Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial

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Summary

Background Patients with non-small-cell lung cancer (NSCLC) that is resistant to PD-1 and PD-L1 (PD[L]-1)-targeted therapy have poor outcomes. Studies suggest that radiotherapy could enhance antitumour immunity. Therefore, we investigated the potential benefit of PD-L1 (durvalumab) and CTLA-4 (tremelimumab) inhibition alone or combined with radiotherapy.

Methods This open-label, multicentre, randomised, phase 2 trial was done by the National Cancer Institute Experimental Therapeutics Clinical Trials Network at 18 US sites. Patients aged 18 years or older with metastatic NSCLC, an Eastern Cooperative Oncology Group performance status of 0 or 1, and progression during previous PD(L)-1 therapy were eligible. They were randomly assigned (1:1:1) in a web-based system by the study statistician using a permuted block scheme (block sizes of three or six) without stratification to receive either durvalumab (1500 mg intravenously every 4 weeks for a maximum of 13 cycles) plus tremelimumab (75 mg intravenously every 4 weeks for a maximum of four cycles) alone or with low-dose (0·5 Gy delivered twice per day, repeated for 2 days during each of the first four cycles of therapy) or hypofractionated radiotherapy (24 Gy total delivered over three 8-Gy fractions during the first cycle only), 1 week after initial durvalumab–tremelimumab administration. Study treatment was continued until 1 year or until progression. The primary endpoint was overall response rate (best locally assessed confirmed response of a partial or complete response) and, along with safety, was analysed in patients who received at least one dose of study therapy. The trial is registered with ClinicalTrials.gov, NCT02888743, and is now complete.

Findings Between Aug 24, 2017, and March 29, 2019, 90 patients were enrolled and randomly assigned, of whom 78 (26 per group) were treated. This trial was stopped due to futility assessed in an interim analysis. At a median follow-up of 12·4 months (IQR 7·8–15·1), there were no differences in overall response rates between the durvalumab–tremelimumab alone group (three [11·5%, 90% CI 1·2–21·8] of 26 patients) and the low-dose radiotherapy group (two [7·7%, 0·0–16·3] of 26 patients; p=0·64) or the hypofractionated radiotherapy group (three [11·5%, 1·2–21·8] of 26 patients; p=0·99). The most common grade 3–4 adverse events were dyspnoea (two [8%] in the durvalumab–tremelimumab alone group; three [12%] in the low-dose radiotherapy group; and three [12%] in the hypofractionated radiotherapy group) and hyponatraemia (one [4%] in the durvalumab–tremelimumab alone group *vs* two [8%] in the low-dose radiotherapy group *vs* three [12%] in the hypofractionated radiotherapy group). Treatment-related serious adverse events occurred in one (4%) patient in the durvalumab–tremelimumab alone group (maculopapular rash), five (19%) patients in the low-dose radiotherapy group (abdominal pain, diarrhoea, dyspnoea, hypokalemia, and respiratory failure), and four (15%) patients in the hypofractionated group (adrenal insufficiency, colitis, diarrhoea, and hyponatremia). In the low-dose radiotherapy group, there was one death from respiratory failure potentially related to study therapy.

Interpretation Radiotherapy did not increase responses to combined PD-L1 plus CTLA-4 inhibition in patients with NSCLC resistant to PD(L)-1 therapy. However, PD-L1 plus CTLA-4 therapy could be a treatment option for some patients. Future studies should refine predictive biomarkers in this setting.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for reports published in English from database inception up to June 1, 2021, using the terms ("radiation" AND ("PD-1" OR "PD-L1") AND "CTLA-4" AND "clinical trial"). There are no data from randomised studies evaluating various radiation doses in combination with PD-1 and PD-L1 (PD[L]-1) plus CTLA-4 inhibition and in a population with NSCLC refractory to PD(L)-1 therapy. Furthermore, data evaluating combined PD-L1 plus CTLA-4 inhibition in patients with NSCLC who have progressed on previous PD(L)-1 therapy are scarce.

Added value of this study

These data are among the first to be published reporting the efficacy and toxicity of PD(L)-1 plus CTLA-4 blockade in patients with NSCLC resistant to previous PD(L)-1-directed therapy, who represent a growing population in need of novel therapeutic approaches. To our knowledge, this Article is the first randomised study evaluating the addition of radiotherapy to PD(L)-1 plus CTLA-4 blockade in any cancer that includes a non-radiation control group. It is also the first randomised study to evaluate the addition of radiotherapy to immune checkpoint blockade exclusively in patients with NSCLC refractory to PD(L)-1-directed therapy, and the first study to prospectively evaluate the effect of low-dose (<1 Gy/fraction) radiotherapy in combination with immune checkpoint blockade. We found that adding low-dose or hypofractionated radiotherapy to durvalumab (PD-L1 inhibitor) plus tremelimumab (CTLA-4 inhibitor) did not improve overall response rates or overall and progression-free survival.

Implications of all the available evidence

PD-L1 plus CTLA-4 inhibition alone or in combination with radiotherapy led to an overall response rate of approximately 10% and a disease control rate of about 30% and represents a potential treatment option in a subset of patients with NSCLC that is resistant to PD(L)-1 inhibitors. Future studies should refine predictive biomarkers in this setting. Our findings and the available evidence do not suggest a benefit for combining either low-dose or hypofractionated radiotherapy to a single disease site with PD-L1 plus CTLA-4 inhibition in this patient population.

Introduction

Immune checkpoint inhibitors targeted at PD-1 and PD-L1 (PD[L]-1), used alone or with chemotherapy, have benefited patients with metastatic non-small-cell lung cancer (NSCLC), and are used in the first-line setting.[1–4] However, the majority of patients do not respond to or progress on therapy.[5,6] Treatment options in the setting of resistance to PD(L)-1 blockade are sparse, and outcomes on standard therapy are poor. Combined PD(L)-1 and CTLA-4 inhibition has shown synergy in preclinical models,[7] and has been approved as a first-line therapy for metastatic NSCLC,[8–10] but whether this combination provides additional clinical benefit beyond chemotherapy plus PD(L)-1 inhibition or PD(L)-1 blockade alone is unclear. Prospective data are scarce for this combination in patients with NSCLC who have progressed on PD(L)-1 blockade.[11]

Radiotherapy with or without chemotherapy is standard for locally advanced, inoperable NSCLC and is sometimes used in the metastatic setting for palliative benefit in conjunction with chemotherapy and immunotherapy. Promising results from a single-arm, phase 2 study[12] have stimulated interest in combining radiotherapy with immune checkpoint inhibitors for the treatment of patients with metastatic NSCLC and have led to the design of numerous planned or ongoing clinical trials. Preclinical data suggest synergy between radiotherapy and combined PD(L)-1 and CTLA-4 blockade.[13] However, the radiotherapy dose best suited for this purpose is unknown. Preclinical studies and clinical observations have suggested that both hypofractionated (high-dose; 8 Gy/fraction) radiotherapy and low-dose (<1 Gy/fraction) radiotherapy might have favourable immunological effects, such as dendritic cell maturation, homing and activation of T cells, and macrophage differentiation;[13–15] however, these radiotherapy regimens have not been tested prospectively in patients in combination with dual PD-L1 and CTLA-4 blockade.

