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Safety and tolerability of stereotactic radiotherapy combined with durvalumab with or without tremelimumab in advanced non-small cell lung cancer, the phase I SICI trial

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ABSTRACT

Introduction: This phase I study primarily addresses the safety and tolerability of Stereotactic radiotherapy on the primary tumor combined with double Immune Checkpoint Inhibition (SICI) in patients with non-small cell lung cancer (NSCLC). Increasing the release of neoantigens by radiotherapy might enhance response to immunotherapy. Especially, by targeting trunk mutations in the primary tumor.

Materials and Methods: In three sequential cohorts, immunotherapy regimes combined with stereotactic body radiotherapy (SBRT) on the primary tumor (1x20 Gy on 9 cc) were studied in stage IIIB/IV NSCLC patients progressing on chemotherapy. The first cohort (n = 3) received durvalumab. The second (n = 6) received a combination of tremelimumab and durvalumab followed by durvalumab monotherapy. The third cohort (n = 6) was similar except that the combination was reversed. Descriptive statistics were used to assess safety parameters and the exploratory outcomes of efficacy. Adverse events were reported using NCI CTCAE version 4.03. Exhaled breath was analyzed at baseline.

Results: Fifteen patients were included. Median irradiated volume was 9.13 cc, on a median primary tumor volume of 79 cc. There were seven patients with grade 1–2, and two patients with grade 3 treatment related adverse events. There was 1 dose limiting toxicity (colitis) with double immunotherapy.

Conclusion: The combination of SBRT to the primary tumor and double immunotherapy in advanced NSCLC patients is safe and feasible.

1. Introduction

It is increasingly understood that cancers can be recognized by the immune system and that *T*-cell inflammation relates to response [1]. Programmed cell death 1 receptor (PD1) and programmed cell death-ligand 1 (PD-L1) inhibitors have been reported to give rapid and durable responses in non-small cell lung cancer (NSCLC) [2,3]. These drugs have remarkable efficacy which is nevertheless limited to a selection of patients, where a strong biomarker is lacking.

A potential strategy to improve tumor response through immunotherapy is to increase the release of tumor neoantigens by radiotherapy and thereby enhancing the first step in the cancer immune cycle [4]. The number of somatic mutations is associated with response to immunotherapy [5]. In NSCLC, over half of mutations found by whole genome sequencing in distant metastases are private and not shared with the primary tumor [6,7]. Swanton et al. showed that mutations of the primary tumor and its metastases can be categorized in ubiquitous, shared and private mutations between different biopsy sites. The ubiquitous and shared mutations, so called “trunk” mutations are present in both primary tumor and its metastasis whereas the private “branch” mutations can be recognized at the metastatic sites [6]. Therefore, targeting the primary tumor by radiotherapy addressing trunk mutations rather

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than branch mutations in the metastasis may result in better tumor responses by skewing the immune system to recognize the most relevant neoantigens of the tumor. In mice, radiotherapy (1x15 Gy) resulted in an increased generation of antitumor immune effector cells and their trafficking to the tumor site 14 days post-radiation [8,9]. Administering a PD-L1 inhibitor directly following radiotherapy has led to synergistic tumor responses in mice [10]. In humans, the combination of radiotherapy to the PD-1 monoclonal antibody pembrolizumab was studied, with a suggestion of better responses without increasing toxicity [11]. Combining an anti-CTLA-4, PD-(L)1 inhibitor and radiotherapy may lead to increased response numbers [12].

Durvalumab is a selective, high affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 and alleviates intracellular negative signaling in *T*-cells [4]. Tremelimumab is a human IgG2 monoclonal antibody directed against cytotoxic *T*-lymphocyte-associated protein 4 (CTLA-4), that enhances human *T*-cell activation. Combining CTLA-4 with PD-L1 inhibition does not clearly improve survival over chemo-immunotherapy [13–16] Additionally, immune double therapy has a higher incidence of immune related adverse events (irAE) than immune monotherapy [17]. Since ideally, response and irAEs could be predicted in an early stage of treatment, we also focused on potential biomarkers for response and irAEs. Nevertheless, the challenge remains to increase patient response and to obtain durable benefit. Exhaled breath analysis by electronic nose (eNose) was previously able to discriminate lung cancer patients from asthma, COPD and healthy controls and NSCLC from COPD [18,19]. Furthermore, eNose technology has been reported to effectively predict individual patient responses to immunotherapy in NSCLC and malignant mesothelioma [20–22]. Here, we aimed to study safety and tolerability of SBRT combined with durvalumab and tremelimumab in PD-L1 unselected, advanced NSCLC lacking sensitizing targetable mutations after failing chemotherapy. Secondarily, we assessed efficacy and explored exhaled breath as a predictor of both response and irAE.

