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A Prospective Trial Evaluating the Safety and Systemic Response From the Use of Radiation Therapy with Checkpoint Inhibitor Immunotherapy in Metastatic Non-Small Cell Lung Cancer

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Abstract

Introduction/Background: This study assessed the safety and systemic (abscopal) response from the addition of local stereotactic body radiation therapy (SBRT) to checkpoint inhibitor (CPI) immunotherapy in patients with metastatic non-small cell lung cancer (NSCLC).

Patients/Methods: Thirty-five patients with at least two sites of measurable disease on PET/CT received standard-of-care CPI immunotherapy alone (n=19), or in combination with 4 cycles doublet carboplatin/pemetrexed chemotherapy (n=16), and 3–5 fractions SBRT to a single extracranial target lesion between cycles 1–2 of the systemic therapy. Adverse events were

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Declarations of Interest

Malcolm D. Mattes has no conflicts of interest. Timothy D. Eubank has no conflicts of interest. Mohammed Almubarak has no conflicts of interest. Sijin Wen has no conflicts of interest. Gary Marano has no conflicts of interest. Geraldine M. Jacobson has no conflicts of interest. Patrick C. Ma is on the speaker's bureau for Merck, AstraZeneca, Bayer, Bristol-Myers Squibb; he also is on the advisory board (Ad hoc) for AstraZeneca and Apollomics.

assessed using CTCAE version 5.0. Best systemic objective response rate (ORR) was assessed using iRECIST criteria, excluding any irradiated lesion(s). Additional SBRT to a different target lesion was offered to patients who continued on immunotherapy with unconfirmed progressive disease or mixed response.

Results: Fifteen patients (44%) experienced 22 grade 1–2 toxicities potentially attributable to radiation, most commonly pneumonitis (n=9) and fatigue (n=6), and no grade 3–5 radiation-induced toxicities. Patients undergoing combined CPI-chemotherapy received a lower median biologically effective dose of SBRT than those undergoing CPI monotherapy (43.2 vs. 60Gy), but had a higher rate of radiation-induced toxcity (56% vs. 32%, $p<0.01$). The best systemic ORR was 53%, with 20.5% stable disease and 26.5% progressive disease. Fifteen patients underwent a subsequent course of SBRT based on their response, among which 3 (20%) had progression-free intervals of 12, 16, and 10 months thereafter.

Conclusions: Addition of SBRT to CPI immunotherapy (with/without chemotherapy) is safe. The favorable systemic response observed warrants further assessment with a randomized trial.

MicroAbstract:

This single-arm prospective trial enrolled 35 patients to assess whether radiation therapy can be added safely to checkpoint inhibitor immunotherapy (with or without chemotherapy) in patients with metastatic non-small cell lung cancer. No grade 3–5 radiation-induced toxicities were observed, and a preliminary assessment of effiacy suggests that radiation may be particularly valuable for patients with high PD-L1 expression who receive CPI without chemotherapy.

Keywords

radiation therapy; non small cell lung cancer; immunotherapy; metastatic; radiobiology

Introduction

Checkpoint inhibitor (CPI) immunotherapy directed at the programmed death–ligand 1 (PD-L1)/programmed death 1 (PD-1) pathway is now standard-of-care first or second/third line therapy for metastatic non-small cell lung cancer (NSCLC). CPIs can be utilized as either single agent or in combination with cytotoxic chemotherapy, depending on predictive biomarkers such as PD-L1 expression and tumor mutational burden.[1] However, many patients have primary resistance to CPI immunotherapy, with expected response rates to single agent therapy of 19–45%,[2–6] and chemo-immunotherapy of 48–58%.[7–9] Furthermore, though a subset of responding patients who continue on maintenance CPI immunotherapy experience a long-lasting antitumor effect, development of secondary resistance mechanisms limits the duration of response to a median of 8–15 months in most initial responders.[2–10]

In recent years, several preclinical studies have demonstrated that radiation therapy can serve as an effective addition to CPI immunotherapy, priming a more robust abscopal/systemic effect on cancer lesions outside of the irradiated area through increased antigen release and presentation, and mobilization of immune effector cells.[10–17] Radiation therapy may also have some potential to overcome secondary resistance mechanisms by boosting an immune response to any subset of resistant tumor clones that develop over time.[18–22] Our primary

hypothesis in this study was that the addition of stereotactic body radiation therapy (SBRT) to CPI immunotherapy would be safe and feasible. Our seconary hypothesis was that SBRT could help overcome both primary and secondary immune resistance and enhance systemic response rates compared to historical standards. This was assessed by conducting a phase I clinical trial in which SBRT was administered up-front with the initiation of immunotherapy, and for subsequent systemic progression, in the treatment of patients with advanced NSCLC.

