Additional File

Figure S1. WJOG10217L Study Design

Abbreviations: NSCLC, non–small cell lung cancer; CAP, chemotherapy after PD-1 inhibitor treatment.

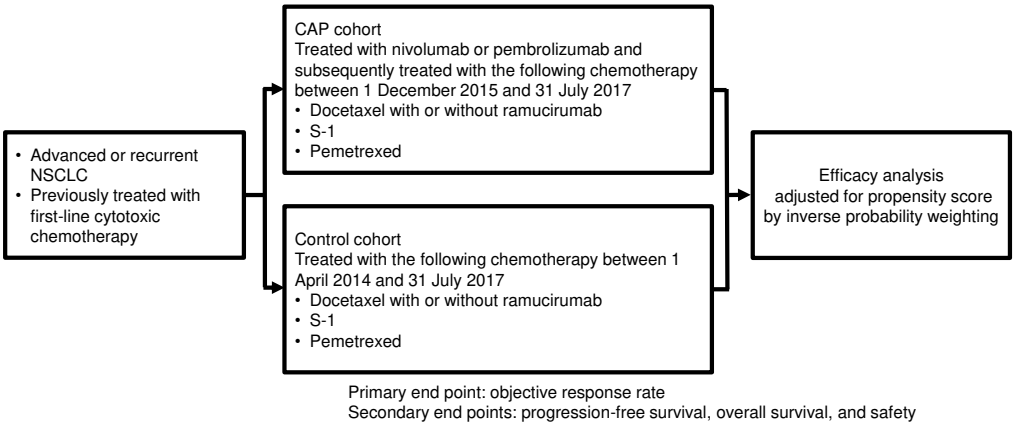

Table S1. Unadjusted Patient Characteristics for the Chemotherapy After PD-1 Inhibitor Treatment (CAP) and Control Cohorts According to Chemotherapy Regimen

Characteristic	Docetaxel			Docetaxel + ramucirumab			S-1			Pemetrexed		
	CAP (n = 105)	Control (n = 778)	*P* value[a]	CAP (n = 77)	Control (n = 94)	*P* value[a]	CAP (n = 49)	Control (n = 174)	*P* value[a]	CAP (n = 12)	Control (n = 150)	*P* value[a]
Age, years[b, c]												
Median (range)	69.0 (41–85)	68.0 (34–87)	.70	66.0 (38–80)	65.5 (30–79)	.97	67.0 (53–81)	72.0 (41–85)	.002	71.5 (49–86)	72.0 (41–87)	.91
<70	56 (53.3)	451 (58.0)	.40	56 (72.7)	71 (75.5)	.73	32 (65.3)	68 (39.1)	.002	6 (50.0)	65 (43.3)	.77
≥70	49 (46.7)	327 (42.0)		21 (27.3)	23 (24.5)		17 (34.7)	105 (60.3)		6 (50.0)	84 (56.0)	
Sex												
Male	74 (70.5)	574 (73.8)	.48	54 (70.1)	57 (60.6)	.20	35 (71.4)	134 (77.0)	.45	6 (50.0)	102 (68.0)	.22
Female	31 (29.5)	204 (26.2)		23 (29.9)	37 (39.4)		14 (28.6)	40 (23.0)		6 (50.0)	48 (32.0)	
Smoking status[d]												
Never	30 (28.6)	182 (23.4)	.49	20 (26.0)	28 (29.8)	.26	8 (16.3)	28 (16.1)	.80	2 (16.7)	40 (26.7)	.54
Past	38 (36.2)	312 (40.1)		36 (46.8)	32 (34.0)		23 (46.9)	73 (42.0)		5 (41.7)	70 (46.7)	
Current	37 (35.2)	277 (35.6)		21 (27.3)	33 (35.1)		18 (36.7)	73 (42.0)		5 (41.7)	40 (26.7)	
Unknown	0 (0.0)	7 (0.9)		0 (0.0)	1 (1.1)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Histology												
Adenocarcinoma	66 (62.9)	547 (70.3)	.07	61 (79.2)	87 (92.6)	.03	23 (46.9)	84 (48.3)	.45	11 (91.7)	141 (94.0)	.16
Squamous cell carcinoma	34 (32.4)	173 (22.2)		12 (15.6)	6 (6.4)		26 (53.1)	83 (47.7)		1 (8.3)	1 (0.7)	
Other	5 (4.8)	58 (7.5)		4 (5.2)	1 (1.1)		0 (0.0)	7 (4.0)		0 (0.0)	8 (5.3)	