Durvalumab is an IgG1 monoclonal antibody and has been shown to improve progression-free survival and overall survival compared with placebo when given to patients with locally advanced NSCLC following definitive chemoradiotherapy.[16] Tremelimumab is an IgG2 antibody that blocks the binding of the inhibitory CTLA-4 receptor to the B7.1 and B7.2 ligands that would otherwise activate T cells through the CD28 receptor. Tremelimumab has been evaluated in combination with durvalumab in multiple settings, including as a first-line therapy for patients with metastatic NSCLC (NCT03164616).[10,17]

We aimed to evaluate the potential benefit of durvalumab plus tremelimumab, either alone or with low-dose radiotherapy or hypofractionated radiotherapy, in patients with metastatic NSCLC who have progressed on previous PD(L)-1-directed therapy.

Methods

Study design and participants

This open-label, multicentre, randomised, phase 2 study was done by the National Cancer Institute (NCI) Experimental Therapeutics Clinical Trials Network at 18 sites (cancer centres and hospitals) in the USA (appendix p 28). Results for a separate cohort of this study, which comprised patients with metastatic colorectal cancers, have been previously reported.[15]

Participants were recruited from outpatient oncology clinics. Patients with histologically or cytologically

confirmed, metastatic NSCLC were eligible if they were aged at least 18 years, had an Eastern Cooperative Oncology Group performance status of 0 or 1, had a life expectancy longer than 6 months, and had evidence of radiological or clinical disease progression during previous treatment with systemic PD(L)-1-directed therapy, as determined by the treating team (this criterion included patients with innate or acquired resistance to previous PD[L]-1 inhibition). This determination was made clinically, although biopsy specimens were obtained from patients after previous PD(L)-1-directed therapy and less than 3 months before study enrolment as a requirement for eligibility. Additional inclusion criteria included the following: measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), with at least one measurable lesion outside of the intended radiation treatment field in the lung, lymph nodes, adrenal glands, or liver (bone metastases were not permitted to be the target of study radiation); at least 21 days must have elapsed since previous chemotherapy or radiotherapy; patients were required to have CT scans of the chest, abdomen, and pelvis, and a brain MRI for screening; adequate bone marrow function (absolute neutrophil count of ≥1500 cells per µL, platelet count of ≥100 000 per µL, and haemoglobin concentration of ≥9·0 g/dL); adequate liver function (alanine aminotransferase or aspartate aminotransferase concentrations of less than or equal to 2·5-times the upper limit of normal, and total bilirubin concentration of ≤1·5-times normal institutional limits); and adequate kidney function (measured or calculated creatinine clearance of >40 mL/min).

Key exclusion criteria included the following: eligibility for approved agents targeting the EGFR, ROS1, or ALK pathways; previous radiotherapy to the intended radiation site or previous radiotherapy that would preclude the safe delivery of additional radiation, as per protocol specifications; previous treatment with CTLA-4-directed therapy; and untreated brain metastases. A complete list of eligibility criteria can be found in the protocol (appendix).

There were 11 protocol deviations due to eligibility: one patient was registered before eligibility screening was completed; six patients had negative brain MRIs after registration instead of before registration (one of whom also had an abdominal and pelvic CT scan outside of the allowable time window); three patients were registered before they had brain MRIs and then withdrew because of evidence of brain metastases; and one patient was registered and then withdrew from the study before MRI evaluation.

The protocol received ethics approval from the NCI central institutional review board and was cleared by the local institutional review boards of all 18 participating centres. The study was done in accordance with the protocol, the principles expressed in the Declaration of Helsinki, and applicable regulatory requirements. All patients provided written informed consent in advance of study-specific procedures.

Randomisation and masking

By use of the web-based Theradex Interactive Web Response System, patients were randomly assigned (1:1:1) to receive either durvalumab plus tremelimumab alone or in combination with low-dose radiotherapy or hypofractionated radiotherapy. Randomisation followed a permuted block scheme with random block sizes of three or six and the randomisation sequence was generated by the study statistician. Participants were enrolled by the study investigators. The interactive web system was used to assign participants to trial groups and did not have clinical involvement in the study. There were no stratifying factors. Participants and the study team were not masked to group assignment.

Procedures

The PD-L1 inhibitor durvalumab was administered intravenously at a fixed dose of 1500 mg every 4 weeks for a maximum of 13 cycles, and the CTLA-4 inhibitor tremelimumab was administered intravenously at a fixed dose of 75 mg every 4 weeks for a maximum of four cycles. Dosing of durvalumab–tremelimumab could be temporarily interrupted due to toxicity, but dose reductions were not allowed. Dosing could be resumed if adverse events had been reduced to grade 1 or 0 on CTCAE version 4.0. Treatment was discontinued for disease progression, unacceptable toxicity, or if the patient or investigator decided to discontinue.

Imaging and Radiation Oncology Core credentialing was required for the most complex radiotherapy modality used at each centre and for image-guided radiotherapy. Following randomisation, patients allocated to the radiotherapy groups underwent CT-based radiotherapy planning, which targeted one or two lesions in the lung, lymph nodes, adrenal glands, or liver. Lesions were prioritised according to the following guidelines: (1) lesions progressing on previous PD(L)-1-directed therapy; (2) lesion location, favouring the liver, then lung, then adrenal glands, and, lastly, the lymph nodes; and (3) the largest feasibly treated lesion that might provide palliative benefit. Radiotherapy techniques are described further in the appendix (p 1). Our hypofractionated radiotherapy regimen was based on preclinical evidence that this modality in particular can stimulate the secretion of interferon via the cyclic GMP-AMP synthase–stimulator of interferon genes pathway and increase immunogenicity,[18] and our low-dose fractionated radiotherapy regimen was supported by previous preclinical studies that showed favourable changes in the tumour microenvironment, specifically regarding macrophage polarisation and T-cell infiltration, which was maximised at a dose of 0·5 Gy.[14]

In the low-dose radiotherapy group, patients received a dose of 2 Gy administered in four fractions over 2 days (0·5 Gy twice per day) repeated for each of the first four 28-day cycles of therapy (total dose 8 Gy). In the hypofractionated radiotherapy group, patients received a

total dose of 24 Gy in three fractions of 8 Gy no more frequently than every other day during the first cycle of therapy only. Radiotherapy was started 1 week following initial durvalumab–tremelimumab administration. Tumour assessments—chest, abdomen, and pelvis CT scans, and an additional brain MRI in patients with a history of brain metastases—were done at baseline and every 12 weeks after an initial restaging scan at 7–8 weeks while on treatment. One patient had their week 21 scans 31 days out of the 5-day window allowed in the protocol and their week 25 treatment 5 days out of the 5-day window allowed in the protocol because of travel.

Participants remained on study until death or for at least 1 year from the time of treatment initiation and at least 12 weeks after removal from study treatment. Laboratory assessments, including haematology, blood chemistry, and liver and kidney function tests, were done on day 1 (before drug administration) of each treatment cycle only.

