ORIGINAL RESEARCH LETTER

Radiation therapy for augmenting the efficacy of immunotherapy in advanced non-small cell lung cancer: a case-controlled study

To the Editor:

Nivolumab, a human IgG4 anti-PD1 monoclonal antibody, has been shown to have promising results in patients with advanced non-small cell lung cancer (NSCLC) [1, 2]. Despite the improved outcomes compared to chemotherapy, only ~20% of patients had a sustained favourable response, which highlights the need to identify measures that can augment the efficacy of immunotherapy in NSCLC [3].

Previous studies have demonstrated that radiation acts as an immune stimulus, facilitating immune mediators to enable antitumour responses within and outside the radiation field [4]. Multiple mechanisms have been shown to be involved in the systemic immune response from radiation therapy [5]. Preclinical studies also suggest that immune checkpoint inhibitors such as nivolumab can have a synergistic effect to radiation with enhancement of the antitumour T-cell activity [6], which should theoretically result in a greater clinical response in patients with NSCLC. There is also evidence to suggest an augmented abscopal effect from the combined treatment [7].

Despite the strong preclinical evidence, the impact of previous radiation therapy on the efficacy and safety of immunotherapy in real-world clinical practice in patients with NSCLC is less well defined. Here, we present the findings of a pilot case-controlled study investigating the impact of radiation therapy on outcomes with nivolumab in patients with advanced NSCLC in a large thoracic oncology unit in Brisbane, Australia.

Consecutive patients with metastatic or progressive locally advanced NSCLC, who had previous radiation therapy to the chest and subsequently received nivolumab (RT group, n=23) were compared to a control group comprised of an age, sex, tumour histology and performance status matched cohort of patients who did not have previous radiation therapy prior to receiving nivolumab (non-RT group, n=23), between January 2015 and June 2017. Disease response was assessed with RECIST (Response Evaluation Criteria in Solid Tumours) version 1.1 [8]. The primary co-endpoints of the study were progression free survival (PFS) and overall survival (OS). The adverse effects of therapy were graded according to the CATCAE (Common Terminology Criteria for Adverse Event) classification. Ethical approval for this study was granted by the Queensland Metro South Human Research Ethics Committee (REC/17/QPAH/338).

A total of 46 patients were included in the study with a median age of 62 years (IQR 55–67 years). All patients had metastatic or progressive locally advanced disease at baseline and the other clinical variables were equal between the two groups. The performance status at baseline was also very closely matched between the two groups. All patients had platinum-based chemotherapy before receiving nivolumab. The majority of patients had received one line of chemotherapy (84.8%, n/N=39/46). A total of 17.4% (n/N=4/23) of patients in the RT group and 13.0% (n/N=3/23) of patients in the non-RT group received more

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This study investigated the effects of previous radiation therapy on outcomes from nivolumab in advanced NSCLC, and found that previous radiation therapy resulted in significantly higher survival in patients treated with nivolumab for advanced NSCLC http://bit.ly/3btOFSL

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TABLE 1 Baseline characteristics

Category	Radiation therapy group	Non-radiation therapy group	p-value
Patients n	23	23	
Age at diagnosis years	63 (41–77)	62 (43–79)	0.26
Females	13 (57)	15 (65.1)	0.14
Smoking history	18 (90)	19 (95)	0.26
Smoking pack-years	43.2±23.4	44.5±21.6	0.85
Body mass index kg·m^{-2}	25.6±4.9	25.8±5.4	0.86
Serum LDH U·L^{-1}	264.8±64.4	380.5±80.1	0.08
FEV_1 % pred	76.75±24.4	61.4±27.9	0.10
FVC %	87.4±21.3	92.5±12.5	0.72
Lung disease on CT scan			0.89
Emphysema	14 (60.9)	12 (52.2)	
Interstitial lung disease	2 (8.7)	1 (4.3)	
Bronchiectasis	0	0	
Histology of tumour			
Adenocarcinoma	16 (69.6)	16 (69.6)	
Squamous cell carcinoma	7 (30.4)	7 (30.4)	
Stage at the time of inclusion#			0.75
Stage IV	19 (82.6)	21 (91.3)	
Stage IIIB	4 (17.4)	2 (8.7)	
Previous chemotherapy cycles	6 (1–18)	4 (2–10)	0.11
Lines of chemotherapy prior to nivolumab	1 (1–3)	1 (1–3)	
Previous chemotherapy			0.59
Carboplatin	22 (95.7)	22 (95.7)	
Cisplatin	1 (4.4)	1 (4.4)	
Gemcitabine	12 (52.2)	19 (82.6)	
Paclitaxel	14 (90.9)	4 (17.4)	
Vinorelbine	1 (4.4)	1 (4.4)	
Pemetrexed	2 (8.7)	3 (13.0)	
Previous radiation therapy			
Thoracic	23 (100)		
Extrathoracic	4 (17.4)		
Previous radiation therapy intent			
Previous definitive concurrent chemoradiation	18 (78.3)		
Previous palliative radiotherapy	5 (21.7)		
ECOG score at the start of nivolumab	2 (1–2)	2 (1–2)	
Nivolumab cycles	9 (1–47)*	5 (1–34)*	0.01