EGFR mutation status												
Positive	19 (18.1)	135 (17.4)	.89[e]	4 (5.2)	23 (24.5)	<.001[e]	2 (4.1)	21 (12.1)	.12[e]	3 (25.0)	22 (14.7)	.40[e]
Negative	67 (63.8)	553 (71.1)		67 (87.0)	68 (72.3)		35 (71.4)	95 (54.6)		8 (66.7)	123 (82.0)	
Unknown	19 (18.1)	90 (11.6)		6 (7.8)	3 (3.2)		12 (24.5)	58 (33.3)		1 (8.3)	5 (3.3)	
ALK rearrangement status												
Positive	5 (4.8)	8 (1.0)	.01[e]	2 (2.6)	3 (3.2)	>.99[e]	0 (0.0)	0 (0.0)		1 (8.3)	2 (1.3)	.21[e]
Negative	72 (68.6)	551 (70.8)		67 (87.0)	76 (80.9)		28 (57.1)	91 (52.3)		10 (83.3)	119 (79.3)	
Unknown	28 (26.7)	219 (28.1)		8 (10.4)	15 (16.0)		21 (42.8)	83 (47.7)		1 (8.3)	29 (19.4)	
PD-L1 TPS[f]												
≥50%	8 (7.6)	21 (2.7)	.52	6 (7.8)	5 (5.3)	.08	7 (14.3)	3 (1.7)	.03	2 (16.7)	4 (2.7)	.40
1–49%	15 (14.3)	41 (5.3)		20 (26.0)	19 (20.2)		5 (10.2)	4 (2.3)		1 (8.3)	12 (8.0)	
<1%	15 (14.3)	62 (8.0)		12 (15.6)	30 (31.9)		4 (8.2)	14 (8.0)		1 (8.3)	9 (6.0)	
Unknown	67 (63.8)	654 (84.1)		39 (50.6)	40 (42.6)		33 (67.3)	153 (87.9)		8 (66.7)	125 (83.3)	
ECOG PS[b, g]												
0–1	90 (85.7)	690 (88.7)	.19[h]	63 (81.8)	85 (90.4)	.23[h]	35 (71.4)	137 (78.7)	.36[h]	9 (75.0)	126 (84.0)	.55[h]
≥2	13 (12.4)	59 (7.6)		6 (7.8)	5 (5.3)		12 (24.5)	27 (15.5)		3 (25.0)	20 (13.3)	
Unknown	2 (1.9)	29 (3.7)		8 (10.4)	4 (4.3)		2 (4.1)	9 (5.2)		0 (0.0)	4 (2.7)	
Stage[i]												
III	14 (13.3)	82 (10.5)	.78	7 (9.1)	6 (6.4)	.88	9 (18.4)	48 (27.6)	.24	1 (8.3)	20 (13.3)	.94
IV	75 (71.4)	557 (71.6)		55 (71.4)	71 (75.5)		32 (65.3)	89 (51.1)		8 (66.7)	95 (63.3)	
Recurrence after surgery	13 (12.4)	105 (13.5)		13 (16.9)	15 (16.0)		4 (8.2)	26 (14.9)		3 (25.0)	29 (19.3)	

Recurrence after CRT	3 (2.9)	34 (4.4)		2 (2.6)	2 (2.1)		4 (8.2)	11 (6.3)		0 (0.0)	6 (4.0)	
Brain metastasis[b]												
Yes	31 (29.5)	167 (21.5)	.08	20 (26.0)	25 (26.6)	>.99	10 (20.4)	22 (12.6)	.17	4 (33.3)	33 (22.0)	.47
No	74 (70.5)	611 (78.5)		57 (74.0)	69 (73.4)		39 (79.6)	152 (77.4)		8 (66.7)	117 (78.0)	

Data are presented as n (%) with the exception of median age.

Abbreviations: TPS, tumor proportion score; ECOG PS, Eastern Cooperative Oncology Group performance status; CRT, chemoradiotherapy.

[a]*P* values were determined with the Wilcoxon test or Fisher's exact test as appropriate.

