Exploring and modulating the tumor immune microenvironment: Towards improving patient outcomes of immunotherapy in lung cancer

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CHAPTER 5

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

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KEY POINTS

Question

Does stereotactic body radiotherapy enhance the effect of immune checkpoint inhibition by increasing tumor response in nonirradiated lung cancer lesions in metastatic non–small cell lung cancer?

Findings

In this phase 2 clinical trial of 76 patients with recurrent metastatic non–small cell lung cancer randomized to either pembrolizumab alone or pembrolizumab after stereotactic body radiotherapy on a single tumor site, the overall response rate at 12 weeks was 18% in the control arm vs 36% in the experimental arm.

Meaning

Stereotactic body radiotherapy prior to pembrolizumab was well tolerated; although a doubling of the overall response rate was observed, the results did not meet the study criteria for meaningful clinical benefit.

ABSTRACT

Importance

Many patients with advanced non–small cell lung cancer (NSCLC) receiving immunotherapy show primary resistance. High-dose radiotherapy can lead to increased tumor antigen release, improved antigen presentation, and T-cell infiltration. This radiotherapy may enhance the effects of checkpoint inhibition.

Objective

To assess whether stereotactic body radiotherapy on a single tumor site preceding pembrolizumab treatment enhances tumor response in patients with metastatic NSCLC.

Design, setting, and participants

Multicenter, randomized phase 2 study (PEMBRO-RT) of 92 patients with advanced NSCLC enrolled between July 1, 2015, and March 31, 2018, regardless of programmed death–ligand 1 (PD-L1) status. Data analysis was of the intention-to-treat population.

Interventions

Pembrolizumab (200 mg/kg every 3 weeks) either alone (control arm) or after radiotherapy (3 doses of 8 Gy) (experimental arm) to a single tumor site until confirmed radiographic progression, unacceptable toxic effects, investigator decision, patient withdrawal of consent, or a maximum of 24 months.

Main outcomes and measures

Improvement in overall response rate (ORR) at 12 weeks from 20% in the control arm to 50% in the experimental arm with $P < .10$.

Results

Of the 92 patients enrolled, 76 were randomized to the control arm ($n = 40$) or the experimental arm ($n = 36$). Of those, the median age was 62 years (range, 35-78 years), and 44 (58%) were men. The ORR at 12 weeks was 18% in the control arm vs 36% in the experimental arm ($P = .07$). Median progression-free survival was 1.9 months (95% CI, 1.7-6.9 months) vs 6.6 months (95% CI, 4.0-14.6 months) (hazard ratio, 0.71; 95% CI, 0.42-1.18; $P = .19$), and median overall survival was 7.6 months (95% CI, 6.0-13.9 months) vs 15.9 months (95% CI, 7.1 months to not reached) (hazard ratio, 0.66; 95% CI, 0.37-1.18; $P = .16$). Subgroup analyses showed the largest benefit from the addition of radiotherapy in patients with PD-L1–negative tumors. No increase in treatment-related toxic effects was observed in the experimental arm.

Conclusions and relevance

Stereotactic body radiotherapy prior to pembrolizumab was well tolerated. Although a doubling of ORR was observed, the results did not meet the study's prespecified end point criteria for meaningful clinical

benefit. Positive results were largely influenced by the PD-L1–negative subgroup, which had significantly improved progression-free survival and overall survival. These results suggest that a larger trial is necessary to determine whether radiotherapy may activate noninflamed NSCLC toward a more inflamed tumor microenvironment.

Trial registration
ClinicalTrials.gov identifier: NCT02492568

INTRODUCTION

In recent years, treatment for non-small cell lung cancer (NSCLC) has changed significantly owing to the introduction of immunotherapy. The programmed death-ligand 1 (PD-L1)/programmed death 1 (PD-1) pathway is one of the most studied tumor immune escape mechanisms [1]. Targeting the PD-L1/PD-1 pathway with immune checkpoint inhibitors has produced long-lasting anti-tumor immune responses in a subset of NSCLC patients [2-5]. Unfortunately, most patients with NSCLC do not benefit from this treatment owing to primary resistance, possibly because certain tumor antigens are not recognized.

Stereotactic body radiotherapy (SBRT) is the delivery of a high radiation dose in generally 3 to 5 fractions with high accuracy to a single tumor site. SBRT may synergize with immunotherapy. Several preclinical studies reported an increased tumor antigen release, improved antigen presentation and T-cell infiltration in irradiated tumors. Combining radiotherapy with immune checkpoint inhibition showed more pronounced tumor regression in several solid tumor types, including in the nonirradiated tumors, than provided by either of these treatments alone [6-12].