Patients and Methods

The primary objective of this prospective, single-armclinical trial (ClinicalTrials.gov Identifier: NCT03035890) was to assess the safety of adding SBRT to standard-of-care CPI immunotherapy (with or without concurrent chemotherapy) in CPI-naïve subjects with advanced recurrent, or metastatic, NSCLC. The primary endpoint of the study was adverse events possibly, probably, or definitely related to radiation, graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The best systemic objective response rate (ORR),defined as complete and partial response per iRECIST criteria,[23] was also measured as a preliminary assessment of efficiacy. Additional secondary endpoints included disease control rate (defined as complete and partial response and stable disease), toxicity, progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS).

Subjects who were 18 years or older would be eligible if they had at least two measurable, previously non-irradiated, sites of disease and histology-confirmed NSCLC treated at the West Virginia University Cancer Institute. All subjects underwent pre-treatment baseline whole body PET/CT and brain MRI. They were required to have adequate organ and marrow function, Zubrod performance status 0–2, and life expectancy of at least 3 months. Subjects were excluded if they had prior treatment with a drug targeting immune stimulation, active autoimmune disease, oral corticosteroid dependency, or any uncontrolled intercurrent illness. Prior palliative or curative-intent radiation therapy was permitted.

The up-front SBRT to a single target lesion was delivered in 3–5 fractions between the 1st and 2nd cycles of CPI immunotherapy, using highly conformal treatment techniques, secure immobilization devices, and respiratory motion management as indicated. No SBRT fractions were delivered within 5 days after chemotherapy administration, but a fraction could be given on the same day as immunotherapy administration. Standard SBRT dose-volume constraints for normal tissue were utilized. The prescribed dose-fractionation scheme and the lesion treated was at the discretion of the treating radiation oncologist. Generally, moderate doses with a lower biologically effective dose (BED) were favored over the high ablative doses commonly used for curative-intent in early-stage NSCLC patients, in order to avoid significant treatment-related morbidity. Preference was given to irradiating lesions in visceral organs that were either symptomatic, had a high potential to become symptomatic, or could be treated with minimal toxicity risk. There were no restrictions on the minimum or maximum tumor volume to be irradiated. The type of standard-of-care systemic therapy utilized was at the treating medical oncologist’s discretion, with options including either pembrolizumab alone, nivolumab alone, atezolizumab alone, or the

combination of doublet carboplatin/pemetrexed with pembrolizumab, each at standard-of-care doses.

Subjects were evaluated for response using either PET/CT or CT with contrast at 2–4 month intervals after initiation of immunotherapy, using iRECIST criteria.[23] The irradiated tumor was excluded from tumor burden calculations in order to monitor only the systemic response rate without bias from the local response to radiation therapy. By iRECIST criteria, classification of complete response (CR), partial response (PR), and progressive disease (PD) required confirmation on two consecutive observations at least 4 weeks apart. At any time while a subject was on study, a finding of unconfirmed PD or mixed response (in the absence of PD) made that subject eligible for an additional course of SBRT to a new single target lesion with an intent to further promote a systemic response. However, this additional SBRT was considered optional, and only given if the treating radiation oncologist felt it could be done safely, the patient consented to treatment, and at least one measurable site of disease would remain unirradiated for continued systemic response assessment.

CPI immunotherapy could be discontinued for intolerance, disease progression, or if the treating physicians determined that it was not in the patient's best interest to continue as per standard of care practice guidelines. Regardless of the date of discontinuation of CPI immunotherapy, each patient remained on study until the time of confirmed disease progression, at which point patients went off study and further decisions on systemic therapy were at the discretion of the treating medical oncologist. Patients were not permitted to switch to an alternative systemic therapy while on-study.