[b]At the time of initiation of docetaxel with or without ramucirumab; S-1; or pemetrexed.

[c]One patient treated with S-1 and one patient treated with pemetrexed in the control cohort had missing data.

[d]Never smokers were defined as individuals who had smoked <100 cigarettes; past smokers as those who had smoked ≥100 cigarettes but had quit >1 year prior to diagnosis; and current smokers as those who had smoked ≥100 cigarettes including at least one within the year prior to diagnosis.

[e]*P* values are for comparison between patients positive for *EGFR* or *ALK* alterations and those negative or of unknown status.

[f]Data for PD-L1 expression in tumor cells were obtained by immunohistochemistry according to the standard practice of each center.

[g]One patient treated with S-1 in the control cohort had missing data.

[h]*P* values are for comparison between a PS of 0–1 and a PS of 2–4 and a PS of unknown.

[i]All patients were classified on the basis of clinical stage according to the 7th edition of the TNM classification.

Figure S2. Distribution of Propensity Score in the Chemotherapy After PD-1 Inhibitor Treatment (CAP) and Control Cohorts

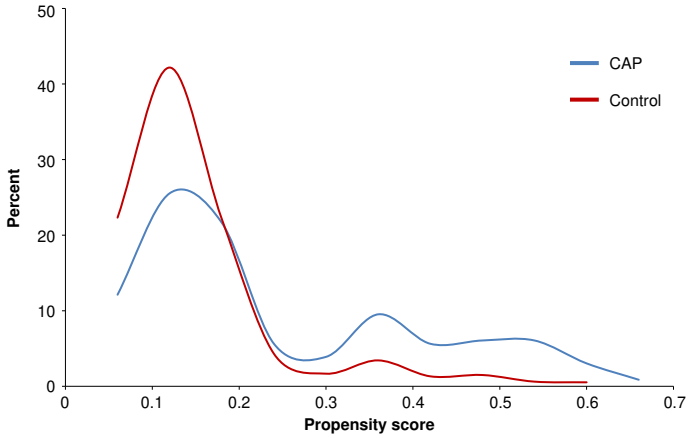

Table S2. Standardized Difference Between the Chemotherapy After PD-1 Inhibitor Treatment (CAP) and Control Cohorts With or Without Adjustment by Inverse Probability Weighting (IPW)

	Standardized Difference	
Parameter	**Unadjusted**	**IPW–adjusted**
Age	0.193	0.018
Sex	0.065	0.005
Smoking status	0.030	0.000
ECOG PS	0.155	0.004
Histology	0.184	0.026
EGFR or *ALK* genetic alterations	0.126	0.114
Brain metastasis	0.144	0.005
History of curative radiotherapy	0.075	0.024
Type of chemotherapy	0.627	0.003

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table S3. First-Line Chemotherapy Regimens

Regimen	CAP Cohort (n = 243)	Control Cohort (n = 1196)
Platinum doublet	225 (92.6)	1040 (87.0)
Cisplatin + pemetrexed	41 (16.9)	213 (17.8)
Cisplatin + pemetrexed + bevacizumab	30 (12.3)	69 (5.8)
Cisplatin + gemcitabine	11 (4.5)	29 (2.4)
Cisplatin + S-1	1 (0.4)	4 (0.3)
Carboplatin + paclitaxel	8 (3.3)	83 (6.9)
Carboplatin + paclitaxel + bevacizumab	11 (4.5)	55 (4.6)
Carboplatin + nab-paclitaxel	31 (12.8)	149 (12.5)
Carboplatin + pemetrexed	39 (16.0)	198 (16.6)
Carboplatin + pemetrexed + bevacizumab	24 (9.9)	112 (9.4)
Carboplatin + S-1	22 (9.1)	65 (5.4)
Other	7 (2.9)	63 (5.3)
Nonplatinum	18 (7.4)	156 (13.0)
Docetaxel	10 (4.1)	71 (5.9)
Pemetrexed	4 (1.6)	57 (4.8)
S-1	0 (0.0)	4 (0.3)
Docetaxel + ramucirumab	0 (0.0)	0 (0.0)
Vinorelbine	1 (0.4)	10 (0.8)
Gemcitabine	0 (0.0)	0 (0.0)
Other	3 (1.2)	14 (1.2)

Data are presented as n (%).