Data are presented as median (range), mean±SD or n (%), unless otherwise stated. LDH: lactate dehydrogenase; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group performance status score. #: stage of non-small cell lung cancer prior to initiation of nivolumab was based on the seventh Tumour, Node, Metastasis classification of lung cancer. *: p<0.05.

than one line of chemotherapy before starting nivolumab. Table 1 summarises the patient characteristics of the two groups at the time of initiating nivolumab.

The RT group had received a mean±SD of 53.3±12.3 Gy radiation therapy to the chest at a median of 11 months (interquartile range 8.6–12.8 months) prior to commencing nivolumab. A total of 78.3% (n/N=18/23) patients received radiation concurrently with chemotherapy for locally advanced disease at the time of initial diagnosis. These patients received 58.4±5.0 Gy radiation over a median of 30 fractions (range 25–30). Nivolumab was initiated due to development of new metastatic disease or progression on follow-up imaging after completing the concurrent chemoradiotherapy in these patients. The other five (21.7%) patients received radiation therapy to the chest for symptom control (airway obstruction or haemoptysis) and received 26.8±6.3 Gy radiation therapy over a median of 10 fractions (range 5–20). A total of four (17.4%) patients in the RT group also received extrathoracic radiation therapy prior to nivolumab. The extrathoracic radiation therapy was for brain metastases in two patients and symptomatic skeletal lesions in the other two. None of the patients in the control group received any thoracic or extrathoracic radiation therapy.

Nivolumab was given on an intention-to-treat basis at a median dose intensity of 99% (range 98–100%), adjusted to body weight at a dose of 3 $mg \cdot kg^{-1}$, until unequivocal progression or intolerable toxicity. The median overall follow-up of patients while receiving treatment with nivolumab was 9.6 months (range 0.1–17.8 months).

The median PFS was 4.4 months (95% CI 3.4–5.3 months) in the RT group compared to 1.4 months (95% CI 1.0–1.8 months) in the non-RT group (p=0.01). The median OS was 10.3 months (95% CI 8.6–11.9 months) in the RT group compared to 5.3 months (95% CI 2.0–8.2 months) in the non-RT group (p=0.04). The objective response rate after four cycles of nivolumab was 30.4% (n/N=7/23) in the RT group and 17.4% (n/N=4/23) in the non-RT group (p=0.23). Stable disease was seen in a further 8.9% (n/N=2/23) of patients in RT group compared to 4.3% (n/N=1/23) in the non-RT group after four cycles of nivolumab. Immunotherapy was discontinued in patients who had disease progression after four cycles. The RT group received a median of nine cycles of nivolumab (range 1–47) and the non-RT group received a median five cycles of nivolumab (range 1–34) (p=0.01). The dose of radiation or the time interval between radiation and nivolumab did not have a statistically significant correlation with outcomes.

Immune-related complications were seen in 30.4% (n=7) and 13.0% (n=3) of patients in the RT and non-RT groups respectively (p=0.17). Grade 3 pneumonitis occurred in one patient in the RT group and two patients in the non-RT group. Additionally, in the RT group, grade 3 hepatitis (n=1) and grade 2 thyroiditis (n=2), colitis (n=2) and rash (n=1) were seen. In the non-RT group, grade 2 thyroiditis (n=1) and colitis (n=1) were seen. One patient in the non-RT group developed both thyroiditis and pneumonitis related to immunotherapy. Among the seven patients in the RT group who had immune-related complications, the PFS was 4.1 months compared to 4.6 months in patients who did not have immune-related complications (p=0.21). The median OS among the patients in the RT group who had immune-related complications was 12.5 months compared to 8.9 months in patients who did not have immune-related complications (p=0.09).

This pilot study demonstrates very encouraging findings of previous radiation therapy augmenting the efficacy of immunotherapy in advanced NSCLC. These findings are in line with other limited clinical studies on this topic. Shaverdian *et al.* [9] demonstrated an improved PFS and OS with previous radiation compared to no radiation (4.4 *versus* 2.1 months for PFS and 10.7 months *versus* 5.3 months for OS respectively) on a retrospective secondary analysis of patients in the phase 1 KEYNOTE-001 study in a single centre who received pembrolizumab at variable doses.

