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

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

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Summary

Background—Patients with PD(L)-1 therapy resistant non-small cell lung cancer (NSCLC) have poor outcomes. Studies suggest radiotherapy may enhance anti-tumor immunity. Therefore,

we investigated combined PD-L1 (durvalumab) and CTLA-4 inhibition (tremelimumab) alone or combined with radiation.

Methods—This multicentre, randomised, open-label phase 2 NCI Experimental Therapeutics Clinical Trials Network trial was conducted at 18 U.S. sites. Patients aged >=18 years with metastatic NSCLC, Eastern Cooperative Oncology Group performance status of 0 or 1, and progression during previous PD(L)-1 therapy were randomised (1:1:1) using a permuted block scheme, without stratification to durvalumab/tremelimumab (1500mg/75mg every 4 weeks, 4 cycles, intravenous) alone (noRT) or with low-dose (LDFRT) or hypofractionated (HFRT) radiotherapy followed by durvalumab until 52 weeks or progression. The primary endpoint was the rate of complete/partial response in patients who initiated study treatment. The trial is registered with ClinicalTrials.gov, NCT02888743, and is now complete.

Findings—90 patients were randomised and 78 patients treated between 24 August 2017 and 29 March 2019. Median follow up was 12.4 months (IQR 7.8-15.1). There were no differences in response rates between the noRT arm (3 [11.5%] of 26, 90% CI 1.2-21.8) and the LDFRT (2 [7.7%] of 26, 0-16.3, p=0.64) or HFRT (3 [11.5%] of 26, 90% CI 1.2-21.8, p=0.99) arms. The most common grade 3-4 adverse event was dyspnea (2 [8%] of 26 NoRT, 3 [11%] LDFRT, and 3 [11%] HFRT). Serious adverse events occurred in 4 (15%, NoRT), 8 (31%, LDFRT) and 3 (12%, HFRT) patients. There was 1 grade-5 respiratory failure potentially related to therapy (LDFRT arm).

Interpretation—Radiation should not be used to increase response to PD-L1/CTLA-4 inhibition in PD(L)-1-resistant NSCLC patients. However, PD-L1/CTLA-4 therapy could be a treatment option for some patients. Future studies should refine predictive biomarkers in this setting.

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Introduction

PD(L)-1 immune checkpoint inhibitors have benefitted patients with metastatic NSCLC either alone or with chemotherapy, and are used in the first line setting.[1-4] However, the majority of patients do not respond or progress on therapy.[5,6] Treatment options in the setting of resistance to PD(L)-1 blockade are limited, and outcomes on standard therapy are poor. Combined PD(L)-1 / CTLA-4 inhibition demonstrated synergy in preclinical models,[7] and has been approved as first-line therapy for metastatic NSCLC,[8-10] but it is unclear if it provides additional clinical benefit beyond chemotherapy + PD(L)-1 inhibition or PD(L)-1 blockade alone. Prospective data are limited for this combination in NSCLC patients who progressed on PD(L)-1 blockade.[11]

Radiation 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 have stimulated interest in radiation / immune checkpoint combinations in metastatic NSCLC patients[12] and led to the design of numerous planned or ongoing clinical trials. Preclinical data suggest synergy between radiation therapy and combined PD(L)-1/ CTLA-4 blockade.[13] However, the dose of radiation best suited for this purpose is uncertain. Preclinical studies and clinical observations have suggested that both hypofractionated

(high-dose) radiation and low-dose radiation may have favorable immunologic effects such as dendritic cell maturation, homing and activation of T-cells, and macrophage differentiation.[13-15]

Durvalumab is an IgG1κ monoclonal antibody that inhibits PD-L1 binding to PD-1 and has demonstrated a progression-free and OS benefit when given following definitive chemoradiation in locally advanced NSCLC patients.[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 acting through the CD28 receptor. Tremelimumab has been evaluated in combination with durvalumab in multiple settings including first-line metastatic NSCLC (NCT03164616).[10,17] As above, preclinical/clinical data suggest potential favorable immune effects both for hypofractionated radiation (8 Gy per fraction) and low-dose radiation (<1 Gy / fraction); however these radiation regimens have not been tested prospectively in human patients in combination with dual PD-L1/CTLA-4 blockade.[13-15] Therefore, we performed a multicenter randomised phase 2 study to evaluate the potential benefit of the durvalumab / tremelimumab combination either alone (NoRT) or with low-dose (LDFRT) or hypofractionated radiation (HFRT) in patients with metastatic NSCLC who progressed on prior PD(L)-1 directed therapy.

Methods

Study design and participants

This open-label, multicentre, randomised, phase 2 study (protocol 10021) was conducted by the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) at 18 sites in the United States. A separate cohort of this study enrolling patients with metastatic colorectal cancers was previously reported.[15]

Patients with histologically confirmed metastatic NSCLC were eligible if they were aged ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 with life expectancy greater than 6 months, and had evidence of radiologic or clinical disease progression during previous treatment with systemic PD(L)-1 directed therapy as determined by the treating team; this included patients with innate or acquired resistance to prior PD(L)-1 inhibition. This determination was made clinically, although patients also had to have a biopsy specimen obtained after prior PD(L)-1 therapy and less than 3 months prior to study enrollment for eligibility. Additional inclusion criteria included: 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 gland or liver; and at least 21 days from prior systemic therapy or radiation. Bone metastases were not permitted to be the target of study radiation. Patients were required to undergo CT of the chest, abdomen, and pelvis and a brain MRI for screening. Patients had to have adequate bone marrow function (absolute neutrophil count of ≥1500 cells per μL, platelet count of ≥100 000 cells per μL, and haemoglobin concentration of ≥9.0 g/dL), adequate liver function (albumin >2.5 g/dL, alanine aminotransferase or aspartate aminotransferase less than 2.5 times the upper limit of normal and total bilirubin level <=1.5 times normal institutional limits), adequate kidney function (measured/calculated creatinine clearance >40mL/min).