2. Materials and Methods

2.1. Participants and study design

From June 2018 to November 2020, this single center, open-label phase 1 study of 3 sequential cohorts with different immunotherapy regimes combined with SBRT was conducted in the University Medical Center Groningen (UMCG), the Netherlands (Fig. 1). Eligible patients were aged ≥ 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and histologically confirmed NSCLC stage IIIB or IV. All patients had progressive disease on prior chemotherapy and at least one unidimensional measurable lesion (according to RECISTv1.1) [23]. Main exclusion criteria were previous immunotherapy, prior radiotherapy to the chest, untreated central nervous system metastases and active autoimmune or inflammatory disorders requiring systemic treatment. Patients received single fraction SBRT on part of the primary tumor (20 Gy on 9 cc) in all cohorts. The volume to be irradiated was chosen based on high fluorodeoxyglucose (FDG)-activity. Usually, a more peripheral high FDG-active part of the tumor was delineated in order to avoid unnecessary dose to organs at risk, but also to the not-to-be-irradiated parts of the tumor (supplementary figure 1).

Treatment planning was based on the average reconstruction of a 4D-CT without iv contrast. The treatment was delivered during free breathing, with patients immobilized on a vacuum mattress. Patient positioning was verified and corrected online. The first cohort (n = 3) started with durvalumab 4 days before SBRT, followed by durvalumab every 4 weeks until 1 year of treatment or disease progression (PD). When the maximal tolerated dose was not reached (i.e. a dose limiting toxicity (DLT) in 33 % of the cases), this cohort was followed by 2 cohorts combining double ICI. Cohort 2 (n = 6) started with tremelimumab 4 days before SBRT and durvalumab 2 days after SBRT, and thereafter 3 cycles of durvalumab combined with tremelimumab, followed by durvalumab monotherapy every 4 weeks for 1 year or until PD. Cohort 3 (n = 6) received durvalumab 4 days before SBRT and tremelimumab 2 days after SBRT, thereafter followed by the same regimen of cohort 2. In all cases, durvalumab (1500 mg) and tremelimumab (75 mg) were given in fixed dose intravenously and a range of 2 days of the treatment was allowed.

2.2. Safety assessment

The primary outcome of this study was safety. Tolerability of the combination of SBRT with the study treatment consisting of (double) immunotherapy (ICI) was assessed by listing and summarizing the number of dose interruptions (skipping at least one dose of study drug) and dose delays (delay of drug with 5 days or more, but<28 days). DLTs were defined as any grade ≥ 3 toxicity that occurred during the first 8 weeks of treatment and summarized by primary system organ class. Adverse events (AEs) and irAEs were categorized according to NCI CTCAE version 4.03. AEs were assessed during the complete study period, i.e. starting from written informed consent until treatment discontinuation. After treatment discontinuation, AEs possibly related to study treatment were reported up to 90 days.