We present the results of the PEMBRO-RT study, the first randomized study, to our knowledge, of pembrolizumab, a highly selective humanized PD-1 monoclonal antibody, with or without prior SBRT to a single tumor site in patients with metastatic NSCLC. This study evaluates whether SBRT enhances the effect of immune checkpoint blockade by increasing tumor response in nonirradiated lung cancer lesions on PD-1 immune checkpoint blockade.

METHODS

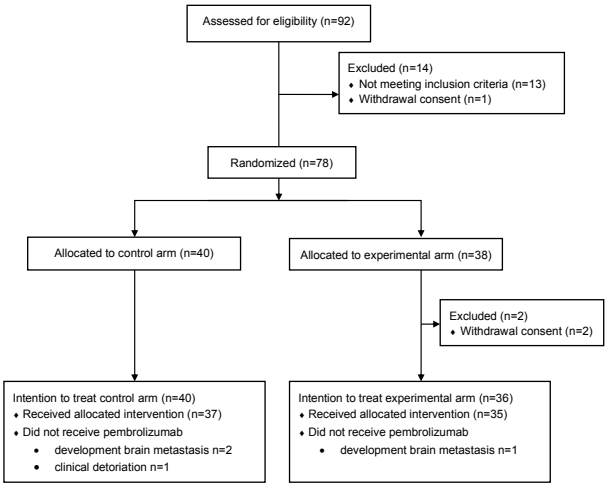
This multicenter, phase 2 randomized clinical trial was conducted at 3 medical sites in the Netherlands. Patients 18 years or older were eligible to participate if they had histological or cytological confirmed metastatic NSCLC that progressed after at least 1 regimen of chemotherapy but who were immunotherapy naive and had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or lower. At least 2 separate lesions were required, one of which was measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) and suitable for biopsy, and the other of which was amenable to irradiation. Patients were ineligible if they had (1) radiotherapy to any tumor site within 6 months prior to randomization; (2) known, active central nervous system metastases and/or carcinomatous meningitis; (3) untreated driver alterations of epidermal growth factor receptor or anaplastic lymphoma kinase; or (4) active autoimmune or interstitial lung disease. The trial protocol and all amendments were approved by the institutional review board or independent ethics committee of the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam. The trial was conducted in accordance with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines of the European Medicines Agency and the US Food and Drug Administration. All patients provided written informed consent before enrollment.

Patients were randomly assigned using a 1:1 ratio to receive treatment with pembrolizumab either after SBRT to a single tumor site (experimental arm) or without SBRT (control arm). Randomization was

stratified to smoking status (<10 pack years vs ≥10 pack years). Pembrolizumab was administered intravenously at 200 mg every 3 weeks. In the experimental arm, the first course was given within 7 days after completion of SBRT, which consisted of 3 doses of 8 Gy delivered on alternate days to a single tumor site that did not overlap with the biopsy site and was deemed most safe and/or convenient for the patient. 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 end point. 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 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].

The primary end point was overall response rate (ORR) -complete response and partial response- at 12 weeks from randomization. Secondary end points included safety, progression-free survival (PFS), overall survival (OS) and disease control rate (DCR) at 12 weeks. End points were assessed in the intention-to-treat (ITT) population, including all patients that underwent randomization with the exception of 2 patients in the experimental arm, who both withdrew consent (Figure 1). Adverse events were graded according to the Common Toxicity Criteria, version 4.0, and were registered from the date of informed consent until discontinuation of trial treatment. Exploratory end points included the effect of PD-L1 expression and prior radiotherapy on efficacy.

Figure 1. Consort diagram.



Efficacy was assessed in the ITT population, and safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least 1 dose of the assigned therapy. A statistical analysis indicated that with a sample of 74 patients, 37 in each arm, the trial would have a power of 82% with an odds ratio of 4 to detect the difference between a response rate of 20% in the control arm and a response rate of 50% in the experimental arm at a 20sided significance level of P < .10. The Kaplan–Meier method was used to estimate OS and PFS. 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.

