Supplementary Online Content

Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non–small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol*. Published online July 11, 2019. doi:10.1001/jamaoncol.2019.1478

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

Response evaluation and duration of treatment

Response evaluation was done according to RECIST, version 1.1, by an independent reviewer. The irradiated lesion was excluded from RECIST measurements and therefor reviewers could not be blinded for the treatment arm. Tumor response was assessed with CT-scans every 6 weeks for one year and every 8 weeks thereafter. Patients were allowed to continue treatment beyond initial radiologic progression in the absence of clinical deterioration. If the subsequent CT scan did not confirm progression, the initial progression was considered to be pseudo-progression, and the patient was allowed to continue treatment with pembrolizumab. Pseudo-progression was not scored as progressive disease for the primary endpoint. Treatment continued until confirmed radiographic progression, unacceptable toxic effects, investigator decision, patient withdrawal of consent or for a maximum of 12 months; extended to 24 months in September 2017 for alignment with other pembrolizumab trials.

PD-L1 staining and scoring criteria

PD-L1 expression was assessed after the study was closed at our local laboratory by the PD-L1 IHC 22C3 LDT assay in formalin-fixed tumor samples from tumor tissue received at baseline. Expression was categorized according to a tumor proportion score (TPS), i.e. the percentage of tumor cells with membranous PD-L1 staining: 0%, 1-49% and ≥50%.[13]

Statistical analyses, primary and secondary endpoints

The Kaplan–Meier method was used to estimate overall and progression-free survival. Data for patients who were alive or lost to follow-up were censored for OS at the time of last follow-up. Data for patients who were alive and did not have disease progression were censored for the analysis of PFS at the time of the last imaging assessment. Fisher's exact test was used to assess group differences in ORR at 12 weeks. DCR was compared using Fisher's test. PFS and OS were compared between arms using the log-rank test. The relation of patient and tumor characteristics to the effect of SBRT on PFS and OS were assessed using Cox proportional Hazard models. The relationship between PD-L1 expression and response at 12 weeks was assessed using the linear-by-linear association test.

eTable 1. Baseline demographics and disease characteristics

	Experimental arm n = 36	Control arm n = 40
Median age, years (range)	62 (35-78)	62 (38-78)
Men	20 (56%)	23 (57%)
Pack years ≥10	29 (81%)	32 (80%)
ECOG performance score		
0	17 (47%)	22 (55%)
1	19 (53%)	17 (43%)
2	0	1 (3%)
Histology		
Non-squamous	31 (86%)	36 (90%)
Squamous	5 (14%)	4 (10%)
Previous radiotherapy	15 (42%)	17 (43%)
Number of previous lines of systemic treatment		
1	26 (72%)	31 (78%)
2	6 (17%)	8 (20%)
3	4 (11%)	1 (3%)
PD-L1 TPS		
0%	18 (50%)	25 (66%)
1-49%	8 (22%)	8 (21%)
≥50%	10 (28%)	5 (13%)

Intention to treat population. Data are n (%), minimum - maximum range of age is given. ECOG = Eastern Cooperative Oncology Group. TPS = tumor proportion score.

eTable 2. Tumor site selected for trial SBRT in experimental arm

Radiated tumor site	n = 36
Lung, metastasis	11
Lymph node, intra thoracic	5
Lymph node, extra thoracic	4
Adrenal	4
Bone	4
Lung, primary tumor	4
Cutaneous	1
Liver	1
Pleural	1
Retroperitoneal	1

eTable 3. Response rates, previous vs. no previous radiotherapy

	No previous RT		**Previous RT**	
	Experimental	**Control**	**Experimental**	**Control**
	n = 21	n = 23	n = 15	n = 17
CR/PR	7 (33%)	4 (17%)	6 (40%)	3 (18%)
SD	7 (33%)	7 (30%)	3 (20%)	2 (12%)
PD	7 (33%)	12 (52%)	6 (40%)	12 (71%)