Treatment-related toxicity was assessed throughout the treatment period with each treatment cycle and every 30 days for 90 days after treatment discontinuation. Toxicities were graded per the Common Terminology Criteria for Adverse Events, version 4.0.

Tissue for correlative analyses was collected from the screening biopsy or from archival tissue obtained less than 3 months before study enrolment and after progression on previous PD(L)-1 therapy. As specified by a study protocol amendment, PD-L1 immunohistochemistry, multiplex immunofluorescence, whole exome sequencing, and RNA sequencing were done through the Cancer Immune Monitoring and Analysis Centers (CIMAC) Immuno-Oncology Biomarkers Network. Detailed procedures have been previously described[15] and are described in more detail in the appendix (p 1).

For more on **CIMAC assays** see https://cimac-network.org/assays/

Outcomes

The primary outcome of the trial was overall response rate (best locally assessed confirmed response of a partial or complete response) by RECIST version 1.1, excluding the irradiated lesion. Secondary endpoints were safety, investigator-assessed progression-free survival; overall survival; overall response according to immune-related response criteria (data not reported because they duplicated overall response data); local control within irradiated fields and abscopal response rates (data not uniformly collected and therefore not reported); the prognostic effect of PD-L1 expression, as determined by immunohistochemistry, on response; and the prognostic effect of T-cell infiltration on response. Progression-free survival was the time from randomisation to either objective disease progression or death, whichever occurred first. For patients without progression, follow-up was censored at the date of last adequate restaging, unless death occurred within 12 weeks following the date the patient was last known to be progression free, in which case the death was counted as a progression-free survival event. Overall survival was the interval between randomisation and death from any cause. For patients lost to follow-up or who had no documentation of death at the time of analysis, follow-up was censored at the last assessment of vital status.

Additional, exploratory correlative and patient-reported outcome analyses exploring changes in circulating T-cell populations, spatial and infiltrating immune populations, and genomics as a result of radiotherapy are ongoing and are therefore not reported.

Statistical analysis

The sample size was based on the primary endpoint of overall response rate. We estimated a null overall response rate of approximately 5% for the combination of durvalumab–tremelimumab alone on the basis of preliminary data from patients with NSCLC refractory to PD-1-directed treatments.[19] Two pairwise comparisons of low-dose fractionated radiotherapy and hypofractionated radiotherapy against the control of durvalumab–tremelimumab alone were planned. Because a positive outcome for each comparison in this trial was the superiority of low-dose radiotherapy or hypofractionated radiotherapy compared with no radiotherapy, we used one-sided χ^2 tests with 10% type I errors for each comparison. A sample size in each pairwise comparison of 80 patients (40 per group) would detect a difference between response rates of 5% and 22%, which was thought to represent a meaningful increase if achieved, with 81% power (target power 80%). Interim analyses were planned after 40 patients within each pairwise comparison (20 per group) had objective response classifications. To assess for early evidence of futility or superiority in the interim analysis of no radiotherapy compared with low-dose fractionated radiotherapy, hypofractionated radiotherapy, or both, each pairwise comparison used a group sequential design with O'Brien-Fleming stopping boundaries for superiority and Gamma family (γ=1) for futility. The critical values of the test statistic for superiority of no radiation compared with either low-dose fractionated radiation or hypofractionated radiotherapy in each comparison for the interim and final analyses were determined to be 2·054 and 1·317, corresponding to nominal significance levels of 0·02 and 0·094, respectively. In addition, if the p value at the interim analysis was greater than 0·463, there would be insufficient evidence to reject the null hypothesis and the trial for that comparison would stop early for futility. An interim safety analysis was also done after ten patients had been enrolled in each group, with a plan to stop treatment if any group contained more than three patients with dose-limiting toxicities. At the time of this early safety analysis, there were no dose-limiting toxicities.

As prespecified, efficacy and safety analyses were done in patients who received at least one dose of study therapy (modified intention-to-treat population).

Progression-free survival, duration of response (post-hoc analysis), and overall survival were estimated by use of the Kaplan–Meier method and compared between groups by use of log-rank tests. We estimated the median follow-up using the Kaplan–Meier method with inverted censoring. Hazard ratios were estimated by use of Cox proportional hazards regression, with 90% CIs calculated by use of log(–log) and the Efron method for ties. PD-L1 expression and T-cell subsets were associated with response across all treatment groups by use of Wilcoxon rank-sum tests.

Disease control was assessed post-hoc and defined as having two or more scans with RECIST version 1.1-defined stable disease, once-documented stable disease followed by a non-confirmed partial response, or a confirmed complete or partial response. Best change from baseline in the size of target lesions was determined in patients with disease control or a partial response. We did post-hoc exploratory analyses of progression-free survival and overall survival according to previous treatment characteristics (previous radiotherapy, intervening therapy, duration of previous PD(L)-1-directed therapy, and the interval from previous PD-1-directed therapy to study therapy).

Response and disease control rates were compared between treatment groups and with tumour PD-L1 expression with a 1% cutoff using Fisher's exact test. Mutational burden by whole exome sequencing and the populations of T cells in the tumour microenvironment (suggested by RNA sequencing and multiplex immunofluorescence) were associated with response in post-hoc analyses by use of Wilcoxon rank-sum tests. Post-hoc comparisons of changes in lymphocyte counts were based on differences between pre-treatment and 6-week measurements. Comparisons according to randomised treatment and radiotherapy target were based on Kruskal–Wallis tests; comparisons according to response were based on Wilcoxon rank-sum tests.

All CIs are 90%, per the protocol; statistical significance is defined by p values of less than 0·05. Analyses were done by use of SAS, version 9.4. This study was registered with ClinicalTrials.gov, NCT02888743. The study was monitored by the Dana-Farber Harvard Cancer Center Data and Safety Monitoring Committee.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 24, 2017, and March 29, 2019, 90 patients were enrolled into our study and randomly assigned, of whom 78 received their assigned study treatment (26 per group) and were included in the efficacy and safety analyses (figure 1). The 12 patients that did not receive any intervention included three patients who were registered before brain MRI and then withdrew because of evidence of brain metastases, one patient who was registered and then withdrew from the study before MRI evaluation, four patients who withdrew consent, and four patients who had disease progression during treatment. At the interim analysis, the p values in both pairwise comparisons exceeded 0·463; therefore, the trial stopped early for futility. At the cutoff date for the final analyses (April 12, 2021), median follow-up was 12·4 months (IQR 7·8–15·1) for the entire population.