RESULTS

Between July 1, 2015, and March 31, 2018, 92 patients were screened for enrollment, and 76 patients who met the eligibility criteria were randomly assigned to either the control arm (n = 40) or the experimental arm (n = 36). Of those, the median age was 62 years (range, 35-78 years), and 44 (58%) were men. Patient demographics, including previous radiotherapy, were well balanced between both arms. The percentage of PD-L1 negative tumors was slightly higher in the control arm (25 of 38 [66%]) than in the experimental arm (18 of 36 [50%]), and the number of patients with a TPS of 50% or higher was lower in the control arm than in the experimental arm (5 of 38 [13%] vs 10 of 36 [28%]) (P = .10) (Table 1). The tumor sites selected for SBRT were primarily lung lesions or lymph node metastases (Table S1).

Table 1. Baseline demographics and disease characteristics.

Total (n = 76)	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.

Thirty-seven patients (92%) in the control arm and 35 patients (97%) in the experimental arm received at least 1 course of pembrolizumab. All patients who did not receive pembrolizumab were categorized as having progressive disease for further analyses. One patient received palliative radiotherapy before the primary end point but remained part of the ITT population. At the cutoff date of July 1, 2018, the median follow-up time was 23.6 months (range, 0.1-34.4 months). Seven patients (18%) in the control arm and 4 patients (11%) in the experimental arm were still receiving treatment. The median duration of treatment for patients with at least 1 dose of pembrolizumab was 2.1 months (95% CI, 1.2-5.6 months) in the control arm and 4.2 months (95% CI, 2.7-11.0 months) in the experimental arm (P = .30).

In the ITT population, the ORR at 12 weeks was 18% (95% CI, 7%-33%) in the control arm vs. 36% (95% CI, 21%-54%) in the experimental arm (P = .07) (Table 2). The increased ORR in the experimental arm (22%) compared with the control arm (4%) was largely influenced by ORR in the PD-L1-negative subgroup, although this ORR in the PD-L1-negative subgroup was not significant (P = .14). Response rates in the 2 PD-L1-positive subgroups were similar in both arms. There was 1 complete response (CR) in the control arm and 3 in the experimental arm. In the control arm, the majority of patients (21 of 40 [53%]) showed progressive disease (PD) as best ORR compared with the experimental arm, in which partial response (PR) was most common (14 of 36 [39%]). Stable disease (SD) as best response was identical in both arms (10 of 40 [25%] and 9 of 35 [25%], respectively). In the overall population, significant improvement (64% vs 40%; P = .04) was observed in the DCR at 12 weeks in the experimental arm. The effect of SBRT on response rates in patients who were previously treated with radiotherapy (ie, >6 months before randomization) and patients who never received any radiotherapy was similar (odds ratios, 3.1 [95% CI, 0.5-23.5] vs 2.4 [95% CI, 0.5-13.1], both in favor of the experimental arm; P = .81), suggesting that previous radiotherapy did not strongly affect study results (Table S2). The distribution of baseline PD-L1 expression did not differ between patients who received radiotherapy more than 6 months before inclusion (PD-L1 expression of 0%, 27 patients; 1%-49%, 7 patients; and ≥50%, 8 patients) and patients who did not receive radiotherapy before inclusion (PD-L1 expression of 0%, 16 patients; 1%-49%, 9 patients; and ≥50%, 7 patients) (P = .37) (Table S3). Two patients in the control arm had an initial increase in tumor burden of more than 20% at week 6 followed by PR at week 12, which was considered pseudoprogression.

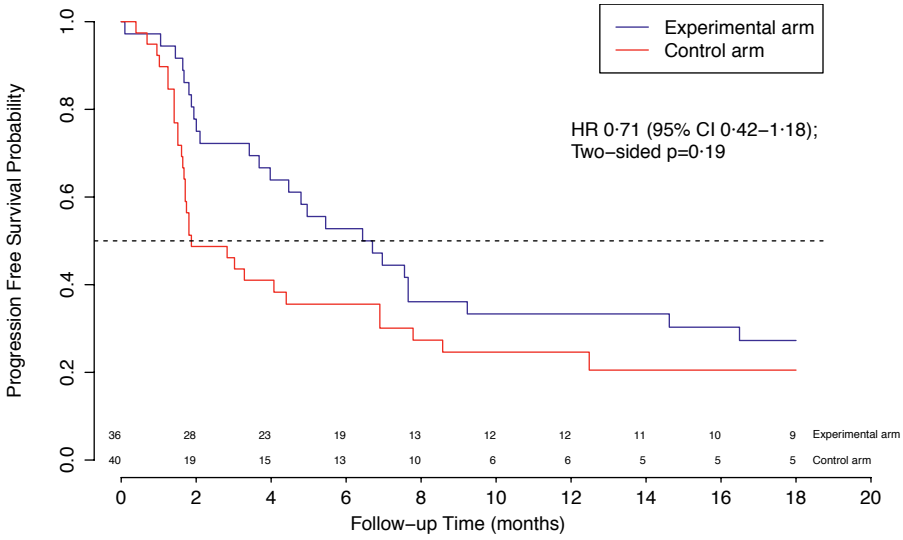
Table 2. Response to treatment.

