ECOG								
≥1 *vs.* 0	3.568 (1.504–8.463)	**0.004**	3.109 (1.287–7.511)	**0.012**	4.531 (1.326–15.488)	**0.016**	3.892 (1.106–13.694)	**0.034**
T stage								
T3–4 *vs.* T1–2	1.351 (0.800–2.280)	0.260			2.150 (0.970–4.766)	**0.059**	1.972 (0.885–4.398)	**0.097**
N stage								
N0–1 *vs.* N2–3	1.004 (0.531–1.896)	0.991			1.625 (0.563–4.693)	0.369		
Stage								
III *vs.* I–II	0.855 (0.405–1.805)	0.681			0.677 (0.257–1.787)	0.431		
Treatment sequence								
SCRT *vs.* CCRT	1.776 (1.056–2.985)	**0.030**	1.928 (1.113–3.340)	**0.019**	2.108 (0.988–4.501)	**0.054**	2.130 (0.981–4.625)	**0.056**
PCI								
No *vs.* Yes	2.211 (1.294–3.776)	**0.004**	1.541 (0.877–2.678)	0.125	1.865 (0.866–4.015)	0.111		
Radiotherapy schedule								
Twice *vs.* Once daily	0.345 (0.195–0.610)	**<0.001**	0.319 (0.177–0.578)	**<0.001**	0.365 (0.155–0.860)	**0.021**	0.331 (0.139–0.791)	**0.013**
Chemotherapy regimens								
EC *vs.* EP	1.003 (0.580–1.734)	0.992			0.641 (0.286–1.434)	0.279		

CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EC, etoposide + carboplatin; EP, etoposide + cisplatin; HR, hazard ratio; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; SCRT, sequential chemoradiation therapy. In the univariate analysis, variables with a *P*-value < 0.1 were selected for inclusion in the multivariate Cox regression analysis. Bold values indicate statistically significant results at the $P < 0.1$ level.

Table S4 Immune-related adverse events

	No. (%) of patients in the I-CRT group (n = 98)	
	All grades	Grade ≥3
Any adverse event of any cause	24 (24.5)	1 (1.0)
Hypothyroidism	4 (4.1)	0
Rash	5 (5.1)	0
Hepatitis	5 (5.1)	0
Pneumonia	12 (12.2)	1 (1.0)

I-CRT, immune-chemoradiotherapy.

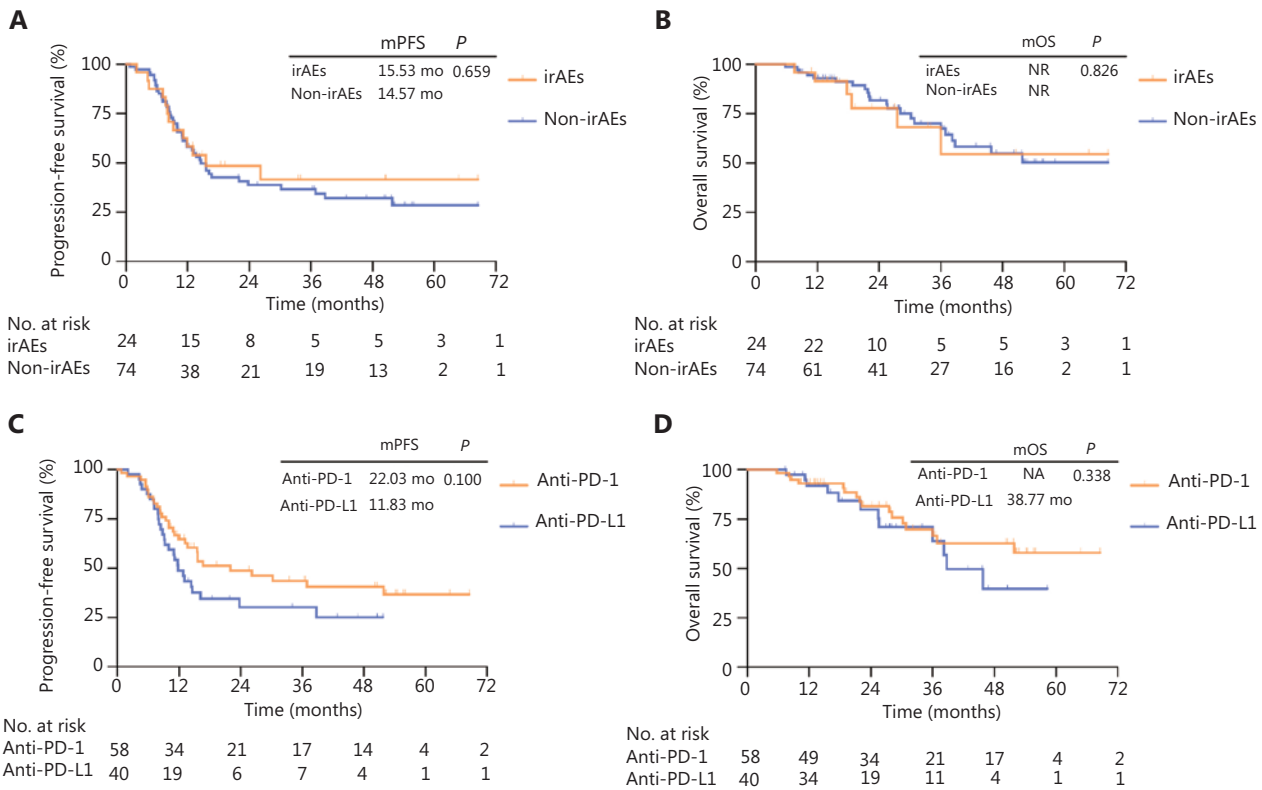

Figure S5 Exploratory subgroup survival analysis. (A, B) PFS and OS of patients in the "irAEs" and "non-irAEs" groups. (C, D) PFS and OS of patients in the "anti-PD-1" and "anti-PD-L1" groups. irAEs, immune-related adverse events; OS, overall survival; PFS, progression-free survival.