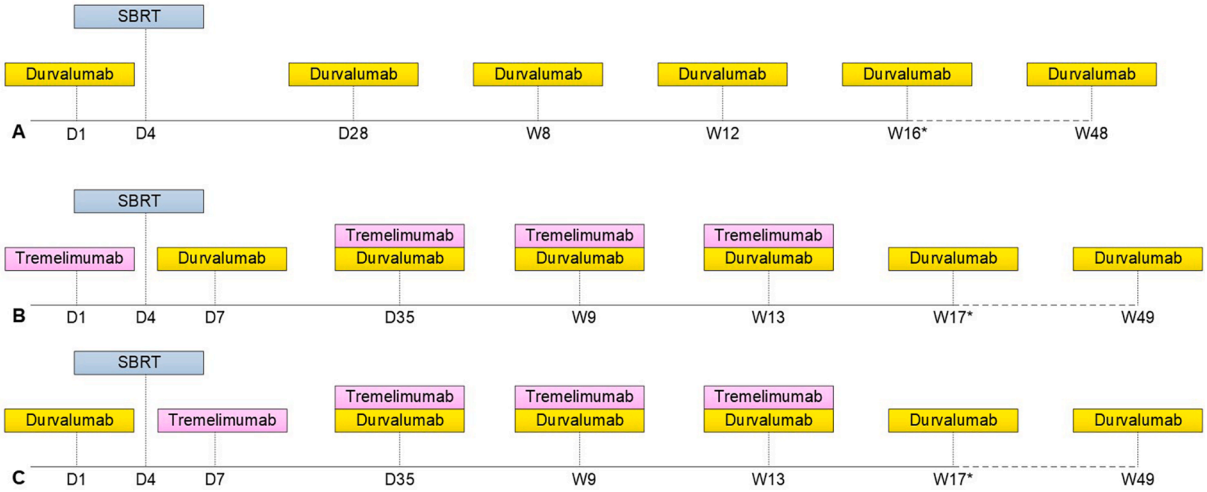

Fig. 1. ***Study design.*** Treatment regime per individual cohort is presented. A: cohort 1, durvalumab monotherapy cohort. B: cohort 2, tremelimumab and durvalumab cohort. C: Cohort 3, durvalumab and tremelimumab cohort. *D: day. SBRT: stereotactic body radiotherapy. W: week.*

2.3. Exploratory analyses

2.3.1. Efficacy assessment

Multiple efficacy outcome parameters were determined. Responses and duration of response (DOR) were defined by RECIST v1.1 criteria. The objective response rate (ORR) was calculated by the number of patients with a confirmed complete response (CR) or confirmed partial response (PR). The disease control rate (DCR) was defined as alive and progression free and determined at 6 and 12 months. Time to response (TTR) was defined as time from start treatment to PR or CR. In addition, duration of response (DOR), duration of clinical benefit (DCB), progression free survival (PFS) and overall survival (OS) were determined. DCB was defined as time from randomization to disease progression or death by any cause, in patients who achieved complete response, partial response or stable diseases for at least 24 weeks [24]. PFS was defined from the date of start of the treatment to the date of the first documented progression or death by any cause. If a patient did not have an event, the PFS was censored at the last date of follow-up. OS was defined from the date of start of treatment to the date of death to any cause. If a patient had not died, the OS was censored at the date of last follow up.

2.3.2. Exhaled breath

The SpiroNose (Breathomix, Leiden, NL) is a technically and clinically validated eNose [18,25]. It contains 7 different metal oxide semiconductor sensors. These sensors analyze the thousands of exhaled volatile organic compounds (VOCs) that originate from systemic and local metabolic processes, associated with normal physiology, pathophysiological inflammatory or oxidative activity. ENose technology captures the complete mixture of VOCs, without the identification of individual components [26,27].

Exhaled breath was measured in real-time (<1 min) by duplicate eNose measurements, performed with a two-minute interval. Patients were asked to rinse their mouth thoroughly with water before the measurements were performed and to put on a nose clip. Measurements consisted of 5 tidal breaths followed by deep inspiration to total lung capacity, a 5-second breath hold and slow maximal expiration towards residual volume. A bacteria and virus filter (Pulmosafe V3/2, Lemon Medical, Germany) was used for every patient. The SpiroNose sent the obtained sensor data directly to the online BreathBase platform where the data is stored. The sensor signals were analyzed with advanced signal processing and corrected for ambient VOCs as previously described [8].