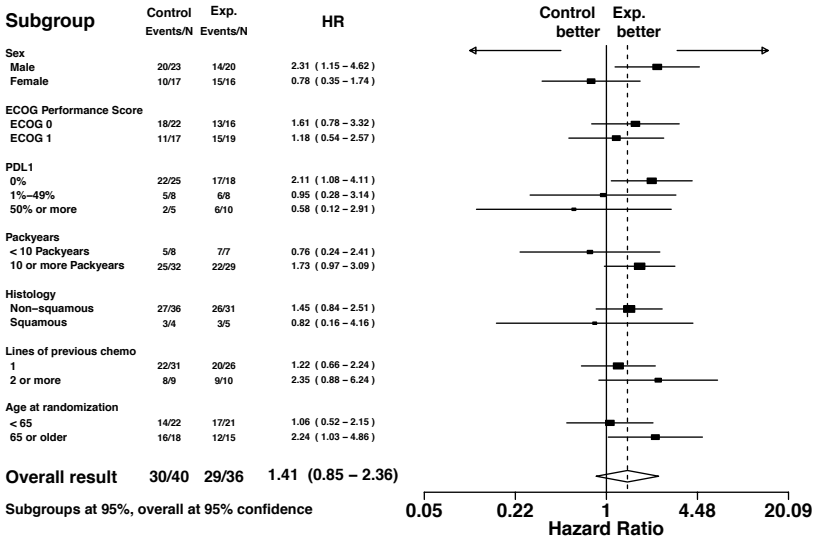
Response	Experimental arm n = 36	Control arm n = 40
Best overall response		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate (ORR) at 12 weeks		
Overall*	13/36 (36%)	7/40 (18%)
PD-L1 TPS 0%	4/18 (22%)	1/25 (4%)
PD-L1 TPS 1-49%	3/8 (38%)	3/8 (38%)
PD-L1 TPS ≥50%	6/10 (60%)	3/5 (60%)
Disease Control Rate (DCR) at 12 weeks**	23/36 (64%)	16/40 (40%)

Data are n/total n (%). TPS = tumor proportion score.
*P = 0.07; **P = 0.04

At the time of analysis, median PFS was 1.9 months (95% CI, 1.7-6.9 months) in the control arm and 6.6 months (95% CI, 4.0-14.6 months) in the experimental arm (Figure 2). The increased PFS in the experimental arm was not significant (hazard ratio [HR], 0.71; 95% CI, 0.42-1.18; P = .19). A significant benefit of SBRT with respect to PFS was seen in the PD-L1-negative subgroup (HR, 0.49; 95% CI, 0.26-0.94; P = .03); however, the limited number of responders must be taken into account. No benefit from the addition of SBRT was seen in the PD-L1-positive subgroups (HR, 1.14; 95% CI, 0.45-2.89; P = .79) (Figure 2).

Figure 2. Progression free survival in the ITT population.