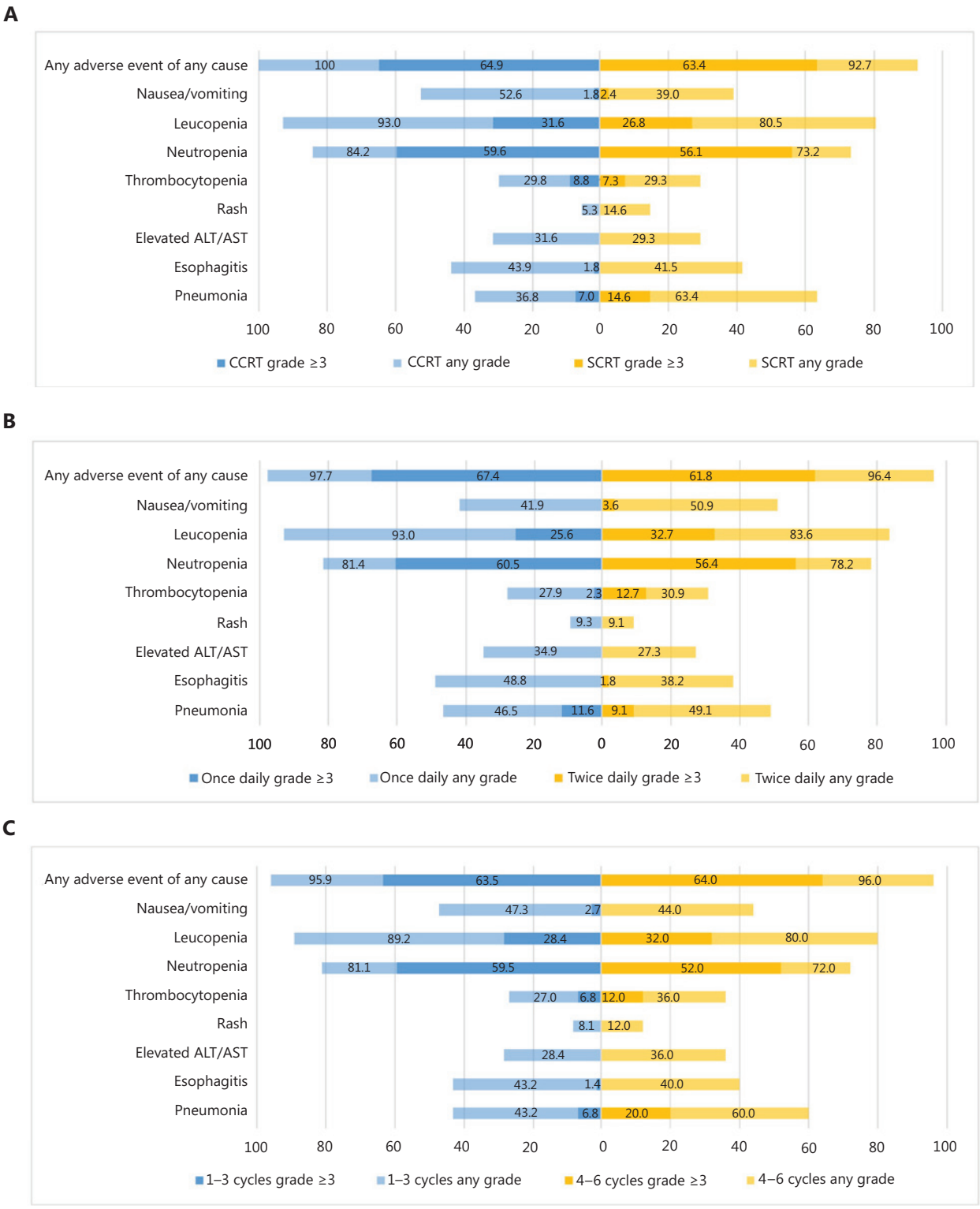

Figure S6 Exploratory subgroup safety data. (A) Incidence of AEs and grade ≥3 AEs in the "CCRT" and "SCRT" groups. (B) Incidence of AEs and grade ≥3 AEs in the "once daily" and "twice daily" groups. (C) Incidence of AEs and grade ≥3 AEs in the "1–3 cycles" and "4–6 cycles" groups. AEs, adverse events; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy.

Table S5 Treatment regimens

Variable	I-CRT (*n* = 98)	CRT (*n* = 284)
Immunotherapy regimens		
Anti-PD-1	58 (59.2)	-
Anti-PD-L1	40 (40.8)	-
Chemotherapy regimens		
Etoposide + cisplatin	34 (34.7)	111 (39.1)
Etoposide + carboplatin	55 (56.1)	161 (56.7)
Others	9 (9.2)	12 (4.2)
Treatment sequence		
CCRT	57 (58.2)	173 (60.9)
SCRT	41 (41.8)	111 (39.1)
Radiotherapy schedule		
Once daily	55 (56.1)	167 (58.8)
Twice daily	43 (43.9)	117 (41.2)

CRT, chemoradiotherapy; CCRT, concurrent chemoradiotherapy; I-CRT, immune-chemoradiotherapy; SCRT, sequential chemoradiotherapy.

Table S6 Immunotherapy regimens

Immunotherapy agent	Patients
Sintilimab	34
Adebrelimab	16
Serplulimab	16
Durvalumab	12
Atezolizumab	9
Camrelizumab	3
Envafolimab	2
Toripalimab	2
Tislelizumab	2
Pembrolizumab	1
Benmelstobart	1