The PACIFIC trial, which assessed the efficacy of durvalumab consolidative therapy following chemoradiotherapy in locally advanced (stage III) NSCLC, was very promising [10]. The median PFS was 17.2 months (95% CI 13.1–23.9 months) in the durvalumab group compared to 5.6 months (95% CI 4.6–7.7 months) in the placebo group. The 12-month OS rate was 83.1% (95% CI 79.4–86.2%) in the durvalumab group compared to 75.3% (95% CI 69.2–80.4%) in the placebo group. The response rate was also higher with durvalumab than with placebo (30.0% *versus* 17.8%, p<0.001). Significantly better outcomes seen with durvalumab, including much lower rates of new distal metastases, suggest that sequential chemoradiotherapy and immunotherapy may have potentially induced antitumour immune responses and contributed to elimination of unknown distal micrometastases. The patients in our study mostly had advanced metastatic disease at the time of inclusion and therefore the results cannot be directly compared to the PACIFIC trial. However, combining immunotherapy and radiation therapy seems to result in beneficial effects in both locally advanced and metastatic disease. There is currently insufficient evidence to determine whether there are differences in outcomes between anti-PD1 *versus* anti-PD1 ligand (PDL1) agents when combined with radiation therapy in advanced NSCLC.

The optimal timing and sequence of combined radiation therapy and immunotherapy is yet to be clarified. In the PACIFIC trial, immunotherapy was given between 1 and 46 days after completion of the last radiation dose. There is some evidence to suggest that immunotherapy administration concurrently with radiation therapy may provide a better immune response [11]. However, in the study by Shaverdian *et al.* [9], patients who received thoracic radiotherapy did so a median of 11.5 months before the first cycle of pembrolizumab, which was similar to our cohort. These results suggest that the patients seem to have prolonged immune related benefits of radiation therapy, which is enhanced by the subsequent immunotherapy. These results also suggest that the augmentation of immunotherapy efficacy with radiation can occur with both anti-PD-1 (nivolumab and pembrolizumab) and anti-PDL1 (durvalumab) agents in NSCLC.

Our study also demonstrates the interesting finding of a trend towards an increased rate of immune-related complications in patients who received radiation therapy prior to immunotherapy. This has been shown on other studies, with Shaverdian *et al.* [9] reporting a trend towards a higher rate of pulmonary toxicity in patients who received pembrolizumab after radiation therapy. Furthermore, our study also shows a trend towards a longer median OS in patients who had immune-related complications

compared to the patients who did not have immune-related complications within the RT group, although the number of patients within these subgroups in this study are too small to draw strong conclusions. The heightened immune response that leads to better survival and favourable disease response seems to also result in an increased rate of complications, which are both augmented by radiation therapy. The findings highlight the importance of close monitoring for immune-related complications when combining radiation therapy and immunotherapy.

The results of the study may partly be explained by the abscopal effect, aqn enhanced response from immunotherapy seen at metastatic sites outside of the initial radiation fields [7]. Even small doses of radiation therapy to single sites have been shown to trigger a heightened immune response at metastatic sites with immunotherapy, particularly in patients with low tumour PDL1 expression [12]. However, the optimal combinations, sequences and doses to generate an abscopal effect are not well defined [13]. There is also increasing preclinical and clinical evidence to suggest that irradiation of multiple sites may enhance the effects of immunotherapy compared to single-site irradiation [14]. Our study did not evaluate the effects of extrathoracic radiation, as only a small proportion of patients in the RT group had received extrathoracic radiation, and therefore could not be accurately generalised to the whole group.

This study has several limitations. Even though majority of patients in both the RT group and the control group had metastatic disease at the time of inclusion, the stage at the time of initial diagnosis was more likely to be stage III than stage IV in the RT group. The tumour burden at initial diagnosis and rate of progression of the malignancy prior to receiving nivolumab was not formally assessed, which raises the possibility of differences in disease severity between the two treatment groups. There was a trend towards a higher mean baseline serum lactate dehydrogenase (LDH) in the non-RT group, although this was not significantly different (380.5 *versus* 264.8 $U{\cdot}L^{-1}$, p=0.08). A recent meta-analysis showed that a high pre-treatment LDH level correlated with shorter PFS and OS in patients treated with immunotherapy for NSCLC [15] but the effect sizes were small. There is evidence to suggest that due to the mechanism of action of immunotherapy agents, a significant disease response can be seen in some patients with high tumour burden [16]. Therefore, the rate of change in LDH with immunotherapy may be a better indirect marker of disease response [16], which was not assessed in our study. Furthermore, the study did not have sufficient power to detect statistically significant differences in disease response rates and adverse effects such as pneumonitis.

In summary, the present study shows new and interesting clinical data for radiation therapy augmenting the efficacy of immunotherapy, leading to better survival in advanced NSCLC. Despite the limitations, this pilot study provides valuable initial evidence in a real-world setting for a novel approach of therapy in advanced NSCLC. The results of larger randomised clinical trials are needed to determine the optimal doses and sequence of the combined therapy to gain the maximal clinical benefit.

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