Abbreviation: CAP, chemotherapy after PD-1 inhibitor treatment.

Table S4. Data for First-Line Chemotherapy, PD-1 Inhibitor Treatment After First-Line Chemotherapy, and Poststudy Systemic Therapy

	CAP Cohort (n = 243)	Control Cohort (n = 1196)
First-line chemotherapy		
Type, n (%)		
Platinum doublet	225 (92.6)	1040 (87.0)
Nonplatinum	18 (7.4)	156 (13.0)
Objective response rate (95% CI), %	48.3 (41.9–54.9)	43.2 (40.3–46.0)
Progression-free survival (months)		
Median (95% CI)	5.6 (5.1–6.2)	5.3 (5.1–5.6)
PD-1 inhibitor treatment after first-line chemotherapy		
Type of PD-1 inhibitor, n (%)		
Nivolumab	237 (97.5)	
Pembrolizumab	6 (2.5)	
Objective response rate (95% CI), %	14.4 (10.2–19.5)	
Progression-free survival (months)		
Median (95% CI)	2.0 (1.8–2.5)	
Time on PD-1 inhibitors, days		
Median (range)	49 (1–489)	
Time from last dose of PD-1 inhibitor to start of subsequent chemotherapy, days		
Median (range)	28 (7–216)	
Poststudy systemic therapy		
Number of regimens		
0	116 (47.7)	468 (39.1)
1	71 (29.2)	362 (30.3)
≥2	56 (23.1)	366 (30.6)
Median (range)	1 (1–6)	1 (1–7)
Type of therapy, n (%)		
Chemotherapy	118 (48.6)	514 (43.0)
Tyrosine kinase inhibitor	15 (6.2)	141 (11.8)
Immune checkpoint inhibitor	15 (6.2)	355 (29.7)

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; CI, confidence interval.

Table S5. Unadjusted Analysis of Objective Response for All Patients and According to Chemotherapy Regimen

	All		Docetaxel		Docetaxel + Ramucirumab		S-1		Pemetrexed	
	CAP	Control	CAP	Control	CAP	Control	CAP	Control	CAP	Control
No. of patients	243	1196	105	778	77	94	49	174	12	150
No. of patients with measurable lesions	240	1186	104	769	75	94	49	174	12	149
ORR (95% CI),[a] %	17.9 (13.3-23.4)	10.8 (9.1-12.7)	18.3 (11.4-27.1)	11.1 (8.9-13.5)	20.0 (11.7-30.8)	17.0 (10.1-26.2)	6.1 (1.3-16.9)	6.3 (3.2-11.0)	50.0 (21.1-78.9)	10.7 (6.3-16.9)
ORR ratio (95% CI),[b] *P* value	1.66 (1.21-2.28), .003		1.65 (1.05-2.60), .051		1.18 (0.62-2.22), .69		0.97 (0.28-3.34), >.99		4.66 (2.24-9.67), .002	
Response type, n (%)										
Complete response	2 (0.8)	3 (0.3)	1 (1.0)	3 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	41 (17.1)	125 (10.5)	18 (17.3)	82 (10.7)	14 (18.7)	16 (17.0)	3 (6.1)	11 (6.3)	6 (50.0)	16 (10.7)
Stable disease	86 (35.8)	477 (40.2)	33 (31.7)	304 (39.5)	36 (48.0)	46 (48.9)	16 (32.7)	73 (42.0)	1 (8.3)	54 (36.2)
Progressive disease	90 (37.5)	500 (42.2)	42 (40.4)	329 (42.8)	17 (22.7)	30 (31.9)	26 (53.1)	75 (43.1)	5 (41.7)	66 (44.3)
Not evaluable	21 (8.8)	81 (6.8)	10 (9.6)	51 (6.6)	7 (9.3)	2 (2.1)	4 (8.2)	15 (8.6)	0 (0.0)	13 (8.7)

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; ORR, objective response rate; CI, confidence interval.

[a]Patients with no measurable lesions were excluded.

[b]The relative risk (95% CI) is shown for the ORR ratio. The control cohort was the reference cohort for calculation of relative risk, with a relative risk of >1 thus favoring the CAP cohort.