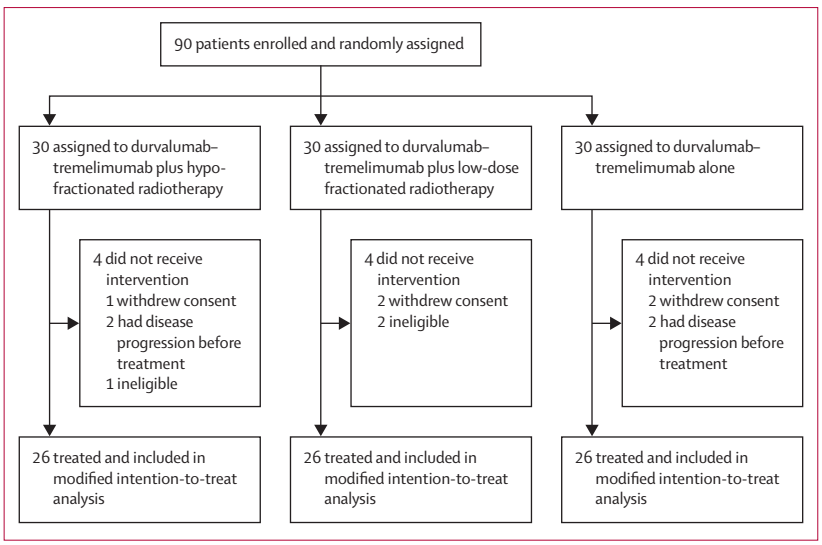

Figure 1: **Trial profile**

Demographic and clinical characteristics were well balanced between the groups at baseline (table 1). Most patients (66 [85%] of 78) had previously received chemotherapy before enrolling, either as part of their initial treatment for localised disease or in the palliative setting. 25 (32%) patients received intervening non-immune therapy, which was most commonly docetaxel (six [8%]) or pemetrexed (six [8%]). The most common sites of radiotherapy delivered on protocol in the radiotherapy groups were the lung (32 [62%] of 52 patients), followed by the lymph nodes (eight [15%]), liver (six [12%]), and adrenal glands (five [10%]).

There was no difference in overall response rate between the durvalumab–tremelimumab alone group (three [11·5%, 90% CI 1·2–21·8] of 26 patients) and the low-dose radiotherapy group (two [7·7%, 0·0–16·3] of 26 patients; p=0·64) or the hypofractionated radiotherapy group (three [11·5%, 1·2–21·8] of 26 patients; p=0·99; table 2). Disease control, assessed post-hoc, is shown in table 2. Characteristics of partial responders are shown in the appendix (p 2). The median duration of response (post-hoc analysis) was 10·3 months (90% CI 4·3–not estimable) across groups, 4·9 months (4·3–5·5) in the low-dose radiotherapy group, and was not reached (10·3–not estimable) in the durvalumab–tremelimumab alone group or the hypofractionated radiotherapy group

	Durvalumab–tremelimumab alone (n=26)	Durvalumab–tremelimumab plus low-dose radiotherapy (n=26)	Durvalumab–tremelimumab plus hypofractionated radiotherapy (n=26)
Age, years	65 (60–70)	65 (60–73)	65 (57–72)
Sex			
Female	9 (35%)	8 (31%)	11 (42%)
Male	17 (65%)	18 (69%)	15 (58%)
Race			
African American	3 (12%)	1 (4%)	1 (4%)
Asian	1 (4%)	3 (12%)	0
White	21 (81%)	22 (85%)	22 (85%)
Unknown or not reported	1 (4%)	0	3 (12%)
Ethnicity			
Hispanic or Latinx	0	1 (4%)	3 (12%)
Not Hispanic or Latinx	25 (96%)	25 (96%)	22 (85%)
Unknown or not reported	1 (4%)	0	1 (4%)
ECOG performance status			
0	5 (19%)	9 (35%)	6 (23%)
1	21 (81%)	17 (65%)	19 (73%)
2	0	0	1 (4%)
Histology			
Adenocarcinoma	19 (73%)	21 (81%)	16 (62%)
Squamous	3 (12%)	1 (4%)	5 (19%)
Not specified	4 (15%)	4 (15%)	5 (19%)
PD-L1 percentage expression			
<1%	4 (15%)	5 (19%)	4 (15%)
1% to <25%	7 (27%)	6 (23%)	10 (38%)
25% to <50%	1 (4%)	2 (8%)	1 (4%)
50% or higher	3 (12%)	2 (8%)	3 (12%)
Not done	11 (42%)	11 (42%)	8 (31%)
Previous radiotherapy			
Yes	20 (77%)	17 (65%)	16 (62%)
No	6 (23%)	9 (35%)	10 (38%)
Site of previous radiotherapy			
Adrenal glands	2/20 (10%)	2/17 (12%)	0
Liver	2/20 (10%)	0	0
Lung	14/20 (70%)	9/17 (53%)	6/16 (38%)
Lymph nodes	2/20 (10%)	1/17 (6%)	5/16 (31%)
Not specified	0	5/17 (29%)	5/16 (31%)
Previous lines of therapy	3 (2–4)	3 (2–3)	3 (2–4)
Median duration of previous PD-1-directed therapy, weeks	21 (8–44)	30 (16–48)	27 (13–42)
Time elapsed between previous PD-1-directed therapy and protocol therapy, months	3·4 (1·5–7·4)	1·6 (1·1–4·8)	2·4 (1·3–8·4)

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Demographics and baseline characteristics in patients who received at least one dose of study therapy**

(2·5–not estimable), with two (66%) of three responders in the durvalumab-tremelimumab plus low-dose radiotherapy group and one (33%) of three responders in the durvalumab-tremelimumab plus hypofractionated radiotherapy group alive and progression free at the time of last follow-up (appendix p 3).

Progression-free survival events occurred in 67 (86%) of 78 patients (24 [92%] of 26 in the hypofractionated radiation group, 22 [85%] of 26 in the low-dose radio_ therapy group, and 21 [81%] of 26 in the durvalumab–tremelimumab alone group) and 39 (50%) patients died (15 [58%] in the hypofractionated radiotherapy group, 15 [58%] in the low-dose radiotherapy group, and nine [35%] in the durvalumab–tremelimumab alone group). There were no differences in progression-free survival between the no radiotherapy group (median 3·3 months, 90% CI 1·8–5·5) and the low-dose radiotherapy group (median 4·6 months, 2·1–7·2) or the hypofractionated radiotherapy group (median 4·0 months, 2·1–7·0; figure 2A). Overall survival was also not significantly different between durvalumab–tremelimumab alone (median not reached, 90% CI 4·9–not reached) and the radiotherapy groups (hyper-fractionated group median 9·7 months, 5·1 to not reached; low-dose group median 9·1 months, 3·8–23·9; figure 2B). Post-hoc exploratory analyses evaluated the effect of previous treatment factors on overall and progression-free survival across all groups (appendix p 4).

Best change from baseline in the size of target lesions in responders or patients with disease control is shown in figure 3.