Key exclusion criteria included patients who were eligible for approved agents targeting the EGFR, ROS1 or ALK pathway; prior radiation to the intended radiation site or prior radiation that would preclude safely delivering additional radiation as per protocol specifications; prior treatment with CTLA-4 directed therapy; and untreated brain metastases. A complete list of eligibility criteria is in the protocol (appendix).

The protocol was approved by the NCI central institutional review board (cIRB) and cleared by local institutional review boards of all 18 participating centres. The study was carried out 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

Patients were randomly assigned (1:1:1) to the three arms: durvalumab/tremelimumab alone or in combination with low-dose or hypofractionated radiation. Randomisation followed a permuted block scheme with random block sizes of 3 or 6 and was developed by the study statistician. There were no stratifying factors. Random treatment assignment was conducted using the web-based Theradex Interactive Web Response System (IWRS). Participants and the study team were not masked to group assignment.

Procedures

Imaging and Radiation Oncology Core (IROC) credentialing was required for the most complex radiation modality used at each center as well as for image guided radiation therapy (IGRT). Following randomisation, patients allocated to the radiation treatment arms underwent CT based radiation planning targeting one to two lesions in the lung, lymph nodes, adrenal glands, or liver. Lesions were prioritised according to the following guidelines: 1) lesions progressing on prior PD-1 directed therapy; 2) liver > lung > adrenals > lymph nodes; and 3) the largest feasibly treated lesion that may provide palliative benefit. Radiation techniques are described further in the appendix p1. Our HFRT regimen was based on preclinical evidence that hypofractionated radiation in particular can stimulate secretion of interferon via the cGAS/ STING pathway and increase immunogenicity[18] and our LDFRT regimen was supported by prior preclinical studies that demonstrated favorable changes in the tumor microenvironment, specifically regarding macrophage polarization and T-cell infiltration which was maximised at a dose of 0.5 Gy[14].

The PD-L1 inhibitor durvalumab was administered intravenously at a fixed dose of 1,500 mg every 4 weeks for a maximum of 13 cycles, and the CTLA-4 inhibitor tremelimumab was administered intraveneously 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 reduction was not allowed. Dosing could be resumed if adverse events had been reduced to grade 1 or 0. Treatment was discontinued for disease progression, unacceptable toxicity, or patient or investigator decision to discontinue.

In the LDFRT arm, patients received a dose of 2 Gy administered in four fractions over 2 days (0.5 Gy BID x 2 days) repeated for the first four 28-day cycles of therapy (total dose 8 Gy). In the HFRT arm, patients received a total dose of 24 Gy in three 8 Gy fractions

no more frequently than every other day during the first cycle of therapy only. Radiation treatment was started one week following initial durvalumab/tremelimumab administration. Tumor assessments with CT chest, abdomen and pelvis and additionally a brain MRI in patients with a history of brain metastases were performed every 12 weeks after an initial restaging scan at 7–8 weeks. One patient had week-21 scans 31 days out of window, and week-25 treatment 5 days out of window because of travel.

Participants remained on study until death or for at least one 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 were done on day 1 (before drug administration) of each treatment cycle. Treatment-related toxicity was assessed throughout the treatment period and every 30 days for 90 days after treatment discontinuation. Toxicities were graded per Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Tissue for correlative analyses was collected from the screening biopsy or from archival tissue obtained <3 months prior to study enrollment and after progression on prior PD(L)-1 therapy. As specified by a study amendment, PD-L1 immunohistochemistry, multiplex immunofluorescence (mIF), whole exome sequencing, and RNA sequencing were performed through the Cancer Immune Monitoring and Analysis Centers (CIMAC) Immuno-Oncology Biomarkers Network. Detailed procedures are available at https://cimac-network.org/assays/ and as previously described[15] and described in more detail in the appendix p1.

Outcomes

The primary outcome of the trial was to compare the overall response rate (ORR, best confirmed response of partial or complete response, locally assessed) using RECIST v1.1 criteria, excluding the irradiated lesion. Secondary endpoints included safety, progression-free survival (PFS) assessed by investigators and overall survival (OS). OS was the interval between study enrollment 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. PFS was the time from enrollment to the earlier of objective disease progression or death. For patients without progression, follow-up was censored at the date of last adequate restaging, unless death occurred within 12 weeks following the date last known to be progression free, in which case the death was counted as a PFS event. Secondary endpoints of local control and abscopal response were not uniformly collected and are therefore not reported. Prespecified correlative analyses evaluated associations between response and the percentage of tumor cells staining positive for PD-L1 as determined by immunohistochemistry, as well as exploratory analyses evaluating associations between response and infiltrating T-cell populations as by multiplex immunofluorescence as counts of cells per mm2. Additional prespecified secondary correlative and patient reported outcome studies exploring changes in circulating T-cell populations, and spatial/infiltrating immune population/genomic analyses as a result of radiation are ongoing and are therefore not reported.