Figure S3. Unadjusted Kaplan-Meier Analysis of Progression-Free Survival (PFS) for the Chemotherapy After PD-1 Inhibitor Treatment (CAP) Cohort Versus the Control Cohort

Comparisons are shown for all patients (A) as well as for those treated with docetaxel (B), with docetaxel plus ramucirumab (C), with S-1 (D), or with pemetrexed (E). Vertical lines on the curves denote censoring. Abbreviations: CI, confidence interval; HR, hazard ratio.

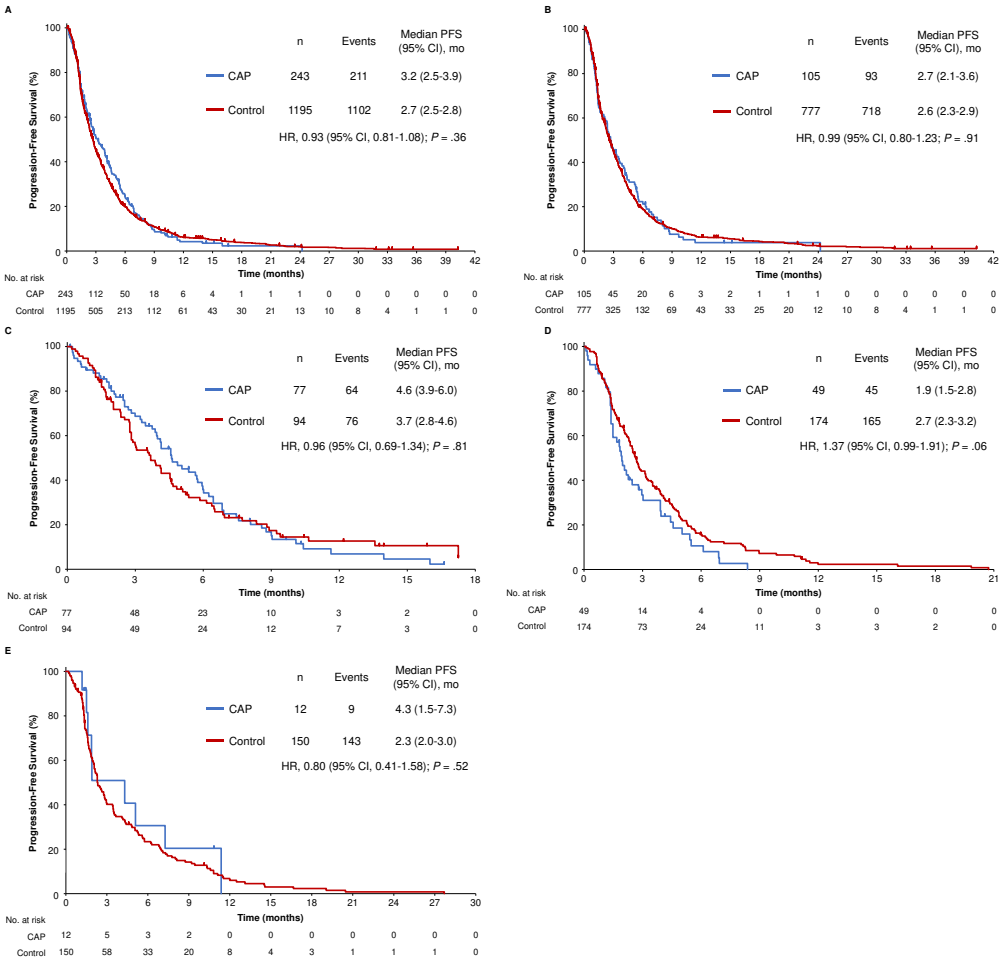

Figure S4. Unadjusted Kaplan-Meier Analysis of Overall Survival (OS) for the Chemotherapy After PD-1 Inhibitor Treatment (CAP) Cohort Versus the Control Cohort

Comparisons are shown for all patients (A) as well as for those treated with docetaxel (B), with docetaxel plus ramucirumab (C), with S-1 (D), or with pemetrexed (E). Vertical lines on the curves denote censoring. Abbreviations: CI, confidence interval; HR, hazard ratio.