Post-hoc correlative exploratory studies found somatic mutations, such as *TP53,* and a tobacco-associated mutational signature (appendix pp 5–6). Two responding patients had nonsense and missense mutations in the mismatch repair pathway genes *MSH3* (durvalumab–tremelimumab alone group) and *POLE* (hypofractionated radiotherapy group). mRNA sequencing exploratory and multiplex immunofluorescence analyses (prespecified, exploratory correlative analyses) evaluated $CD8^+PD\text{-}1^+$, $CD8^+PD\text{-}1^+Ki67^+$, and $CD4^+PD\text{-}1^+Ki67^+$ T-cell populations in relation to response (appendix p 7). Response was significantly associated with pretreatment tumour-infiltrating $CD8^+PD\text{-}1^+$ T cells (n=52; median cell count 37 cells per mm² [IQR 4–83] in responders across all treatment groups *vs* 4 cells per mm² [0–17] in non-responders; p=0·032), $CD8^+PD\text{-}1^+Ki67^+$ T cells (12 cells per mm² [2–45] *vs* 2 cells per mm² [0–8]; p=0·043), and $CD4^+PD\text{-}1^+Ki67^+$ T cells (9 cells per mm² [2–14] *vs* 1 cell per mm² [0–3]; p=0·014), as measured by multiplex immunofluorescence (appendix p 7). There were no differences in tumour PD-L1 expression between responders and non-responders (n=49; median expression 2·5% [IQR 0·0–10·0] *vs* 2·0% [1·0–11·2], respectively; p=0·69) or when using a 1% cutoff (p=0·32).

Post-hoc exploratory analyses of circulating lymphocyte counts (n=52) identified significant on-treatment changes in the radiotherapy groups (median change 0·1% [IQR –2·7 to 2·6] in the durvalumab–tremelimumab alone group, –2·6% [–8·0 to –0·4] in the low-dose radiotherapy group, and –5·1% [–6·5 to –0·2] in the hypofractionated radiotherapy group (appendix p 8; Kruskal-Wallis p=0·0069), but no association with

	Durvalumab–tremelimumab alone (n=26)	Durvalumab–tremelimumab plus low-dose radiation (n=26)	Durvalumab–tremelimumab plus hypofractionated radiation (n=26)
Overall response rate	3 (11·5%, 1·2 to 21·8)	2 (7·7%, 0·0 to 16·3)	3 (11·5%, 1·2 to 21·8)
Complete response	0	0	0
Partial response	3 (12%)	2 (8%)	3 (12%)
Stable disease	11 (42%)	12 (46%)	10 (38%)
Progressive disease	10 (38%)	8 (31%)	10 (38%)
Not evaluable	2 (8%)	4 (15%)	3 (12%)
Difference in overall response rate (*vs* durvalumab–tremelimumab alone group)	NA	−3·8% (−17·3 to 9·6); p=0·64	0·0% (−14·6% to 14·6%); p=0·99
Disease control rate	8 (30·8%, 15·9 to 45·7)	6 (23·1%, 9·5 to 36·7)	9 (34·6%, 19·3 to 50·0)
Difference in disease control rate (*vs* durvalumab–tremelimumab alone group)	NA	−7·7% (−27·9 to 12·5); p=0·53	3·8% (−17·5 to 25·2); p=0·77

Data are n (%, 90% CI by normal approximation), n (%), or difference (90% CI); χ^2 p value. Response was based on investigator assessment per the modified Response Evaluation Criteria in Solid Tumors, version 1.1, excluding irradiated lesions. NA=not applicable.

Table 2: **Best overall response in the participants receiving at least one dose of study therapy**

radiotherapy target (appendix p 9; Kruskal-Wallis p=0·85). A decrease in percentage lymphocyte count was inversely associated with response across all groups (median change in responders 1·7% [IQR −0·3 to 3·8]; median change in non-responders −3·3% [−6·0 to 0·0]; p=0·0028; appendix p 10).

Overall, 59 (76%) of 78 patients had an adverse event at least possibly related to therapy (19 [73%] in the durvalumab–tremelimumab alone group; 20 [77%] in the low-dose radiotherapy group; and 20 [77%] in the hypofractionated radiotherapy group; appendix pp 11–27). The most common grade 3 or worse adverse events were dyspnoea (two [8%] in the durvalumab–tremelimumab alone *vs* three [12%] in the low-dose radiotherapy group *vs* three [12%] in the hypofractionated radiotherapy group), hyponatraemia (one [4%] in the durvalumab–tremelimumab alone *vs* two [8%] in the low-dose radiotherapy group *vs* three [12%] in the hypofractionated radiotherapy group) and gamma-glutamyl transferase increased (zero [0%] in the durvalumab–tremelimumab alone *vs* one [4%] in the low-dose radiotherapy group *vs* three [12%] in the hypofractionated radiotherapy group; table 3). Overall, seven (9%, 90% CI 4–16) patients discontinued therapy due to drug-related adverse events (one [4%] in the durvalumab–tremelimumab alone group due to colitis; four [15%] in the low-dose radiotherapy group due to increases in lipase and serum amylase concentrations [n=1], rhoea [n=1], dyspnoea [n=1], or headache and giant cell arteritis syndrome [n=1]; and two [8%] in the hypofractionated radiotherapy group due to adrenal insufficiency). Ten serious treatment-related adverse events were reported: maculopapular rash in the durvalumab–tremelimumab group, adrenal insufficiency, colitis, diarrhoea and hyponatraemia in the hypofractionated radiotherapy group, and abdominal pain, diarrhoea, dyspnoea, hypokalaemia, and respiratory failure in the low-dose radiotherapy group (n=1 for each; appendix p 27). One patient in the low-dose radiotherapy

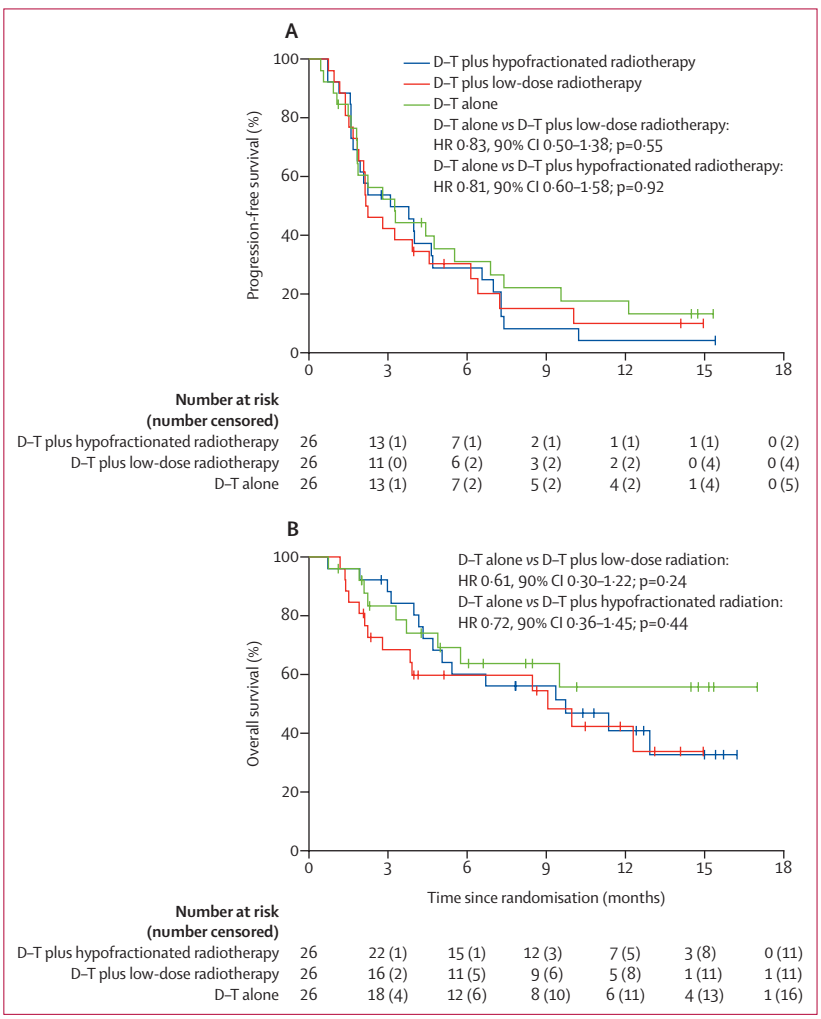

Figure 2: **Kaplan–Meier estimates of survival**
(A) Progression-free survival. (B) Overall survival. D–T=durvalumab–tremelimumab.