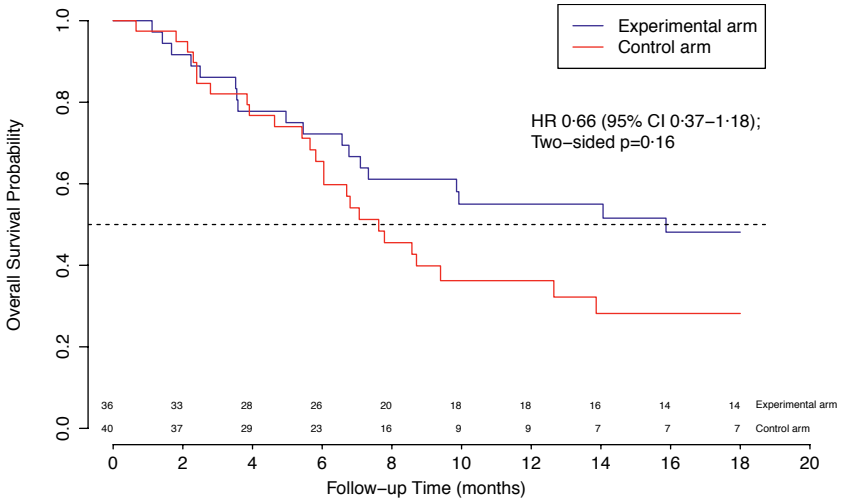


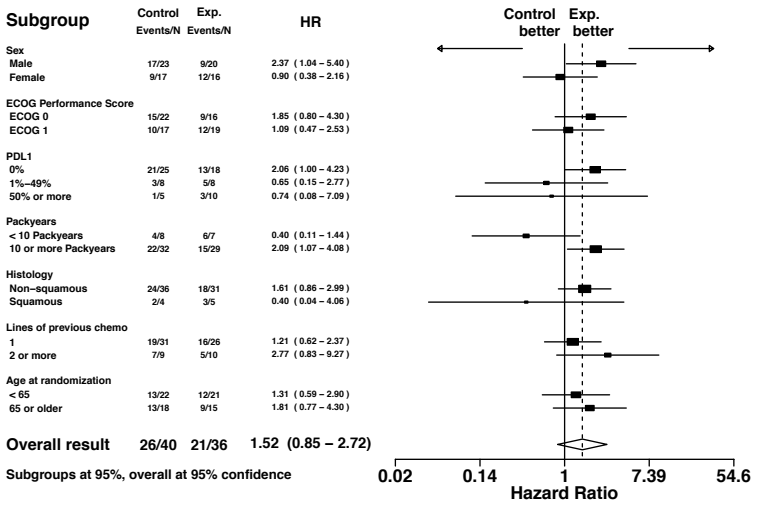


ITT = intention to treat. HR = hazard ratio. ECOG = Eastern Cooperative Oncology Group

At the time of analysis, 51 patients had died. A median OS of 7.6 months (95% CI, 6.0-13.9 months) in the control arm and 15.9 months (95% CI, 7.1 months to not reached) in the experimental arm was observed (Figure 3). This increased OS was not significant (HR, 0.66; 95% CI, 0.37-1.18; P = .16). The benefit of SBRT with respect to OS was observed only in the PD-L1-negative subgroup (HR, 0.48; 95% CI, 0.24-0.99; P = .046), and no benefit was seen in the combined PD-L1-positive subgroups (HR, 1.4; 95% CI, 0.42-4.66; P = .58). Male patients (HR, 0.42; 95% CI, 0.19-0.96; P = .04) and smokers (HR, 0.48; 95% CI, 0.25-0.93; P = .03) performed significantly better in the experimental arm compared with the control arm (Figure 3). After correction for other variables, only PD-L1 status remained a predictive factor for OS in the experimental arm.

Figure 3. Overall survival in the ITT population.





ITT = intention to treat. HR = hazard ratio. ECOG = Eastern Cooperative Oncology Group

The most common adverse events were fatigue (28 of 72 patients [39%]), flulike symptoms (23 of 72 [32%]), and cough (20 of 72 [28%]). Fatigue (10 of 37 patients [27%] vs 18 of 35 [51%]; P = .05) and pneumonia (3 of 37 [8%] vs 9 of 35 [26%]; P = .06) occurred more often in the experimental arm than in the control arm. Pembrolizumab-related toxic effects were primarily fatigue (18%), flulike symptoms (15%), and pruritus (14%). Grade 3 to 5 pembrolizumab-related toxic effects were reported in 12 patients (17%), with no significant differences between arms. Adverse events that appeared in more than 10% of patients and relevant pembrolizumab-related toxic effects are presented in Table 3. The number of patients that experienced an immune-related toxicity was similar in both arms (26 of 37 patients [70%] in the control arm vs 24 of 35 patients [69%] in the experimental arm; P = 1.0). The total number of immune-related toxicities showed a trend in favor of the control arm (68 vs 85 events; P = .08). One patient who received SBRT to a lung lesion developed a pneumonitis grade 2. Pembrolizumab was temporarily interrupted and the patient was retreated successfully, leading to a long-lasting PR. Five patients in the experimental arm experienced pneumonitis (n = 3) or grade 3 dyspnea (n = 2), but all 5 patients received SBRT on an extrathoracic lesion, therefore no SBRT-related toxicity was suspected. One patient developed a nephritis after 3 courses of pembrolizumab and SBRT to a retroperitoneal lesion in close relation to the kidney, which was deemed as related to the combination treatment, and immunotherapy was terminated. 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 administration. 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 2 grade 5 toxicities observed: an ileus in the experimental arm (considered not treatment-related) and 1 patient in the control arm died from multi-organ failure possibly related to the pembrolizumab treatment.