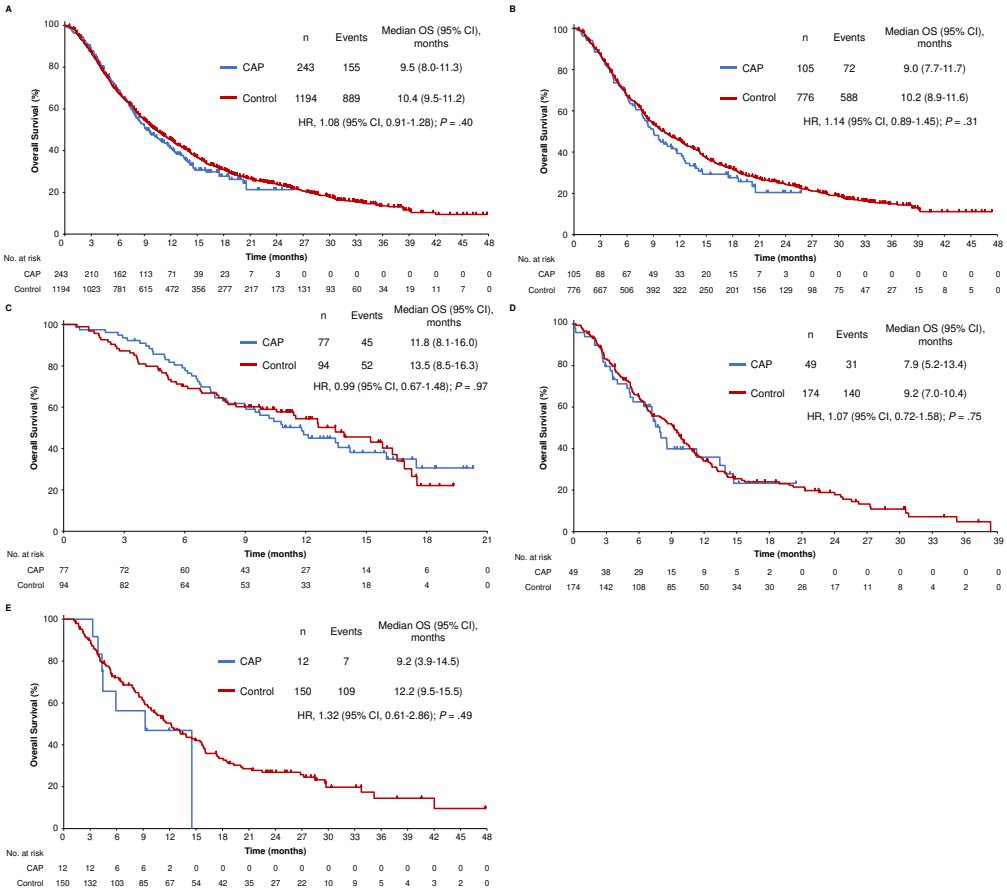

Table S6. Sensitivity Analysis

	ORR Ratio or Hazard Ratio[a]	95% CI	*P* value
Stabilized IPW[b]			
ORR	1.71	1.19–2.46	.004
PFS	0.95	0.80–1.12	.55
OS	1.05	0.86–1.28	.63
Multivariable linear regression model[b]			
ORR	1.61	1.14–2.28	.007
Multivariable Cox regression model[b]			
PFS	0.98	0.83–1.14	.76
OS	1.02	0.85–1.23	.82

Abbreviations: ORR, objective response rate; CI, confidence interval; IPW, inverse probability weighting; PFS, progression-free survival; OS, overall survival.

[a]The relative risk (95% CI) is shown for the ORR ratio. The control cohort was the reference cohort for calculation of relative risk, with a relative risk of >1 thus favoring the chemotherapy after PD-1 inhibitor treatment (CAP) cohort. The hazard ratio (95% CI) is shown for PFS and OS. The control cohort was the reference cohort for calculation of hazard ratio, with a hazard ratio of <1 thus favoring the CAP cohort.