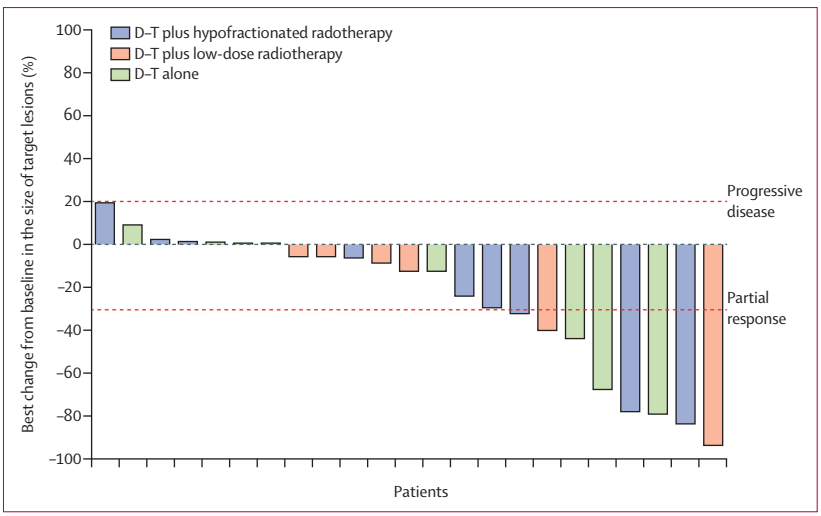

Figure 3: **Best change from baseline in the size of target lesions in patients with disease control or a response (n=23)**
D–T=durvalumab–tremelimumab.

group died from grade 5 respiratory failure potentially related to study therapy. This patient received radiotherapy to a subcarinal lymph node and had previously received radiation to the rib and femur. The respiratory failure occurred in the context of disease progression in the lung. Non-treatment-related deaths occurred in three (12%) of 26 patients in the durvalumab–tremelimumab alone group (due to respiratory failure [n=1], multiorgan failure [n=1], or progressive disease [n=1]), four (15%) of 26 patients in the low-dose radiotherapy group (due to cardiac arrest [n=1], death not otherwise specified [n=2], or lung cancer [n=1]), and three (12%) of 26 patients in the hypofractionated radiotherapy group (due to death not otherwise specified [n=1], encephalitis [n=1], or respiratory failure [n=1]).

Discussion

We conducted a randomised, phase 2 study testing the hypothesis that either repeated low-dose fractionated radiotherapy or hypofractionated radiation would increase the systemic overall response rate to durvalumab–tremelimumab (combined PD-L1 and CTLA-4 blockade) in patients with NSCLC who had previously progressed on PD(L)-1-directed therapy. We did not identify any benefit in overall response rate for the addition of either radiation regimen to durvalumab–tremelimumab (difference in overall response rate for low-dose radiotherapy *vs* durvalumab–tremelimumab alone –3·8%, 90% CI –17·3 to 9·6%; χ^2 p=0·64; difference for hypofractionated radiotherapy *vs* durvalumab–tremelimumab 0·0%, –14·6 to 14·6%; p=0·99); there were also no differences in progression-free survival and overall survival between treatment groups. To our knowledge, this randomised study is the first to evaluate the combination of radiotherapy and dual CTLA-4 plus PD-L1 blockade by use of a randomised design, to test low-dose radiotherapy (0·5 Gy/fraction), and to evaluate the role of radiotherapy as a systemic immune activator exclusively in patients who had progressed on previous PD(L)-1-directed therapy.

Other randomised studies testing the ability of focal radiotherapy to improve systemic response rates to PD-1 inhibition in NSCLC and other histologies have not met their primary endpoints;[20–22] however, a combined analysis of two trials showed that adding radiotherapy to pembrolizumab improved outcomes, including progression-free survival and overall survival.[23] Although we did not show benefit associated with the addition of radiotherapy to immune checkpoint blockade, we cannot exclude the possibility that radiotherapy administered in another tumour type, with different immunotherapy drugs, with different timings relative to immune checkpoint blockade, or using alternative radiotherapy doses or fractionation, would be beneficial. Although we did not observe a difference in response rate according to previous receipt of radiotherapy, we were unable to discriminate previous definitive versus palliative radiotherapy. Additionally, our small sample size could have obscured a more limited benefit for the addition of radiotherapy. Our patients received multiple lines of previous therapy and had measurable lesions that remained unirradiated to monitor response; other studies treating patients with newly diagnosed or oligometastatic NSCLC and delivering radiotherapy to most or all of the visible tumour volume have shown more promising benefits in pathological response, progression-free survival, and overall survival with the addition of radiotherapy.[16,24,25] In a separate cohort[15] of this trial comprising patients with metastatic colorectal cancers, we also did not observe a benefit in response with the addition of radiotherapy, which followed the same radiation regimens and targeted liver lesions, to durvalumab–tremelimumab. On-treatment biopsies obtained from this colorectal cancer cohort showed local infiltration of $CD8^+$ T-cell populations into the tumour microenvironment accompanied by systemic declines in T-cell populations following liver-directed radiotherapy, which were greater with higher radiation doses. In the current cohort of patients with NSCLC, despite the differences in disease histology and the location of irradiated lesions, we again observed systemic declines in lymphocyte counts in the radiotherapy groups that were associated with the likelihood of progression, which is consistent with previous retrospective data.[26] Although speculatory, it is possible that lymphocyte death resulting from incidental treatment of circulating blood and surrounding normal tissue could have blunted any favourable immunological effects of radiotherapy. Future studies that limit radiation-associated lymphotoxicity or administer immune checkpoint inhibitors after radiotherapy might be more beneficial, consistent with translational data.[27] These factors might explain why the addition of low-dose or hypofractionated radiotherapy to durvalumab–tremelimumab did not improve outcomes,

despite the promising preclinical data. Preclinical studies might not have fully captured the systemic immune suppressive effects of low-dose and hypofractionated radiotherapy administered with clinical techniques, given that more surrounding tissues are subject to radiation; the heterogeneity and immune suppressive nature of advanced metastatic human tumours might also have blunted any positive immunological events.