Statistical analysis

Efficacy and safety analyses were performed in patients who received at least one dose of study therapy. The sample size was based on the primary endpoint of ORR. We estimated a null ORR of approximately 5% for the combination of durvalumab/tremelimumab alone based on preliminary data in a PD-1 refractory population.[19] Two pair-wise comparisons of LDFRT and HFRT against the control of NoRT were planned. Since a positive outcome for each comparison in this trial was the superiority of LDFRT or HFRT compared with NoRT, we used one-sided chi-squared tests with 10% type-I errors for each comparison. To assess for early evidence of futility or superiority of NoRT with LDFRT and/or HFRT, each pairwise comparison employed a group sequential design with O'Brien-Fleming stopping boundaries for superiority and Gamma family boundaries (gamma=1) for futility.

A sample size in each comparison of 80 patients (40 per arm) would detect a difference between response rates of 5% and 22% with 81% power (target 80%). Interim analyses were planned after 40 patients within each comparison (20 per arm) had objective response classifications within each comparison. The critical values of the test statistic for superiority of NoRT with either LDFRT or HFRT 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 performed after 10 patients had been enrolled in each arm, with a plan to stop treatment if any arm had more than 3 patients with dose-limiting toxicities.

Disease control was defined post hoc as having two or more scans with RECIST-defined stable disease (SD), one documented SD followed by non-confirmed partial response (PR), or a confirmed complete or partial response and was assessed by response group. We performed post hoc exploratory analyses of duration of response and of PFS and OS according to prior treatment characteristics (prior RT, intervening therapy, duration of prior PD-1 therapy and interval from prior PD-1 therapy). Response and disease control rates were compared between arms and within clinical subgroups using chi-squared tests (pairwise differences between treatment arms) and Fisher's exact test (other overall differences). The distributions of PFS, duration of response and OS were estimated using the method of Kaplan-Meier and compared between groups using log-rank tests. Median follow-up was estimated using the Kaplan-Meier method with inverted censor. Hazard ratios were estimated using Cox proportional hazards regression with confidence intervals calculated using log(-log)) and the Efron method for ties. PD-L1 expression and T-cell subsets were associated with response using Wilcoxon rank-sum tests. Post hoc analyses of mutational burden as by whole exome sequencing, and populations of immune cells in the tumor microenvironment as suggested by RNA sequencing were associated with response using Wilcoxon rank-sum tests. Post hoc comparisons of lymphocyte change are based on differences between pre-treatment and 6-week measurements (post-pre). Comparisons according to randomised treatment arm are based on Kruskal-Wallis tests; comparisons according to response are based on Wilcoxon rank-sum tests. , All confidence intervals are

90%, per protocol; statistical significance is defined as p<0.05. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

This study was registered with ClinicalTrials.gov, number NCT02888743.

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. All authors have had access to all of the data reported in the study.

Results

Between August 24, 2017 and March 29, 2019, 90 patients were enrolled and randomized. 78 subjects received assigned study treatment (26 per arm, Figure 1) and were included in the efficacy and safety analyses. There were 11 deviations due to eligibility: one patient was registered before eligibility screening was completed, 6 patients had negative brain MRI after registration instead of before, one of whom also had a CT abd/pelvis outside the allowable time window. Three patients were registered before brain MRI and then withdrew because of evidence of brain metastases and 1 was registered and then withdrew from the study before MRI evaluation. At the interim analysis, the p-values in both pairwise comparisons exceeded 0.463; therefore, the trial stopped early for futility. Baseline characteristics are shown in Table 1. 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.

Demographic and clinical characteristics were well balanced between groups at baseline (table 1). The majority of subjects had previously received chemotherapy (66 [85%] of 78) before enrolling on protocol, either as part of initial treatment for localised disease or in the palliative setting. Twenty-five (32%) patients received intervening non-immune therapy (most commonly docetaxel, 6 [8%], or pemetrexed, 6 [8%]). The most common site of radiation in the radiation arms was the lung (32 [62%] of 52), followed by lymph nodes (8 [15%]), liver (6, [12%]) and adrenals (5, [10%]).

ORR across arms are shown in table 2. PFS events occurred in 67 of 78 patients (figure 2, 85.9%: 24 [92.3%) of 26 HFRT; 22 [84.6%] of 26 LDFRT; 21 [80.8%] NoRT] and there were 39 deaths (50.0%: 15 [57.7%] of 26 HFRT; 15 [57.7%] of 26 LDFRT; 9 [34.6%] of 26 NoRT]. There were no differences in PFS between NoRT and LDFRT or HFRT(figure 2a). OS was also not significantly different between NoRT and LDFRT or HFRT(figure 2b). A post-hoc exploratory evaluation of rates of disease control also revealed no differences between the treatment arms (p=0.74, table 2). Degree of best response among responders or patients with disease control is shown in figure 3.

Characteristics of responders are shown in appendix p2. The median duration of response across arms was 10.3 months (90% CI 4.3, infinite, median NoRT not reached, median HFRT not reached, median LDFRT 4.9 months, 90% CI 4.3-5.5 months), with two (66%) of 3 responders in the NoRT arm and one (33%) of 3 responders in the HFRT arm alive and progression-free at the time of last follow up (appendix p3). Post hoc exploratory analyses

evaluated prior treatment factors associated with overall and PFS across all arms (appendix p4).