[b]The model was adjusted for age, sex, smoking status, Eastern Cooperative Oncology Group performance status, histology, *EGFR* or *ALK* genetic alterations, brain metastasis, history of curative radiotherapy, and type of chemotherapy

Table S7. Treatment-Related Select Adverse Events for PD-1 Inhibitors in the CAP Cohort (n = 243)

Event	Any Grade	Grade 1–2	Grade 3–5
Rash	22 (9.1)	22 (9.1)	0 (0.0)
Pruritus	17 (7.0)	17 (7.0)	0 (0.0)
Stomatitis	2 (0.8)	1 (0.4)	1 (0.4)
Diarrhea	9 (3.7)	9 (3.7)	0 (0.0)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	8 (3.3)	8 (3.3)	0 (0.0)
Hyperthyroidism	5 (2.0)	5 (2.0)	0 (0.0)
Hypophysitis	1 (0.4)	1 (0.4)	0 (0.0)
Hyperglycemia	6 (2.4)	4 (1.6)	2 (0.8)
AST increase	18 (7.4)	18 (7.4)	0 (0.0)
ALT increase	18 (7.4)	18 (7.4)	0 (0.0)
Total bilirubin increase	1 (0.4)	1 (0.4)	0 (0.0)
Creatinine increase	8 (3.3)	8 (3.3)	0 (0.0)
Pneumonitis	3 (1.2)	3 (1.2)	0 (0.0)

Data are presented as n (%).

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table S8. Treatment-Related Select Adverse Events for Docetaxel

Event	CAP Cohort (n = 105)			Control Cohort (n = 778)			*P* Value[a]
	Any Grade	Grade 1–2	Grade 3–5	Any Grade	Grade 1–2	Grade 3–5	
Rash	5 (4.9)	4 (3.9)	1 (1.0)	63 (8.1)	60 (7.7)	3 (0.4)	.33
Pruritus	2 (1.9)	2 (1.9)	0 (0.0)	25 (3.3)	23 (3.0)	2 (0.3)	.76
Stomatitis	13 (12.4)	12 (11.4)	1 (1.0)	67 (8.7)	58 (7.5)	9 (1.2)	.21
Diarrhea	15 (14.3)	13 (12.3)	2 (1.9)	69 (8.8)	61 (7.8)	8 (1.0)	.11
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.7)	3 (0.4)	2 (0.3)	>.99
Hypothyroidism	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	.12
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypophysitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperglycemia	3 (2.9)	2 (1.9)	1 (1.0)	15 (1.9)	15 (1.9)	1 (0.1)	.46
AST increase	16 (15.3)	13 (12.4)	3 (2.9)	99 (12.8)	95 (12.2)	4 (0.6)	.44
ALT increase	17 (16.3)	13 (12.4)	4 (3.9)	78 (10.1)	72 (9.3)	6 (0.8)	.06
Total bilirubin increase	5 (4.8)	5 (4.8)	0 (0.0)	9 (1.2)	8 (1.1)	1 (0.1)	.02
Creatinine increase	2 (1.9)	0 (0.0)	0 (0.0)	44 (5.7)	42 (5.4)	2 (0.3)	.16
Pneumonitis	10 (9.6)	4 (3.8)	6 (5.8)	62 (8.0)	32 (4.1)	30 (3.9)[b]	.57

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]*P* values are for between-cohort comparisons of rates of any-grade adverse events and were determined with Fisher's exact test.

[b]Data include three patients with treatment-related pneumonitis of grade 5.

Table S9. Treatment-Related Select Adverse Events for Docetaxel Plus Ramucirumab

Event	CAP Cohort (n = 77)			Control Cohort (n = 94)			*P* Value[a]
	Any Grade	Grade 1–2	Grade 3–5	Any Grade	Grade 1–2	Grade 3–5	
Rash	10 (13.0)	10 (13.0)	0 (0.0)	7 (7.5)	7 (7.5)	0 (0.0)	.31
Pruritus	3 (3.9)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	.33
Stomatitis	16 (20.8)	12 (15.6)	4 (5.2)	20 (21.2)	17 (18.0)	3 (3.2)	>.99
Diarrhea	9 (11.7)	9 (11.7)	0 (0.0)	10 (10.7)	9 (9.6)	1 (1.1)	>.99
Colitis	2 (2.6)	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	.20
Hypothyroidism	2 (2.6)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	.20
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypophysitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperglycemia	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.1)	2 (2.1)	0 (0.0)	>.99
AST increase	14 (18.2)	13 (16.9)	1 (1.3)	19 (20.3)	18 (19.2)	1 (1.1)	.85
ALT increase	11 (14.3)	8 (10.4)	3 (3.9)	17 (18.1)	17 (18.1)	0 (0.0)	.54
Total bilirubin increase	1 (1.3)	1 (1.3)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	>.99
Creatinine increase	7 (9.1)	7 (9.1)	0 (0.0)	5 (5.4)	5 (5.4)	0 (0.0)	.38
Pneumonitis	5 (6.5)	3 (3.9)	2 (2.6)[b]	9 (9.6)	4 (4.3)	5 (5.3)[c]	.58

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]*P* values are for between-cohort comparisons of rates of any-grade adverse events and were determined with Fisher's exact test.

