Supplementary Table S1. Treatment-Related Adverse Events Among Patients who Received SBRT in the Phase II Trial Evaluable for Toxicity

	Concurrent RT with Pembrolizumab No. (%) (n=19)				Pembrolizumab (Salvage RT as applicable) No. (%) (n=21)			
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
General								
Fatigue	6 (32)	0	0	0	7 (33)	5 (24)	0	0
Arthralgias	1 (5)	0	0	0	3 (14)	2 (10)	0	0
Myositis	0	0	0	0	0	0	1 (5)	0
Pain	0	0	0	0	1 (5)	2 (10)	1 (5)	0
Skin								
Rash, Maculopapular	1 (5)	4 (21)	0	0	4 (19)	2 (10)	0	0
Rash, Acneiform	1 (5)	0	0	0	0	0	0	0
Skin Ulceration	0	1 (5)	0	0	0	0	0	0
Pruritis	1 (5)	0	0	0	1(5)	0	0	0
Dry Skin	0	0	0	0	0	1 (5)	0	0
Rash, Urticarial	0	0	0	0	2 (5)	0	0	0
Cardiac								
Ventricular Tachycardia	0	0	0	1 (5)	0	0	0	0
Right Ventricular Dysfunction	0	0	1 (5)	0	0	0	0	0
Myocardial Infarction	0	0	0	1 (5)	0	0	0	0
Respiratory								
Dyspnea	2 (10)	1 (5)	0	0	2 (10)	1 (5)	1 (5)	0
Cough	0	0	0	0	1 (5)	2 (10)	0	0
Pneumonitis	0	0	1 (5)	0	0	0	0	0
Hypoxia	0	1 (5)	0	0	0	0	0	0
Hemoptysis	0	0	0	0	1(5)	0	0	0
Gastrointestinal								
Dysphagia	0	0	0	0	0	0	1(5)	0
Esophagitis	0	0	0	0	1 (5)	0	0	0
Colitis	1 (5)	0	0	0	0	0	0	0
Nausea	1 (5)	0	0	0	1 (5)	0	0	0
Diarrhea	1 (5)	1 (5)	0	0	2 (10)	1(5)	0	0
Endocrine								
Hypothyroidism	0	1 (5)	0	0	1 (5)	0	0	0

Hematologic								
Anemia	0	0	0	0	1 (5)	0	0	0
leukopenia	0	0	0	0	1 (5)	1 (5)	2 (10)	0
Investigations								
AST Elevation	0	0	0	0	0	0	1 (5)	0
ALT Elevation	0	0	0	0	0	0	1 (5)	0
Hyponatremia	0	0	0	0	1 (5)	0	0	0
Hyperkalemia	0	0	0	0	0	1 (5)	0	0
Hypercalcemia	0	0	0	0	0	1 (5)	0	0
Hyperlipidemia	0	1 (5)	0	0	0	0	0	0

Supplementary Table S2. Treatment-Related Adverse Events Among Patients who Received Traditional RT in the Phase II Trial Evaluable for Toxicity