Correlative studies revealed somatic mutations such as TP53 (tumor protein p53) common to NSCLC and a tobacco associated mutational signature (appendix p5-6). Two responding patients had nonsense and missense mutations in the mismatch repair pathway genes *MSH3* (mutS homolog 3) (NoRT arm) and *POLE* (DNA polymerase epsilon, catalytic subunit) (HFRT arm). mRNA sequencing data and multiplex immunofluorescence (mIF) analyses evaluated CD8/PD-1, CD8/PD-1/ki67 and CD4/PD-1/ki67 T-cell populations in relation to response (appendix p7, with significant associations between pretreatment tumor-infiltrating CD8/PD-1+ and CD8/PD-1+/Ki67+ as well as CD4/PD-1+/Ki67+ T-cells (n=52, median (IQR) 37/mm2 (4.1-82.7) versus 4/mm2 (0-17), p=0.03; median 12/mm2 (2.1-44.6) versus 2/mm2 (0-8.0), p=0.04; and median 9/mm2 (2-13.5) versus 1/mm2 (0-3), p=0.01, respectively) as measured by mIF. There were no differences in tumor PD-L1 expression between responders and non-responders (n=49, median (IQR) 2.5% (0-10.0) versus 2% (1-11.2), p=0.69) or when using a 1% cutoff (p=0.32). Post-hoc exploratory analyses of circulating lymphocytes (n=52) identified significant on-treatment changes in the radiation arms (median change (IQR) +0.1% (−2.7 to 2.6) NoRT, −2.6% (−8.0 to - 0.4) LDFRT, and −5.1% (−6.5 to −0.2) HFRT, p=0.007), appendix p8, but no association with radiation target (p=0.85, appendix p9). Decrease in percent lymphocyte count was inversely associated with response across all arms (p=0.003, median change in responders (IQR) +1.7% (−3 to 3.8), median change in non-responders-3.3% (−6.0 to 0.0), appendix, p10).

Overall, 59 of 78 patients (75.6%, 90% exact CI: 66%-83%) experienced toxicity at least possibly related to therapy (19/26 [73.1%] NoRT; 20/26 [76.9%] LDFRT; 20/26 [76.9%] HFRT; Table 3, appendix p11-27). The most common grade 3 or 4 adverse event was dyspnea (2 [8%] of 26 with NoRT; 3 [11%] with LDFRT; and 3 [11%] with HFRT). Toxicities potentially related to treatment occurred in 19 patients treated with NoRT, 20 patients with LDFRT, and 20 patients with HFRT. The most commonly reported potentially related adverse events of any grade were: fatigue (22 of 78, 29%), diarrhea (18, 24%), pruritis (14, 18%), and maculo-papular rash (12, 16%). Fifteen of 78 patients (19%, 90% exact CI: 12%-28%) had grade 3-5 adverse events that were considered at least possibly related to study therapy (4/26 [15%] NoRT; 8/26 [31%] LDFRT; 3/26 [12%} HFRT; p=0.27). Seven patients (9.0%, 90% CI: 4%-16%) discontinued therapy due to drug-related toxicities (1/26 [3.8%] NoRT (colitis); 4/26 [15.4%] LDFRT (increase in lipase and serum amylase, diarrhea, dyspnea, headache and giant cell arteritis syndrome); 2/26 [7.7%] HFRT (adrenal insufficiency (2)). Ten SAEs were reported (1 NoRT; 5 LDFRT; 4 HFRT; appendix p27). There was one grade-5 respiratory failure potentially related to study therapy in a patient treated with LDFRT. This patient received radiation 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 (11.5%) of 26 NoRT patients (respiratory failure, multiorgan failure, progressive disease), four (15%) of 26 LDFRT patients (cardiac arrest, death NOS (2), lung cancer) and three (11.5%) of 26 HFRT patients (death NOS, encephalitis, respiratory failure).

Discussion

We conducted a randomised phase 2 study testing the hypothesis that either repeated LDFRT or HFRT would increase the systemic ORR to combined PD-L1 / CTLA-4 blockade in NSCLC patients who previously progressed on PD(L)-1 directed therapy. We didn't identify any ORR benefit for either radiation regimen (difference in response for LDFRT −3.8% [90% CI: −17.3%-9.6%], Chi-squared p=0.64 and for HFRT difference in response 0% [−14.6%, 14.6%], p=0.99); there were also no differences in PFS and OS between arms. To our knowledge, this represents the only study evaluating the combination of radiation and dual CTLA-4/PD-L1 blockade using a randomised design and testing low-dose radiation (.5 Gy per fraction), and the only randomised study to evaluate the role of radiation as a systemic immune activator exclusively in patients that had progressed on prior PD(L)-1 directed therapy.

Other randomised studies testing the ability of focal radiation to improve systemic response rates to PD-1 inhibition in NSCLC and other histologies have failed to meet their primary endpoints,[20-22] although a combined analysis of two trials adding radiation to pembrolizumab demonstrated improved outcomes including progression-free and overall survival.[23] While we didn't demonstrate benefit associated with the addition of radiation to immune checkpoint blockade (ICB), we cannot exclude the possibility that radiation administered in another setting, with different immunotherapy agents, with different timing relative to ICB or using alternative radiation parameters would be beneficial. Although we didn't observe a difference in response rate according to prior receipt of radiotherapy, we were unable to discriminate prior definitive versus palliative radiation. Additionally, our sample size may have obscured a more limited benefit for the addition of radiotherapy. Our patients received multiple lines of prior therapy and had measurable lesions that remained unirradiated to monitor response; other recent studies treating newly diagnosed or oligometastatic patients and delivering radiation to most or all of the visible tumor volume have demonstrated more promising benefits in pathologic response, PFS and OS.[16,24,25]

Using the same radiation regimens targeting liver lesions in the colorectal cohort of this trial,[15] we also didn't observe enhancement of response to durvalumab-tremelimumab with radiation. On-treatment biopsies obtained on this cohort demonstrated local infiltration of CD8+ T-cell populations into the tumor microenvironment, accompanied by systemic declines in T-cell populations following liver directed radiotherapy, greater with higher radiation dose. In this NSCLC cohort, despite the difference in disease type and location of the irradiated lesions, we again observed systemic declines in lymphocytes in the radiotherapy arms that were associated with likelihood of progression, which is also consistent with prior retrospective data.[26] Although speculatory, it is possible that lymphocyte death resulting from incidental treatment of circulating blood and surrounding normal tissue may have blunted any favorable immunologic effects of radiation. Future studies that limit radiation associated lymphotoxicity or sequence ICB following radiation may be more beneficial and are consistent with recent translational data.[27] These factors may explain the failure to improve survival outcomes with either LDFRT or HFRT, despite the promising preclinical data. Preclinical studies may not have fully captured the systemic immune suppressive effects of LDFRT or HFRT administered with clinical techniques; the

heterogeneity and immune suppressive nature of advanced metastatic human tumors may have also blunted positive immunological events.