Table 3. AEs 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 clinical relevant immune-related toxicities are mentioned.

DISCUSSION

The PEMBRO-RT study is the first randomized trial, to our knowledge, to show an augmenting effect of SBRT on the response to PD-1 blockade in patients with metastatic NSCLC. The experimental arm showed an increase in ORR, DCR at 12 weeks, and median PFS and OS without an increase in toxic effects. The study did not meet its primary end point because the improvements did not meet the study's prespecified criteria -an increase of ORR from 20% in the control arm to 50% in the experimental arm at 12 weeks- for meaningful clinical benefit.

In recent trials, response rates of pembrolizumab-treated patients with advanced NSCLC were dependent of PD-L1 expression levels of the tumor [2, 4, 13, 14]. The response rates in the combined PD-L1-positive subgroups (PD-L1 ≥ 1%) in our study was much higher compared with other trials (52% [16 of 31] vs 18 to 27% [2, 13]. Patient and tumor characteristics in this study were comparable with previously reported studies. The reason for this study's high response rate remains unclear, but the excellent patient outcomes observed in both PD-L1-positive subgroups may have masked a potential augmenting effect of SBRT in this setting.

An imbalance of PD-L1 distribution in favor of the experimental arm has to be taken into account for the overall cohort; however, when data from the PD-L1-negative subgroups were evaluated, a significant benefit was observed from the experimental approach. Blood and tumor samples collected during this trial may assist in gaining better insight regarding whether this improvement can be attributed to an augmenting effect from SBRT in these PD-L1-negative patients.

LIMITATIONS

Little is known about the effects of radiotherapy dose, fractionation, and treatment site on the antitumor immune response. Several immunogenic mice studies reported that the immune-modulating effect of hypofractionated radiotherapy was more pronounced compared with single-dose radiotherapy [6, 15-17]. Thus, a dose of 3 × 8 Gy was chosen for SBRT preparation and delivery because of its high accuracy, which minimized the potential for toxic effects caused by the addition of radiotherapy. To further reduce the possibility of toxic effects, SBRT was administered to the experimental arm sequentially rather than concurrently, with no longer than 1 week between the last radiotherapy dose and the first pembrolizumab dose to minimize delay of systemic treatment. A study by Dovedi et al. reported a decrease in PD-L1 expression and anergy of tumor-reactive T-cells 7 days after the last dose of fractionated radiotherapy in mice models [8]. Further research is needed to explore whether the radiotherapy dose and schedule used in this clinical trial were optimal with respect to the immune-modulating potential of radiation in combination with immune checkpoint inhibition in patients with cancer.

The safety profile observed in this clinical trial was consistent with previous studies of pembrolizumab treatment for advanced NSCLC [2, 4, 13]. Most immune-mediated events were grade 1 or 2. No significant differences in toxic effects between arms were observed. Only 1 patient experienced an

immune-related adverse event that may have been augmented by SBRT. Nephritis developed in 1 patient after the administration of SBRT on a retroperitoneal lesion and the third course of pembrolizumab, resulting in discontinuation of treatment. Luke et al. reported safety data on 73 patients with solid tumors who were treated with pembrolizumab after SBRT to 2 to 4 tumor lesions [18]. The timing of SBRT was similar to this study, but doses varied from 30 to 50 Gy in 3 to 5 fractions, depending on the tumor site. They concluded that the administration of SBRT before pembrolizumab treatment was well tolerated. In a KEYNOTE-001 phase 1 clinical trial, Shaverdian et al analyzed the effects of previous radiotherapy on the efficacy and safety of pembrolizumab treatment in patients with NSCLC [19]. They reported that the safety profile was acceptable, with a longer PFS and OS in the subgroup that received previous radiotherapy. The effects of previous radiotherapy on the efficacy and safety of pembrolizumab could not be established in this study, but this possible bias should be further investigated.

CONCLUSIONS

The results of this study are encouraging, and further evaluation in a larger phase 2/3 trial is recommended to confirm the findings and elucidate the processes by which SBRT may activate noninflamed NSCLC tumors towards an inflamed tumor microenvironment, rendering them receptive to immune checkpoint inhibition.

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SUPPLEMENTARY DATA

Table S1. Tumor site selected for trail 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

Table S2. Response rates previous vs. no previous radiotherapy.

	No previous RT		Previous RT	
	Experimental	Control	Experimental	Control
Response	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 2.3 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 = .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 = .61).

Table S3. 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).