When comparing responders (CR/PR) vs. non-responders (SD/PD) we found an odds ratio of 2.4 in favor of the experimental arm in the patients that did not receive previous RT and an odds ratio of 3.1 in the same direction among the patients that did receive previous RT. These odds ratios are not significantly different from each other (p=0.81). When comparing disease control (CR/PR/SD) vs. progression (PD) we found an odds ratio of 2.2 in favor of the experimental arm in the patients that did not receive previous RT and an odds ratio of 3.6 in the same direction among the patients that did receive previous RT. These odds ratios are also not significantly different from each other (p=0.61).

eTable 4. PD-L1 expression, previous vs. no previous radiotherapy

	No previous RT	Previous RT
TPS	n = 42	n = 32
0%	27 (64%)	16 (50%)
1-49%	7 (17%)	9 (28%)
≥50%	8 (19%)	7 (22%)

The distribution of PD-L1 expression between patient receiving previous RT vs. no previous was not significantly different (p=0.37).

eTable 5. Adverse events present in at least 10% of patients and immune-related toxicities related to pembrolizumab

	All grades		Grades 3-5	
Adverse events	Experimental arm n = 35	Control arm n = 37	Experimental arm n = 35	Control arm n = 37
Fatigue	18 (51%)*	10 (27%)*	1 (3%)	0
Flu like symptoms	12 (34%)	11 (30%)	0	0
Cough	12 (34%)	8 (22%)	0	0
Dyspnea	9 (26%)	8 (22%)	4 (11%)	2 (5%)
Nausea	5 (14%)	10 (27%)	1 (3%)	2 (5%)
Pruritis	7 (20%)	5 (14%)	0	0
Pneumonia	9 (26%)*	3 (8%)*	4 (11%)	1 (3%)
Weight loss	5 (14%)	6 (16%)	2 (6%)	1 (3%)
Immune-related toxicities**				
All (n)	85	68	5	11
Pneumonitis	4 (11%)	2 (5%)	0	2 (5%)
Colitis	1 (3%)	2 (5%)	0	0
Duodenitis	1 (3%)	0	0	0
Hepatitis	0	1 (3%)	0	0
Hypothyroidism	2 (6%)	2 (5%)	0	0
Hyperthyroidism	1 (3%)	2 (5%)	0	0
Nephritis	1 (3%)	0	0	0
Nausea	0*	6 (16%)*	0	2 (5%)
Dyspnea	2 (6%)	1 (3%)	2 (6%)	1 (3%)
Skin rash	3 (9%)	1 (3%)	2 (6%)	0

Data are n (%).

* There were no significant differences between the arms at the alpha = 0.1 level, except fatigue (p=0.052), pneumonia (p=0.060) and nausea (p=0.025). After applying the Holms-Bonferroni correction to compensate for the number of different adverse events categories compared, no significance differences between arms remained.

** Only the most relevant immune-related toxicities are mentioned. Number of patients that experienced an immune-related toxicity was similar in both arms (26/37 patients in the control arm vs. 24/35 patients in the experimental arm, p=1.0). Total number of immune-related toxicities showed a trend towards in favor of the control arm (68 events in the control arm vs. 85 events in the experimental arm, p=0.076). One patient that had received SBRT to a lung lesion developed a pneumonitis grade 2. Five patients in the experimental arm experienced pneumonitis (n=3) or grade 3 dyspnea (n=2), but all five patients had received SBRT on an extrathoracic lesion, therefore no SBRT-related toxicity was suspected. One patient developed a nephritis after the SBRT on a retroperitoneal lesion in close relation to the kidney third and three courses of pembrolizumab, which was deemed as relation to the study radiation. Eight patients stopped treatment due to grade 3 AEs: in the control arm because of pneumonitis (n=1), hepatitis (n=1) and dyspnea (n=1); in the experimental arm because of nephritis (n=1), duodenitis (n=1) and a spinal fracture (n=1). All except the spinal fracture were considered to be related to pembrolizumab. A cerebrovascular accident occurred in both arms (n=2), but neither were related to study treatment. Both patients died because of complications several weeks to months afterwards. There were two grade 5 toxicities observed: an ileus in the experimental arm (considered not treatment-related) and one patient in the control arm died from multi-organ failure possibly related to the pembrolizumab treatment.