Although not the primary aim of our study, we present data evaluating the safety of combined PD(L)-1/CTLA-4 inhibition in PD(L)-1 inhibitor resistant NSCLC. We find durvalumab / tremelimumab treatment is relatively well-tolerated in this setting; overall rates of grade 3-4 adverse events were favorable compared with a 22% rate that has been observed with durvalumab / tremelimumab in the ARCTIC trial.[17] With a median follow up of 12.4 months (impacted by a 9.7 month median survival), we identified patients with prolonged responses and disease control, suggesting durvalumab/tremelimumab can provide meaningful clinical benefit in a subgroup of NSCLC patients who 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 in metastatic melanoma that suggest that patients who progress on PD(L)-1 directed therapy can respond to combined PD(L)-1 / CTLA-4 blockade.[28] The rates of response and disease control in this trial are higher compared with data from another trial testing durvalumab / tremelimumab in a PD(L)-1 resistant population, which demonstrated a 7% response rate.[11] In contrast to that study, we allowed intervening systemic therapy following progression on prior PD(L)-1 directed therapy; however, these were the minority of patients included in our study (n=25). It is also notable that we observed a 10% response rate 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 biomarkers of tumor-infiltrating CD8+ and CD4+ T-cells at baseline may predict for response to combined PD-L1/CTLA-4 blockade. This is consistent with the potential ability of combined ICB 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+ and CD8+ PD-1 and Ki67+ populations to enrich for patients more likely to benefit from combined PD(L)-1 / CTLA-4 therapy, helping to guide patient selection. Decreases in peripheral percent lymphocyte count following treatment were associated with progression; this potential biomarker could be further investigated in future trials. PD-L1 tumor expression levels were not predictive in this setting, consistent with other studies evaluating combined PD(L)-1/CTLA-4 therapy.

Limitations of our study include the variability in the number of lesions and disease burden at baseline, heterogeneity in radiation target/modality/prior PD(L)-1 directed therapy, and inclusion of patients who received intervening therapy following progression on initial PD(L)-1 directed therapy, although our subgroup analyses did not suggest these latter factors had a large impact on our observed outcomes. Exclusively irradiating oligoprogressive lesions or lesions in more suppressive tumor microenvironments such as the liver[29] could have had a more positive effect; stratifying by site of irradiation or other factors such as prior radiation administration for prior locoregional disease could have better controlled

for these variables. Indeed, we were unable to determine which patients received prior palliative versus definitive locoregional radiation prior to enrolling on trial, a factor that may have impacted outcomes. Serial PET-CT scans were not mandated and are potentially more sensitive for our primary endpoint of RECIST response, especially for detecting response in certain metastatic sites such as bone. We allowed both patients with innate and acquired PD(L)-1 inhibitor resistance and are cognizant that definitions of these groups continue to be refined over time. We did not see a clear impact of duration of prior PD(L)-1 directed therapy on our response and PFS outcomes. Among responding patients, we cannot isolate the effect of PD-L1 versus CTLA-4 inhibition or exclude the possibility that either treatment alone may have been effectual in at least some patients. Radiation planning technique employed by treating physicians may also have differed among patients treated with HFRT versus LDFRT, and unfortunately, local control data were not uniformly captured to compare in-field effects.

In conclusion, our randomised data suggest durvalumab/tremelimumab should be further explored for its ability to benefit NSCLC patients who have progressed on prior PD-L1 therapy. Improved patient selection by T-cell-infiltrated tumors or other markers could be a worthy strategy to try to improve response rates and clinical benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

There are no randomised data evaluating various radiation doses in combination with PD(L)-1 / CTLA-4 inhibition and in a PD(L)-1 refractory NSCLC population. Furthermore, data evaluating combined PD-L1 / CTLA-4 inhibition with or without radiation in NSCLC patients who have progressed on prior PD(L)-1 therapy are scarce. We conducted a literature search of PubMed for reports published in English up to June 1, 2021 with the terms ("radiation" AND ("PD-1" OR "PD-L1") AND "CTLA-4" AND "clinical trial"). We identified no prospective published studies fitting these criteria.

Added value of this study

These are among the first published data reporting the efficacy and toxicity of PD(L)-1/CTLA-4 blockade in NSCLC patients resistant to prior PD(L)-1 directed therapy, a growing population of patients in need of novel therapeutic approaches. To our knowledge, this is the first report of a randomised study evaluating the addition of radiation to PD(L)-1/CTLA-4 blockade in any cancer that includes a non-radiation control arm. It is also the first randomised study to evaluate the addition of radiation to immune checkpoint blockade exclusively in PD(L)-1 refractory NSCLC patients, and the first study to prospectively evaluate the effect of low-dose (<1 Gy) radiation in combination with immune checkpoint blockade.