Descriptive statistics were used to summarize the demographic characteristics of our patient population, adverse event rates, and systemic objective response rate. Adverse events are reported for the entire cohort, and the Fisher's exact test was used to compare two subgroups of patients undergoing CPI monotherapy compared to combined CPI-chemotherapy. ORR is reported for the entire cohort, as well as three subgroups stratified according to expected response rate based on prior studies. A high probability of response (48–58%) was expected in those receiving combined chemo-immunotherapy regardless of PD-L1 expression, and intermediate probability of response (38–45%) was expected in those receiving CPI immunotherapy alone with PD-L1 ≥ 50%, and a low probability of response (19–27%) was expected in those receiving CPI immunotherapy alone with PD-L1 < 50%.[2–9] The Kaplan-Meier method was used to estimate PFS, TTP, and OS; each was calculated from the date of the first cycle of immunotherapy. All procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2000.

Results

Enrollment of all 35 patients was completed between March 2017 and April 2019. Patient demographics, tumor and treatment characteristics are shown in Tables 1 and 2. The median patient age was 66 years (interquartile range (IQR) 58.5 – 70.5). The majority of patients (94%) were Caucasian. The median number of pack-years cigarette smoking was 35 (IQR 24 – 60) for past and current smokers. The median baseline tumor burden by iRECIST

criteria was 10.7 cm^2 (IQR 5.9 – 15.6 cm^2). Fifty-four percent of patients underwent prior radiation therapy, either as part of a prior curative-intent treatment (n=3), or for palliation (n=16) of a symptomatic area of malignancy (e.g. brain or bone metastases) prior to enrollment. Fourteen percent of patients underwent prior platinum-based doublet chemotherapy for curative (n=3) or palliative (n=2) intent.

PD-L1 tumor proportion score was positive (defined as ≥1%) in 86% of patients, with high expression (≥50%) in 57% of patients. A total of 54% of patients received immunotherapy alone whereas 46% received combined chemotherapy and immunotherapy. Chemo-immunotherapy was used in 30% of patients (n=6) with PD-L1 TPS ≥ 50%, 66% of patients (n=6) with PD-L1 TPS 1–49%, and 75% of patients (n=3) with PD-L1 TPS 0%. All patients underwent an initial course of RT concurrently with the start of immunotherapy, with the primary tumor targeted in 23 patients (65%). The median BED of the initial SBRT course was 48 Gy (interquartile range 43 – 60 Gy), with the most common dose-fractionation schemes being 24 – 36 Gy in 3 fractions (n=17) or 30–35 Gy in 5 fractions (n=11). The median gross tumor volume (GTV) of the targeted lesion was 16.8 cm^3 (IQR 7.8 – 57.0 cm^3).

The median OS of all enrolled patients was 15.0 months (95% confidence interval 11.0 – 40.0 months), median PFS was 6.9 months (95% confidence interval 4.3 – 26.0 months), and median TTP was 11.2 months (5.5 – 40.0 months). Only one patient experienced progressive disease in an irradiated lesion over the course of the study, for a local control rate of 97%.

Fifteen patients (44%) experienced 22 grade 1–2 toxicities considered to be potentially attributable to radiation, including 9 pneumonitis, 6 fatigue, 3 nausea, 2 skin erythema, 1 abdominal pain, and 1 dysphagia. No patients experienced grade 3–5 radiation-induced toxicities. Patients undergoing combined CPI-chemotherapy received a lower median biologically effective dose of SBRT than those undergoing CPI monotherapy (43.2 vs. 60Gy), but had a higher rate of radiation-induced toxcity (56% vs. 32%, $p<0.01$). Severe immune-related adverse events were experienced by 3 patients, resulting in a prolonged interval off immunotherapy in the absence of disease progression; two of these patients successfully resumed immunotherapy several months later after their toxicity resolved. Four patients died of infectious (n=3) and cardiac (n=1) causes in the absence of disease progression at 2, 4, 4, and 6 months after enrollment, respectively; each of these patients had received combined CPI-chemotherapy.

Thirty-four patients were evaluable for response, with one patient with a history of cardiovascular disease deceased of a cardiac arrest prior to any follow-up imaging being performed. At a median follow-up of 14.0 months (IQR 5.4 – 23.5 months), the best systemic ORR was 53%, and the disease control rate was 73.5%. The best observed response was CR in 2 patients, PR in 16 patients, stable disease (SD) in 7 patients, and PD in 9 patients. The five subjects with a low probability of response (CPI monotherapy and PD-L1 0–49%) had an observed ORR of 20.0%, the 14 subjects with an intermediate probability of response (CPI alone and PD-L1 50–100%) had an observed ORR of 64.3%, and the 14 subjects with a high probability of response (combined CPI-chemo and any PD-L1) had an observed ORR of 53.3%.