Although not the primary aim of our study, we present data on the safety of combined PD(L)-1 and CTLA-4 inhibition in NSCLC resistant to PD(L)-1 inhibition. We found that durvalumab–tremelimumab

	Durvalumab–tremelimumab plus hypofractionated radiotherapy (n=26)			Durvalumab–tremelimumab plus low-dose radiotherapy (n=26)				Durvalumab–tremelimumab alone (n=26)			
	Grades 1–2	Grade 3	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders											
Anaemia	0	1 (4%)	0	0	1 (4%)	0	0	0	1 (4%)	0	0
Leukocytosis	0	1 (4%)	0	0	0	0	0	0	0	0	0
Cardiac disorders											
Atrial fibrillation	0	0	0	0	0	0	0	0	1 (4%)	0	0
Cardiac arrest	0	0	0	0	0	0	1 (4%)	0	0	0	0
Pericardial effusion	0	1 (4%)	0	0	0	0	0	0	0	0	0
Endocrine disorders											
Adrenal insufficiency	0	1 (4%)	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders											
Abdominal pain	0	1 (4%)	0	0	1 (4%)	0	0	0	1 (4%)	0	0
Ascites	0	0	0	0	0	0	0	0	1 (4%)	0	0
Colitis	0	1 (4%)	0	0	1 (4%)	0	0	0	1 (4%)	0	0
Constipation	0	0	0	0	0	0	0	0	1 (4%)	0	0
Diarrhoea	4 (15%)	1 (4%)	0	6 (23%)	1 (4%)	0	0	6 (23%)	1 (4%)	0	0
Nausea	2 (8%)	0	0	4 (15%)	0	0	0	2 (8%)	1 (4%)	0	0
Vomiting	0	0	0	0	1 (4%)	0	0	0	1 (4%)	0	0
General disorders and administration site conditions											
Death not otherwise specified	0	0	1 (4%)	0	0	0	2 (8%)	0	0	0	0
Fatigue	8 (31%)	0	0	7 (27%)	1 (4%)	0	0	6 (23%)	1 (4%)	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	0	0	0	1 (4%)	0
Multiorgan failure	0	0	0	0	0	0	0	0	0	0	1 (4%)
Neck cellulitis	0	0	0	0	1 (4%)	0	0	0	0	0	0
Pain	0	0	0	0	1 (4%)	0	0	0	1 (4%)	0	0
Infections and infestations											
Infectious encephalitis	0	0	1 (4%)	0	0	0	0	0	0	0	0
Lung infection	0	1 (4%)	0	0	0	0	0	0	1 (4%)	0	0
Meningitis	0	0	0	0	1 (4%)	0	0	0	0	0	0
Urinary tract infection	0	0	0	0	0	0	0	0	1 (4%)	0	0
Injury, poisoning, and procedural complications											
Hip fracture	0	0	0	0	0	0	0	0	1 (4%)	0	0
Investigations											
Alanine aminotransferase increased	0	1 (4%)	0	0	0	0	0	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	1 (4%)	0	0
Blood bilirubin increased	0	1 (4%)	0	0	1 (4%)	0	0	0	0	0	0
γ-glutamyl transferase increased	0	3 (12%)	0	0	1 (4%)	0	0	0	0	0	0
Lipase increased	0	1 (4%)	0	0	0	2 (8%)	0	0	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	0	0	1 (4%)	0	0
Serum amylase increased	0	1 (4%)	0	0	0	1 (4%)	0	0	0	0	0

(Table 3 continues on next page)

	Durvalumab–tremelimumab plus hypofractionated radiotherapy (n=26)			Durvalumab–tremelimumab plus low-dose radiotherapy (n=26)				Durvalumab–tremelimumab alone (n=26)			
	Grades 1–2	Grade 3	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)											
Metabolism and nutrition disorders											
Hypercalcaemia	0	0	0	0	0	0	0	0	0	1 (4%)	0
Hypoalbuminaemia	0	0	0	0	1 (4%)	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	1 (4%)	0	0	0	0	0
Hyponatraemia	0	3 (12%)	0	0	2 (8%)	0	0	0	1 (4%)	0	0
Hypophosphataemia	0	0	0	0	1 (4%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders											
Back pain	0	0	0	0	1 (4%)	0	0	0	1 (4%)	0	0
Generalised muscle weakness	0	0	0	0	0	0	0	0	1 (4%)	0	0
Neoplasms (benign, malignant, and unspecified [eg, cysts and polyps])											
Metastatic primary lung cancer	0	0	0	0	0	0	1 (4%)	0	0	0	0
Progressive disease	0	0	0	0	0	0	0	0	0	0	1 (4%)
Nervous system disorders											
Headache	0	1 (4%)	0	0	0	0	0	0	0	0	0
Recurrent laryngeal nerve palsy	0	0	0	0	1 (4%)	0	0	0	0	0	0
Spinal cord compression	0	0	0	0	1 (4%)	0	0	0	0	0	0
Psychiatric disorders											
Confusion	0	0	0	0	1 (4%)	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders											
Bronchial haemorrhage	0	0	0	0	0	0	0	0	1 (4%)	0	0
Bronchial obstruction	0	0	0	0	0	0	0	0	1 (4%)	0	0
Dyspnoea	0	3 (12%)	0	0	3 (12%)	0	0	0	2 (8%)	0	0
Hypoxia	0	1 (4%)	0	0	0	0	0	0	0	0	0
Pleural effusion	0	0	0	0	0	0	0	0	2 (8%)	0	0
Pneumonitis	0	0	0	0	0	0	0	0	1 (4%)	0	0
Respiratory failure	0	0	1 (4%)	0	0	0	1 (4%)	0	0	0	1 (4%)
Sore throat	0	1 (4%)	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders											
Pruritus	8 (31%)	0	0	4 (15%)	0	0	0	2 (8%)	0	0	0
Maculopapular rash	6 (23%)	0	0	2 (8%)	0	0	0	3 (12%)	1 (4%)	0	0
Vascular disorders											
Hypotension	0	1 (4%)	0	0	0	0	0	0	0	0	0
Superior vena cava syndrome	0	1 (4%)	0	0	0	0	0	0	1 (4%)	0	0
Thromboembolic event	0	1 (4%)	0	0	1 (4%)	1 (4%)	0	0	1 (4%)	0	0

Data are n (%). Data shown are all grade 3–5 adverse events regardless of attribution and grade 1–2 adverse events at least possibly related to therapy with at least 10% incidence. There were no grade 4 events in the durvalumab–tremelimumab plus hypofractionated radiotherapy group.

Table 3: **Adverse events in patients who received at least one dose of study therapy**

treatment was relatively well tolerated in this setting; the overall prevalence of grade 3 or higher treatment-related adverse events was similar compared with the 22% prevalence that was observed with durvalumab–tremelimumab in the ARCTIC trial.[17] With a median follow-up of 12·4 months, we identified patients with prolonged responses and disease control, suggesting that durvalumab–tremelimumab can provide meaningful clinical benefit in a subgroup of patients with NSCLC who have progressed on PD-1-directed therapy. Further studies are warranted to identify the clinical and molecular features associated with benefit in this setting.