Implications of all the available evidence

PD-L1/CTLA-4 inhibition alone or in combination with radiation led to durable responses in approximately 10% of patients and disease control in 30% of patients and represents a potential treatment option in a subset of PD(L)-1 inhibitor resistant patient population. Our findings and the available evidence do not suggest a benefit for either low-dose or hypofractionated radiation to a single site of disease combined with PD-L1/CTLA-4 inhibition in NSCLC patients resistant to prior PD(L)-1 directed therapy.

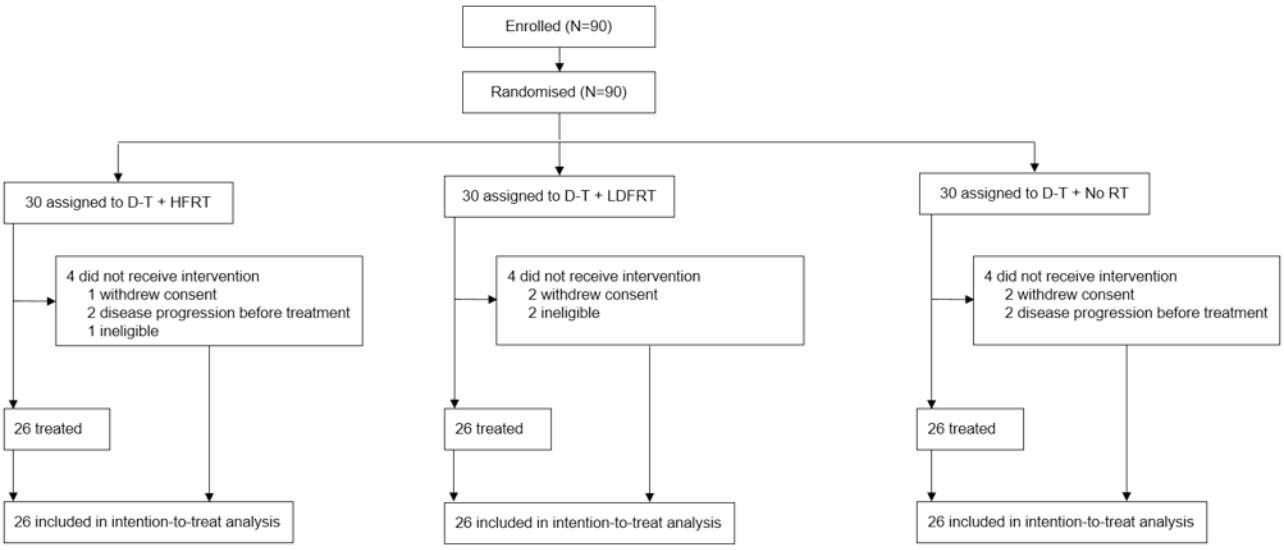

Figure 1.

Study CONSORT diagram. D= durvalumab; T- tremelimumab; HFRT- hypofractionacted radiation; LDFRT- low dose fractionated radiotherapy.

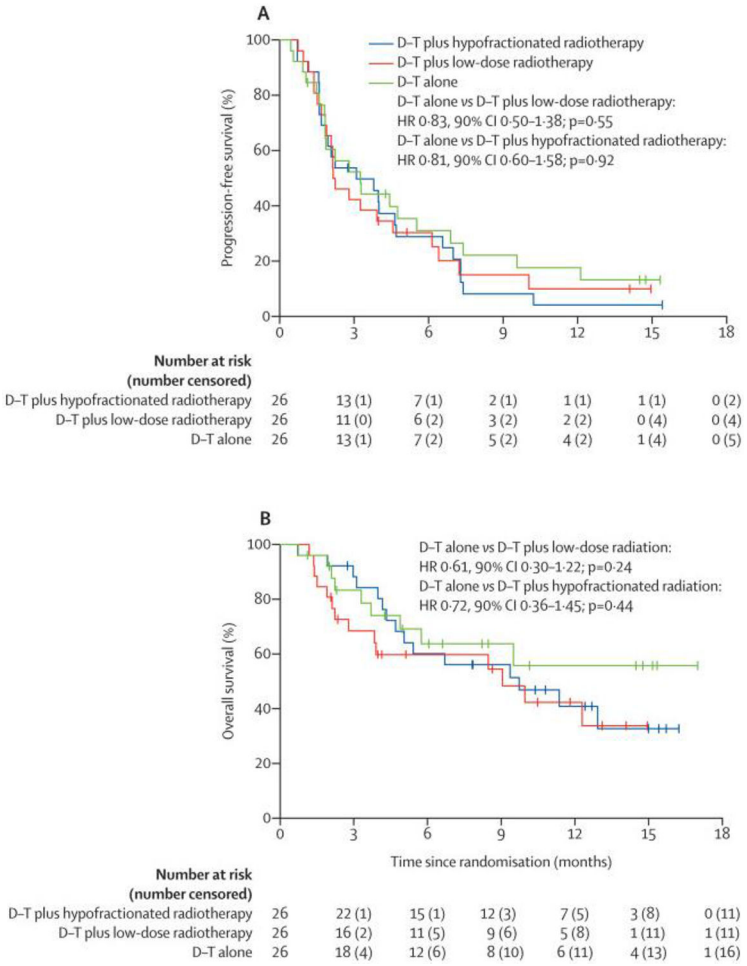

Figure 2:

Kaplan-Meier estimates of progression free survival (A) and overall survival (B). LDFRT= low-dose fractionated radiation therapy; HFRT = hypofractionated radiation therapy; No RT = no radiation (durvalumab/tremelimumab only).