Fifteen patients (44%) underwent a subsequent course of RT while on immunotherapy; 12 of these patients (80%) continued to develop PD, but 3 patients (20%) experienced progression-free intervals of 12, 16, and 10 months thereafter, after targeting a single site of progressive disease in an intramedullary spine metastasis, para-aortic lymph node metastasis, and bone metastasis, respectively. Only one of these patients had an improvement in their best response (SD converted to PR) as a result of the additional SBRT.

Discussion

Preclinical data has suggested that radiation therapy may act synergistically with CPI immunotherapy to enhance a systemic response, though the magnitude of this effect in patients, as well as the optimal approach to radiation therapy delivery in this setting, remain to be defined. This prospective clinical trial has demonstrated that in patients with advanced recurrent or metastatic NSCLC, the addition of SBRT to CPI immunotherapy is safe and feasible, with minimal added treatment-related toxicities or morbidity. Although our assessment of efficacy should be considered preliminary and hypothesis-generating due to the relatively heterogeneous patients enrolled and treatments administered, the 64.3% ORR in the subjects who had PD-L1 50–100% and were treated with CPI monotherapy appears most favorable compared to prior studies reporting a 38–45% response rate in this patient population.

The relative safety of combined radiation therapy and immunotherapy has been demonstrated in several restrospective as well as prospective studies.[24–29] Our findings are unique in including patients receiving combined chemo-immunotherapy, rather than immunotherapy alone, and while the rate of Grade 1–2 radiation-induced toxicity was higher in this cohort of patients receiving chemotherapy, still no grade 3 or higher toxicities were observed at moderate radiation doses using highly conformal treatment planning techniques.

A summary of prospective studies that have assessed the immune priming effect of radiation therapy in patient populations that included metastatic NSCLC is shown in Table 3.[26–29] In a randomized phase II trial, Theelen *et al* reported that the addition of SBRT to pembrolizumab in 76 metastatic NSCLC patients led to an improvement in ORR from 18% to 36%, with associated non-significant improvements in median PFS from 1.9 to 6.6 months, and in median OS from 7.6 to 15.9 months.[27] Campbell *et al* also evaluated the ability of SBRT to overcome secondary resistance to CPI immunotherapy, reporting that SBRT delivered at the time of PD on pembrolizumab monotherapy resulted in a 10% response rate and 58% disease control rate.[22] We observed a more modest disease control rate of 20% when radiation therapy was used to overcome acquired resistance, but still these findings suggest its effectiveness in this context. Altogether, the findings from these studies are promising, but a larger randomized trial is necessary to determine if the extent of radiation-induced immune priming may translate into a long term survival benefit.

There remain many uncertainties in the optimal approach to combining radiation and immunotherapy. Though Theelen *et al* reported the greatest synergistic effect of radiation in patients with PD-L1 negative tumors,[26] Formenti *et al* did not find any correlation with PD-L1 status,[27] and our findings suggest that patients treated with high PD-L1 expression may

experience the greatest relative benefit from SBRT. While the optimal dose-fractionation scheme to use is uncertain, preclinical data suggest that a shorter course of hypofractionated radiation therapy in 3–5 fractions is more immune-stimulatory than more protracted courses.[30–31] Furthermore, there is some evidence that moderate dose, less ablative regimens that would result in inferior local control in the curative setting may actually be more systemically immune-stimulating in the metastatic setting.[32] From a practical standpoint, SBRT at high doses usually used for curative intent is also associated with higher toxicity rates with or without concurrent immunotherapy,[27, 29] which is suboptimal in the metastatic treatment setting. It is also relevant to consider the relative benefit of irradiating some sites of disease with the goal of an abscopal response, or all sites of disease, the latter of which is being evaluated in prospective trials such as NRG Oncology LU-002 (NCT03137771) or SABR-COMET 10 (NCT03721341).

We acknowledge that our study has several limitations. As a small single arm study, the findings should be interpreted with appropriate caution, and not as definitive due to its intrinsic limitations. Heterogeneity in the types of systemic therapy used, tumor PD-L1 expression, radiation dose-fractionation schemes, and a mixture of 1st/2nd line systemic therapy, also limits direct comparisons to other reported studies. With a relatively small number of enrolled patients, the power of subgroup analysis to determine which patients are most likely to benefit from the addition of radiation therapy is also limited.