These data are consistent with data that suggest that patients with metastatic melanoma who progress on PD-(L)1-directed therapy can respond to combined PD(L)-1 and CTLA-4 blockade.[28] The rates of response and disease control in the current trial are higher than those from another trial by Leighl and colleagues[11] that tested durvalumab–tremelimumab in a PD(L)-1 resistant

population, which showed a 7% overall response rate amd 45% disease control rate.[11] By contrast with the study by Leighl and colleagues,[11] we allowed intervening systemic therapy following progression on previous PD(L)-1-directed therapy; however, only a minority (n=25) of patients in our study had intervening systemic therapy. Notably, we observed response rates of 7·7–11·5% despite the fact that our study population was heavily pretreated and most commonly received initial PD(L)-1-directed therapy following progression on first-line chemotherapy.

Although exploratory and limited to the subset of our cohort with translational samples available, our correlative studies suggest that biomarkers of tumour-infiltrating $CD8^+$ and $CD4^+$ T cells at baseline are associated with response to combined PD-L1 and CTLA-4 blockade. This finding is consistent with the potential ability of combined immune checkpoint blockade to reinvigorate a T cell-driven immune response in patients previously treated with PD(L)-1 inhibitors.[7] These results are hypothesis generating. Future studies can seek to validate these findings, and could use baseline $CD4^+PD\text{-}1^+Ki67^+$ T cells, $CD8^+PD\text{-}1^+$ T cells, and $CD8^+PD\text{-}1^+Ki67^+$ T cells for patient selection. Decreases in peripheral percentage lymphocyte counts following treatment were associated with progression; this potential biomarker could be further investigated in future trials. PD-L1 tumour expression was not predictive in this setting, consistent with other studies[8,9] evaluating combined PD(L)-1 and CTLA-4 therapy.

The limitations of our study include the variability in the number of lesions and disease burden at baseline; heterogeneity in the radiotherapy target, modality, and previous PD(L)-1-directed therapy; and the inclusion of patients who received intervening therapy following progression on initial PD(L)-1-directed therapy, although our subgroup analyses suggested that receipt of previous radiotherapy, intervening therapy, and interval since previous anti-PD-1 therapy had no effect on our observed outcomes. Exclusively irradiating oligoprogressive lesions or lesions in more suppressive tumour microenvironments, such as the liver,[29] could have had a more positive effect; stratifying by site of irradiation or other factors, such as previous radiotherapy administration for previous locoregional disease, could have better controlled for these variables. Indeed, we were unable to determine which patients received previous palliative versus definitive locoregional radiotherapy before enrolling onto the trial, a factor that could have affected the outcomes. Serial PET-CT scans were not mandated and are potentially more sensitive than CT scans for our primary endpoint of overall response rate by RECIST, especially for detecting response in certain metastatic sites, such as bone. We included patients with innate and acquired PD(L)-1 inhibitor resistance and are aware that the definitions of these groups continue to be refined over time. We did not see a clear impact of the duration of previous PD(L)-1-directed therapy on our response and progression-free survival outcomes. Among responding patients, we cannot isolate the effects of PD-L1 versus CTLA-4 inhibition or exclude the possibility that either treatment alone might have been efficacious in at least some patients. The radiotherapy planning technique used by treating physicians might also have differed among patients treated with hypofractionated radiotherapy versus low-dose radiotherapy, and, unfortunately, local control data were not uniformly captured to compare in-field effects.

In conclusion, data from our randomised trial suggest that durvalumab–tremelimumab should be further explored for its ability to benefit patients with NSCLC who have progressed on previous PD(L)-1-directed therapy. Improved patient selection by T cell-infiltrated tumours or other markers could be a worthy strategy to try to improve response rates and clinical benefit.

Contributors

JDS, AG-H, ES, HS, ManMA, RHM, MarMA, HXC, AMM, and FSH designed the study. JDS, AG-H, and HXC supervised the study. JDS, AG-H, KZK, AL, JT, YL, HL, CC, NL, AJ, LY, JA, JLW, SJR, CJW, and AMM analysed and interpreted the data. JDS and AG-H wrote the manuscript. JDS, AG-H, SR, and LG revised the manuscript. JDS and AG-H accessed and verified the underlying study data. All authors collected data and participated in the writing or reviewing and editing of drafts of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JDS declares research support paid to their institution from Merck, BMS, Regeneron, Debiopharm, and the NCI; consulting or participation on a scientific advisory board, and travel fees and payment for lectures from Genentech, Immunitas, Debiopharm, BMS, Nanobiotix, Tilos, AstraZeneca, LEK, Catenion, ACI Clinical, Astellas, Stimit, and Merck; expert witness fees from Pearson Doyle Mohre and Pastis, Kline and Specter, and Heidell, Pittoni, Murphy and Bach; stock options from Immunitas; and equity in Doximity. SMA declares research support paid to her institution from Merck, Exilixis, Abbvie, Kura Oncology, Amgen, and Nektar. RDG declares support for the present manuscript from a grant from the NCI of the National Institutes of Health (NIH); grants or contracts (to his institution) from Pfizer, Mirati, Daiichi Sankyo, Jounce Therapeutics, Helsinn, BMS, Merck, Janssen, and Takeda; honoraria from Rockpointe CME, Targeted Oncology, OncLive, and the Society for Immunotherapy of Cancer; reimbursement for travel for meetings from Pfizer and AstraZeneca; participation on advisory boards for Mirati, Daiichi Sankyo, AstraZeneca, Sanofi, Oncocyte, Jazz Pharmaceuticals, BluePrint Medicines, and Pfizer; and that he is co-chair of the Hoosier Cancer Research Network Thoracic Clinical Trial Working Group. CL declares honorarium for chairing the data and safety monitoring board for Delcath. JH declares participation on advisory boards for Bayer and Merck, and research funding from Merck, Boston Biomedical, Treos Bio, Senhwa Biosciences, Bayer, Incyte, TriOncology, Seattle Genetics, Hutchison MediPharma, Pionyr Immunotherapeutics, Trovogene, Taiho Pharmaceutical, Effector Therapeutics, and G1 Therapeutics. JLA declares research support from Pfizer; scientific advisory board membership for the Lustgarten Foundation, Stand Up to Cancer, Moleculin Biotech, Bessor Pharma, and Fujifilm; stock options from Bessor Pharma and Moleculin Biotech; and honoraria for data and safety monitoring board membership from Panbela Therapeutics and the Pancreatic Cancer Action Network. SKJ declares grant funding to her institution from the NCI and the Cancer Therapy Evaluation Program, and is a consultant and adjudication committee member for Merck, IMX Medical, and Syntactx. NVU has consulted for QED, Ipsen, Taiho, Incyte, AstraZeneca, and Astellas, and declares research funding from Taiho, Eli Lilly, Ipsen, and EMD Serono, and long position holdings in Natera and Exact Sciences. KLS is a member of the data and safety monitoring committee for the Case Comprehensive Cancer Center. JMJ declares consulting for

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Data sharing

Individual participant data are not publicly available because this requirement was not anticipated in the study protocol. The study protocol is available in the appendix. Correlative data obtained through the Cancer Immune Monitoring and Analysis Centers (CIMAC) Immuno-Oncology Biomarkers Network will be made available via the Cancer Immunologic Data Commons (CIDC), according to CIMAC-CIDC guidelines.

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