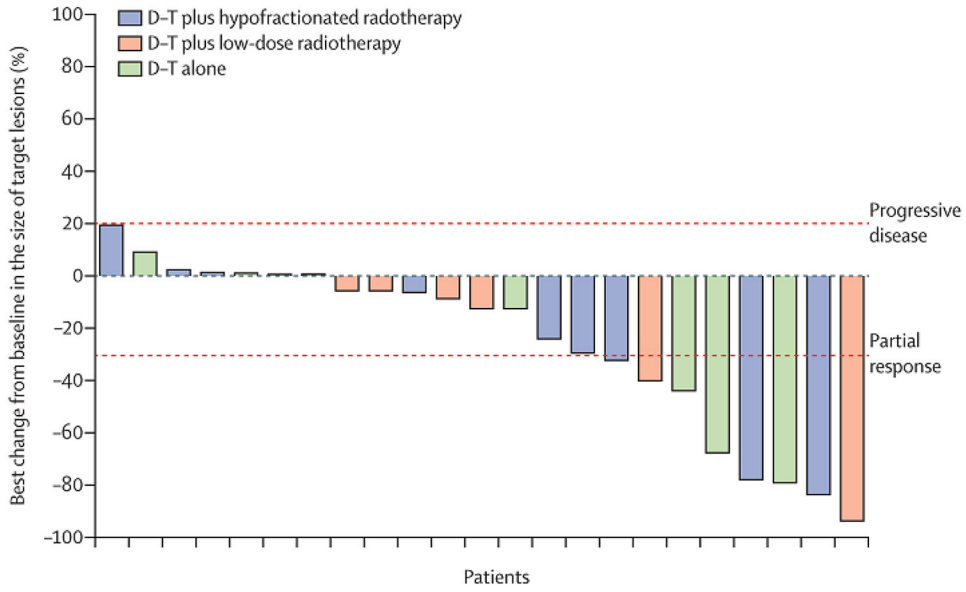

Figure 3.

Best change in target lesions in patients with disease control or response (n=23). D/T= Durvalumab/tremelimumab; HFRT = hypofractionated radiation; LDFRT = low-dose fractionated radiation therapy

Table 1.

Demographics and baseline characteristics of the analytic population

	Durva/treme (n=26)	**Durva/treme Low-dose radiation (n=26)**	**Durva/treme Hypofractionated radiation (n=26)**	**Total population (n=78)**
Age, years	65.5 (60-70)	65.5 (60-73)	65.1 (57-72)	66 (59-72)
Sex				
Male	17 (65)	18 (69)	15 (58)	50 (64)
Female	9 (35)	8 (31)	11 (42)	28 (36)
Race				
African American	3 (11.5)	1 (3.8)	1(3.8)	5 (6.4)
Asian	1 (3.8)	3 (11.5)	-	4 (5.1)
White	21 (80.8)	22 (84.6)	22 (84.6)	65 (83.3)
Unknown/not reported	1 (3.8)	-	3 (11.5)	4 (5.1)
Ethnicity				
Hispanic/Latino	-	1 (3.8)	3 (11.5)	4 (5.1)
Not Hispanic/Latino	25 (96.2)	25 (96.2)	22 (84.6)	72 (92.3)
Unknown/not reported	1 (3.8)	-	1 (3.8)	2 (2.6)
ECOG performance status				
0	5 (19)	9 (35)	6 (23)	20 (26)
1	21 (81)	17 (65)	19 (73)	57 (73)
2			1 (4)	1 (1)
Histology				
Adenocarcinoma	19 (73)	21 (81)	16 (62)	56 (72)
Squamous	3 (12)	1 (4)	5 (19)	9 (12)
Not specified	4(15)	4 (15)	5 (20)	13 (17)
PD-L1 percent expression				
<1%	4 (15)	5 (19)	4 (15)	13 (17)
1-25%	7 (27)	6 (23)	10 (38)	23 (29)
25-50%	1 (4)	2 (7)	1 (4)	4 (5)
>50%	3 (12)	2 (7)	3 (12)	8 (10)

	Durva/treme (n=26)	Durva/treme Low-dose radiation (n=26)	Durva/treme Hypofractionated radiation (n=26)	Total population (n=78)
Not done	11 (42)	11 (42)	8 (31)	30 (38)
Prior radiation				
Yes	20 (77)	17 (65)	16 (62)	53 (68)
No	6 (23)	9 (35)	10 (39)	25 (32)
Site prior RT				
Adrenal	2 (10)	2 (12)	0 (0)	4 (8)
Liver	2 (10)	0 (0)	0 (0)	2 (4)
Lung	14 (70)	9 (53)	6 (38)	29 (55)
Lymph nodes	2 (10)	1 (6)	5 (31)	8 (15)
Not specified		5 (29)	5 (31)	10 (19)
Prior lines of therapy	3 (2-4)	3 (2-3)	3 (2-4)	3 (2-4)
Median Duration of prior PD-1 therapy, weeks	21.5 (8-44)	30.1 (16-48)	27.5 (13-42)	27.5 (13-45)
Time elapsed between prior PD-1 therapy and protocol therapy (months)	3.4 (1.5-7.4)	1.6 (1.1-4.8)	2.4 (1.3-8.4)	2.5 (1.3-6.9)

Data are median (IQR), n (%), ECOG = Eastern Cooperative Oncology Group; Durva/treme = durvalumab/tremelimumab

Table 2:

Best overall response based on investigator assessment by modified RECIST 1.1

	Durva/treme (n=26)	**Durva/treme Low-dose radiation (n=26)**	**Durva/treme Hypofractionated radiation (n=26)**	**Total population (n=78)**
Best overall response				
Partial response	3 (11.5, 1.2-21.8)	2 (7.7, 0-16.3)	3 (11.5, 1.2-21.8)	8 (10.3, 5-18)
Stable disease	11 (42.3)	12 (46.2)	10 (38.5)	33 (42.3)
Progressive disease	10 (38.5)	8 (30.8)	10 (38.5)	28 (35.9)
Not Evaluable	2 (7.7)	4 (15.4)	2 (7.7)	8 (10.3)
Pairwise comparison with no radiation arm				
Difference in response rate	NA	−3.8% (90% CI: −17.3%-9.6%)	0% (−14.6%, 14.6%)	NA
Chi-squared p-value	NA	0.64	0.99	NA
Disease control	8 (30.8, 15.9-45.7)	6 (23.1, 9.5-36.7)	9 (34.6, 19.3-50.0)	23 (29.5, 21-39)
Pairwise comparison with no radiation arm			]	
Difference in response rate	NA	−7.7% (90% CI: −27.9%-12.5%)	3.8% (90% CI: −17.5%-25.2%)	NA
Chi-squared p-value	NA	0.53	0.77	NA

Data are n (%, 90% confidence interval) according to RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1 excluding responses in irradiated lesions. Note: No complete responses were observed.

Table 3

All grade 3-5 adverse events regardless of attribution; grade 1-2 adverse events at least possibly related to therapy with at least 10% incidence.

		D/T + HFRT						D/T + LDFRT								D/T + No RT							
		1-2		3		5		1-2		3		4		5		1-2		3		4		5	
			%		%		%		%		%		%		%		%		%		%		%
System/Organ Class	**Toxicity Description**																						
Blood and lymphatic system disorders	Anemia	-	-	1	3.8	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-
	Leukocytosis	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiac disorders	Atrial Fibrillation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Cardiac Arrest	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-
	Pericardial Effusion	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Endocrine disorders	Adrenal Insufficiency	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal disorders	Abdominal Pain	-	-	1	3.8	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-
	Ascites	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Colitis	-	-	1	3.8	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-
	Constipation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Diarrhea	4	15.4	1	3.8	-	-	6	23.1	1	3.8	-	-	-	-	6	23.1	1	3.8	-	-	-	-
	Nausea	2	7.6	-	-	-	-	4	15.4	-	-	-	-	-	-	2	7.8	1	3.8	-	-	-	-
	Vomiting	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-
General disorders and administration site conditions	Death NOS	-	-	-	-	1	3.8	-	-	-	-	-	-	2	7.6	-	-	-	-	-	-	-	-
	Fatigue	8	30.8	-	-	-	-	7	26.9	1	3.8	-	-	-	-	6	23.1	1	3.8	-	-	-	-
	Metabolism and Nutrition Disorders	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-
	Multi-Organ Failure	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8
	Neck Cellulitis	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
	Pain	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-
Infections and infestations	Encephalitis Infection	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Lung Infection	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Meningitis	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
	Urinary Tract Infection	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-

		D/T + HFRT						D/T + LDFRT								D/T + No RT							
		1-2		3		5		1-2		3		4		5		1-2		3		4		5	
			%		%		%		%		%		%		%		%		%		%		%
Injury, poisoning and procedural complications	Hip Fracture	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
Investigations	Alanine Aminotransferase Increased	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Aspartate Aminotransferase Increased	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Blood Bilirubin Increased	-	-	1	3.8	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
	Gamma-Glutamyl Transferase	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	GGT Increased	-	-	2	7.6	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
	Lipase Increased	-	-	1	3.8	-	-	-	-	-	-	2	7.6	-	-	-	-	-	-	-	-	-	-
	Lymphocyte Count Decreased	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Serum Amylase Increased	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-
Metabolism and nutrition disorders	Hypercalcemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-
	Hypoalbuminemia	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
	Hypokalemia	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-
	Hyponatremia	-	-	3	11.4	-	-	-	-	2	7.6	-	-	-	-	-	-	1	3.8	-	-	-	-
	Hypophosphatemia	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	Back Pain	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-
	Generalized Muscle Weakness	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic Primary Lung Cancer	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-
	Progressive Disease	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8
Nervous system disorders	Headache	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Recurrent Laryngeal Nerve Palsy	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
	Spinal Cord Compression	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
Psychiatric disorders	Confusion	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	Bronchial Hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-

		D/T + HFRT						D/T + LDFRT								D/T + No RT							
		1-2		3		5		1-2		3		4		5		1-2		3		4		5	
			%		%		%		%		%		%		%		%		%		%		%
	Bronchial Obstruction	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Dyspnea	-	-	3	11.4	-	-	-	-	3	11.4	-	-	-	-	-	-	2	7.6	-	-	-	-
	Hypoxia	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pleural Effusion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	7.6	-	-	-	-
	Pneumonitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Respiratory Failure	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8	-	-	-	-	-	-	1	3.8
	Sore Throat	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders	Pruritus	8	30.6	-	-	-	-	4	15.4	-	-	-	-	-	-	2	7.6	-	-	-	-	-	-
	Rash Maculo-Papular	6	23.0	-	-	-	-	2	7.8	-	-	-	-	-	-	3	11.5	1	3.8	-	-	-	-
Vascular disorders	Hypotension	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Superior Vena Cava Syndrome	-	-	1	3.8	-	-	-	-	-	-	-	-	-	-	-	-	1	3.8	-	-	-	-
	Thromboembolic Event	-	-	1	3.8	-	-	-	-	1	3.8	1	3.8	-	-	-	-	1	3.8	-	-	-	-