Conclusions

The addition of SBRT to standard-of-care CPI immunotherapy or chemo-immunotherapy in advanced NSCLC is safe and feasible. A hypothesis-generating assessment of response rates in subgroups of patients suggests that those patients with high PD-L1 expression who are reciving CPI monotherapy may be most likely to benefit from the addition of radiation therapy.

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Clinical Practice Points

An emerging body of literature supports the role of radiation therapy as promoting a more robust systemic response to checkpoint inhibitor immunotherapy. In this study, the addition of SBRT to standard-of-care CPI immunotherapy in advanced NSCLC was found to be safe, and may improve the systemic response rate to cancer immunotherapy, supporting further evaluation in a larger randomized phase study. Radiation therapy may be particularly useful in patients with high PD-L1 expression who will receive immunotherapy alone without chemotherapy.

Table 1.

Patient and Tumor Characteristics

Characteristic	N (%)
Gender	
Male	17 (49%)
Female	18 (51%)
Zubrod Performance Status	
0	9 (26%)
1	21 (60%)
2	5 (14%)
Weight Loss (past 3 months)	
<5% of body weight	26 (75%)
5–10% of body weight	5 (14%)
>10% of body weight	4 (11%)
Smoking Status at Enrollment	
Never	3 (9%)
Former	14 (40%)
Current	18 (51%)
Tumor Histology	
Adenocarcinoma	29 (83%)
Squamous Cell Carcinoma	5 (14%)
Non-Small Cell NOS	1 (3%)
N-stage at Enrollment	
N0–1	6 (17%)
N2–3	29 (83%)
Metastatic at Initial Diagnosis	
Yes	32 (91%)
No	3 (9%)
Oligometastatic at Stage IV Diagnosis	
Yes	18 (51%)
No	17 (49%)
Prior Treated Brain Metastases	
Yes	13 (37%)
No	22 (63%)
PD-L1 Tumor Proportion Score	
0%	4 (11%)
1–49%	9 (26%)
≥50%	20 (57%)
Unknown	2 (6%)
Prior Radiation Therapy	

Characteristic	N (%)
Yes	19 (54%)
No	16 (46%)
Prior Chemotherapy	
Yes	5 (14%)
No	30 (86%)

Table 2.

Treatment Characteristics

Characteristic	N (%)
Type of Systemic Therapy	
Immunotherapy Alone	19 (56%)
Immunotherapy + Chemotherapy	16 (44%)
PD-1/PD-L1 Inhibitor	
Pembrolizumab	33 (94%)
Nivolumab	1 (3%)
Atezolizumab	1 (3%)
Expected Probability of Response	
Low (CPI alone, PD-L1 0–49%)	5 (15%)
Intermediate (CPI alone, PD-L1 50–100%)	14 (42%)
High (chemo-CPI, any PD-L1)	14 (42%)
Initial Irradiated Site	
Peripheral Lung Primary	15 (44%)
Central Lung Primary/Hilum	8 (21%)
Lymph Node Metastasis	4 (12%)
Liver Metastasis	3 (9%)
Adrenal Metastasis	2 (6%)
Soft Tissue/Bone Metastasis	2 (6%)
Lung Metastasis	1 (3%)
Subsequent Course(s) of Radiation	
Yes	15 (44%)
No	20 (56%)

Table 3.

Comparison of the current study with other prospective trials combining RT and CPI immunotherapy.

Author	Cancer Histology	Systemic Therapy	SBRT Dose	SBRT timing (and lesions treated)	Response Rate	Disease Control	Median PFS
This Study	NSCLC	Mostly Pembrolizumab, +/− Chemotherapy	Moderate	Up-Front (single lesion) and Response Adapted	53%	74%	6.9 months
[26]Theelen *et al.*	NSCLC	Pembrolizumab	Moderate	Up-Front (single lesion)	36%	61%	6.6 months
[27]Formenti *et al.*	NSCLC	Ipilimumab	Moderate	Up-Front (single lesion)	18%	31%	3.8 months
[28]Luke *et al.*	Various	Pembrolizumab	High	Up-Front (multiple lesions)	13%	44%	3.1 months
[29]Welsh *et al.*	Various	Ipilimumab	High	Up-Front (single lesion)	10%	26%	2.9 months

Abbreviations: SBRT, stereotactic body radiation therapy; PFS, progression-free survival; NSCLC, non-small cell lung cancer