[b]Data include one patient with treatment-related pneumonitis of grade 5.

[c]Data include two patients with treatment-related pneumonitis of grade 5.

Table S10. Treatment-Related Select Adverse Events for S-1

Event	CAP Cohort (n = 49)			Control Cohort (n = 174)			*P* Value[a]
	Any Grade	Grade 1–2	Grade 3–5	Any Grade	Grade 1–2	Grade 3–5	
Rash	10 (20.3)	9 (18.3)	1 (2.0)	18 (10.3)	18 (10.3)	0 (0.0)	.09
Pruritus	3 (6.1)	3 (6.1)	0 (0.0)	6 (3.4)	6 (3.4)	0 (0.0)	.42
Stomatitis	5 (10.1)	4 (8.1)	1 (2.0)	15 (8.6)	10 (5.7)	5 (2.9)	.78
Diarrhea	6 (12.3)	4 (8.2)	2 (4.1)	23 (13.2)	20 (11.5)	3 (1.7)	>.99
Colitis	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	.39
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypophysitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperglycemia	2 (4.0)	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	.048
AST increase	9 (18.3)	9 (18.3)	0 (0.0)	8 (4.6)	8 (4.6)	0 (0.0)	.004
ALT increase	6 (12.3)	6 (12.3)	0 (0.0)	4 (2.3)	4 (2.3)	0 (0.0)	.009
Total bilirubin increase	3 (6.1)	1 (2.0)	2 (4.1)	4 (2.3)	4 (2.3)	0 (0.0)	.18
Creatinine increase	3 (6.1)	3 (6.1)	0 (0.0)	9 (5.2)	9 (5.2)	0 (0.0)	.73
Pneumonitis	2 (4.0)	1 (2.0)	1 (2.0)	7 (4.0)	4 (2.2)	3 (1.8)[b]	>.99

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]*P* values are for between-cohort comparisons of rates of any-grade adverse events and were determined with Fisher's exact test.

[b]Data include one patient with treatment-related pneumonitis of grade 5.

Table S11. Treatment-Related Select Adverse Events for Pemetrexed

Event	CAP Cohort (n = 12)			Control Cohort (n = 150)			*P* Value[a]
	Any Grade	Grade 1–2	Grade 3–5	Any Grade	Grade 1–2	Grade 3–5	
Rash	2 (16.7)	0 (0.0)	0 (0.0)	22 (14.7)	18 (12.0)	4 (2.7)	.69
Pruritus	2 (16.7)	2 (16.7)	0 (0.0)	8 (5.3)	7 (4.6)	1 (0.7)	.16
Stomatitis	1 (8.3)	1 (8.3)	0 (0.0)	3 (2.0)	2 (1.3)	1 (0.7)	.27
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.3)	>.99
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypophysitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hyperglycemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.7)	4 (2.7)	0 (0.0)	>.99
AST increase	2 (16.6)	2 (16.6)	0 (0.0)	39 (26.0)	38 (25.3)	1 (0.7)	.73
ALT increase	3 (25.0)	3 (25.0)	0 (0.0)	37 (24.7)	36 (24.0)	1 (0.7)	>.99
Total bilirubin increase	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.7)	7 (4.7)	0 (0.0)	>.99
Creatinine increase	2 (16.7)	2 (16.7)	0 (0.0)	9 (6.0)	9 (6.0)	0 (0.0)	.19
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	10 (6.7)	5 (3.3)	5 (3.4)[b]	>.99

Abbreviations: CAP, chemotherapy after PD-1 inhibitor treatment; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]*P* values are for between-cohort comparisons of rates of any-grade adverse events and were determined with Fisher's exact test.

[b]Data include one patient with treatment-related pneumonitis of grade 5.