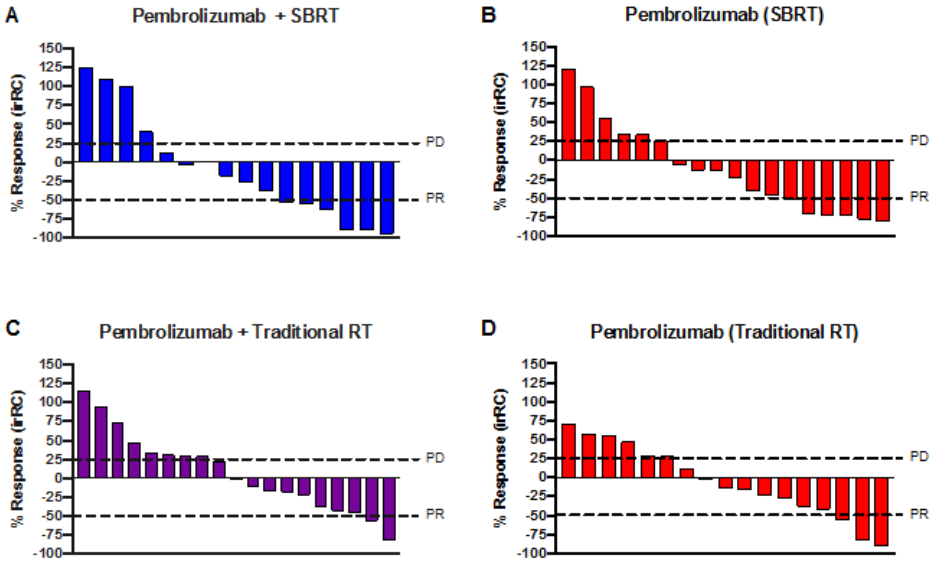
	Traditional RT with Pembrolizumab No. (%) (n=21)				Pembrolizumab (salvage RT as applicable) No. (%) (n=19)			
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
General								
Fatigue	2 (10)	1 (5)	0	0	4(21)	2 (11)	0	0
Anorexia	1 (5)	0	0	0	0	0	0	0
Myalgias	1 (5)	0	0	0	0	0	0	0
Arthralgias	2 (5)	1 (5)	0	0	2 (11)	2 (11)	0	0
Chills	0	0	0	0	1 (5)	0	0	0
Pain	1 (5)	0	0	0	0	0	0	0
Skin								
Rash, Maculopapular	1 (5)	1(5)	1 (5)	0	3 (16)	5 (26)	0	0
Rash, Acneiform	1 (5)	0	0	0	3 (16)	0	0	0
Pruritis	2 (10)	0	0	0	2 (11)	1 (5)	0	0
Dermatitis	1 (5)	0	0	0	0	0	0	0
Erythema Multiform	0	0	0	0	2 (11)	1 (5)	0	0
Mucositis	0	0	0	0	0	0	1 (5)	0
Cardiac								
Pericardial Effusion	0	0	1(5)	0	0	0	0	0
Respiratory								
Dyspnea	0	1 (5)	1 (5)	0	1 (5)	1 (5)	0	0
Hypoxia	0	1 (5)	0	0	0	1 (5)	0	0
Cough	0	1 (5)	0	0	0	1 (5)	0	0
Pneumonitis	1 (5)	0	2 (10)	0	0	0	0	0
Atelectasis	0	0	1 (5)	0	0	0	0	0
Pleural effusion	0	0	1 (5)	0	0	0	0	0
Gastrointestinal								
Abdominal Pain	0	0	0	0	1 (5)	0	0	0
Dysphagia	1 (5)	0	0	0	1 (5)	0	0	0
Esophagitis	4 (19)	0	0	0	1 (5)	0	0	0
Colitis	0	0	0	0	0	1 (5)	0	0
Nausea	1 (5)	1 (5)	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	1 (5)	0	0
Endocrine								
Hypothyroidism	1 (5)	0	0	0	0	2 (11)	0	0
Hyperthyroidism	0	0	0	0	1 (5)	0	0	0
Thyroiditis	0	0	0	0	0	1 (5)	0	0

Investigations								
AST Elevation	0	1 (5)	0	0	0	0	1 (5)	0
ALT Elevation	0	1 (5)	0	0	0	0	1 (5)	0
Creatinine Elevation	2 (10)	0	0	0	0	0	0	0
Hyponatremia	1 (5)	0	0	0	0	1 (5)	0	0
Hypokalemia	1 (5)	0	0	0	0	0	0	0
Hyperkalemia	2 (10)	0	0	0	0	1 (5)	0	0

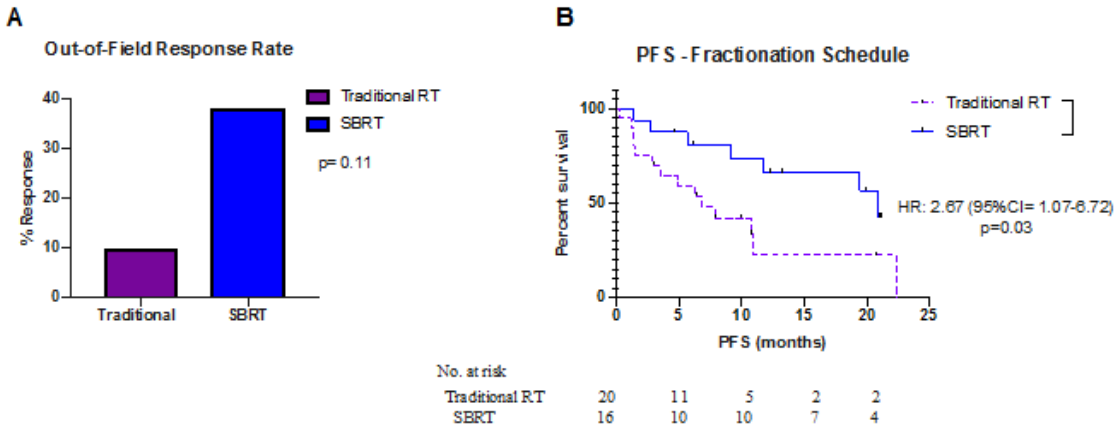
Supplementary Table S3. Best overall response by the Immune-Related Response Criteria for non-irradiated lesions

Response Type	Value or No. of Patients (%)			
	Pembrolizumab (Salvage SBRT as applicable) (n=18)	Pembrolizumab + SBRT (n=16)	Pembrolizumab (Salvage RT if applicable) (n=18)	Pembrolizumab + Traditional RT (n=20)
Objective response rate (%)	6 (33%)	6 (38%)	3 (17%)	2 (10%)
Best overall response (n)				
Complete response	0	0	0	0
Partial response	6	6	3	2
Stable disease	6	6	8	9
Progressive disease	6	4	7	9

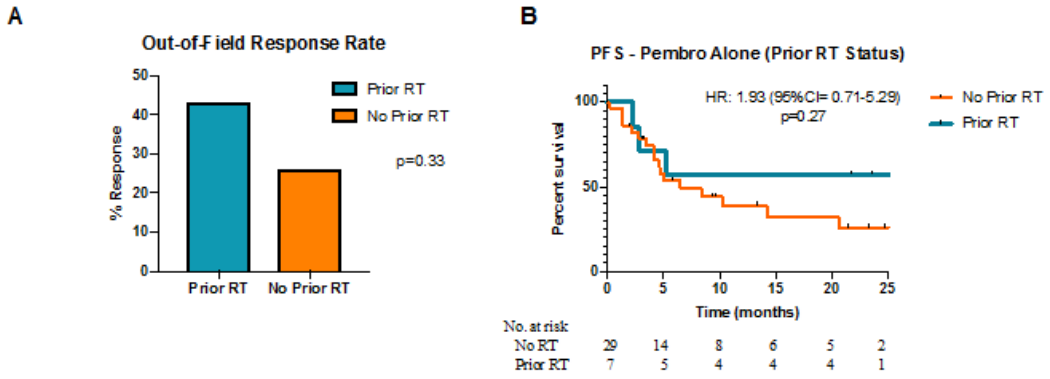
Supplementary Figure S1. Waterfall plots of response of out-of-field lesions to treatment in the (A) pembrolizumab+concurrent stereotactic radiation therapy (SBRT) group, (B) pembrolizumab + salvage (SBRT) group, (C) pembrolizumab+concurrent traditional RT group, and (D) pembrolizumab and salvage (traditional RT) group. irRC, immune-related response criteria.



Supplementary Figure S2. Treatment response in the stereotactic radiation therapy (SBRT) and traditional RT groups. (A) The out-of-field overall response rates (ORRs) were 38% for SBRT and 10% for traditional RT (P=0.11). (B) Median progression-free survival (PFS) times were 20.8 months for the SBRT group and 6.8 months for the traditional RT group (P=0.03).

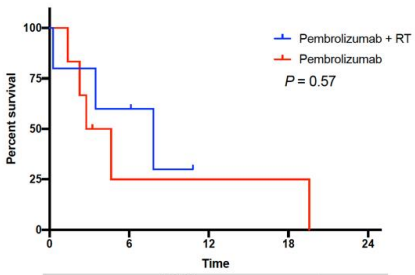


Supplementary Figure S3. Treatment response in patients with metastatic non-small cell lung cancer given pembrolizumab alone, with and or without prior radiation therapy (RT). (A) The out-of-field overall response rates (ORRs) were 43% in the pembrolizumab with prior RT group and 20% in the pembrolizumab without prior RT group (P=0 .33). (B) The median PFS time was not reached in the pembrolizumab (Pembro) with prior RT group but was 6.5 months in the pembrolizumab without prior RT group.



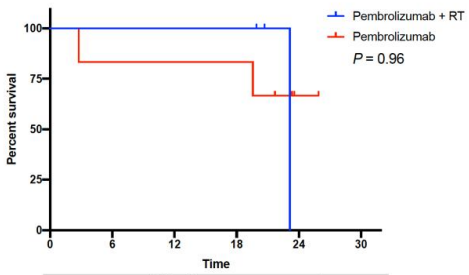
Supplementary Figure S4. Treatment response in patients with metastatic non-small cell lung cancer with different mutations. (A) Out-of-field disease control rates for patients with EGFR mutations were 50% for pembrolizumab (Pembro) alone and 60% for pembrolizumab and radiation therapy (RT) (P =0.74), with corresponding median PFS times of 3.7 months and 7.8 months (P=0 .57). (B) The out-of-field overall response rates (ORRs) for patients with P53 and Kras mutations were 50% for pembrolizumab alone and 66.7% for pembrolizumab and RT (P=0 .16). Median PFS times was were undefined for pembrolizumab alone but 23.1 months for pembrolizumab and RT (P=0.96).

A



EGFR+			
	Pembro (N=6)	Pembro+RT (N=5)	*P*
PR	0	0	
SD	3 (50%)	3 (60%)	0.74
PD	3 (50%)	2 (40%)	

B



P53+, Kras+			
	Pembro (N=6)	Pembro+RT (N=3)	P
PR	3 (50%)	2 (66.7%)	0.16
SD	3 (50%)	0	
PD	0	1 (33.3%)	