2.4. Statistics

Descriptive statistics were used to summarize baseline characteristics, DLTs and irAEs. TTR and DOR were estimated for responders and the range reported. Median PFS and OS were determined, and the ranges presented. Assessing the ability of eNose technology to predict treatment response and irAEs at baseline was tested by Mann-Whitney *U* test followed by linear discriminant analysis and receiver operating characteristics (ROC) analysis. Patients were divided into groups based on PFS for the prediction of treatment response (above versus below median PFS). Prediction of irAEs was based on patients with versus patients without irAEs. SPSS 23.0 (IBM Corporation Amonk, NY, USA) was used to analyze all data, a p-value < 0.05 was considered as statistically significant.

2.5. Ethical and regulatory requirements

This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-Good Clinical Practice, and applicable regulatory requirements Subject data protection. The study protocol was approved by the local medical ethic committee (EudraCT: 2017–002797-39). All patients gave their written informed consent prior to the start of any study related procedures.

2.6. Role of the funding source

AstraZeneca provided a research grant for this study. AstraZeneca had no role in the design of the study, data collection, data analysis, data interpretation and the writing of the manuscript.

3. Results

Between June 2018 and November 2020, a total of fifteen patients were included, three in cohort 1 (durvalumab monotherapy), six in cohort 2 and six in cohort 3 (both durvalumab and tremelimumab). Baseline characteristics are presented in Table 1. Patients had a median age of 68 years old [52–85] and 87 % was male. The majority was former smoker (73 %), 20 % was current smoker and 7 % never smoker. Adenocarcinoma was present in 73 %. PD-L1 expression was < 1 % in 10 patients (67 %), 1–49 % in 3 patients (20 %) and ≥ 50 % in 2 patients (13 %). Site of metastasis at baseline varied with 5 patients (33 %) having brain, 6 patients (40 %) having liver and 8 patients (53 %) having bone metastasis. Five patients (33 %) had no brain, liver or bone metastasis. The median primary tumor volume was 79 cc (range 13–279 cc). The median irradiated tumor volume was 9.13 cc (range:8.98–9.60 cc) with a median of the Mean lung dose (MLD) of 0.44 Gy (range

Table 1
Baseline characteristics.

Characteristics	Durvalumab group* (N = 3)	Doublet ICI groups† (N = 12)	Total (N = 15)
Age – years			
Median [range]	60 [52–85]	68.5 [52–78]	68 [52–85]
Female sex	1 (33)	1 (8)	2 (13)
Smoking status			
Never smoker	–	1 (8)	1 (7)
Former smoker	2 (67)	9 (75)	11 (73)
Current smoker	1 (33)	2 (17)	3 (20)
ECOG performance score			
0	–	3 (25)	3 (20)
1	3 (100)	9 (75)	12 (80)
Prior chemotherapy lines			
1	2 (67)	12 (100)	14 (93)
2	1 (33)	–	1 (7)
M−status			
M1a	–	1 (8)	1 (7)
M1b	1 (33)	2 (17)	3 (20)
M1c	2 (67)	9 (75)	11 (73)
Site of metastatic lesions			
Brain	–	5 (42)	5 (33)
Liver	1 (33)	5 (42)	6 (40)
Bone	1 (33)	7 (58)	8 (53)
No brain, liver or bone	2 (67)	3 (25)	5 (33)
Histological tumor diagnosis			
Adenocarcinoma	2 (67)	9 (75)	11 (73)
KRAS p. (G12C)	1 (33)	4 (33)	5 (33)
Squamous-cell carcinoma	1 (33)	3 (25)	4 (27)
PD-L1 expression level			
< 1 %	3 (100)	7 (58)	10 (67)
1 – 49 %	0 (0)	3 (25)	3 (20)
≥ 50 %	0 (0)	2 (17)	2 (13)

Data is presented as n (%), unless otherwise specified. * Patients from cohort 1: durvalumab – SBRT – durvalumab. †: Patients from cohort 2: tremelimumab – SBRT – durvalumab(+tremelimumab) and patients from cohort 3: durvalumab – SBRT – durvalumab(+tremelimumab). *ECOG: Eastern Cooperative Oncology Group. N: number. PD-L1: programmed death ligand 1. SBRT: Stereotactic body radiation therapy.*

0.14–0.73 Gy). The V20 of the lung (i.e., the volume of the lung receiving ≥ 20 Gy) was nihil (range 0–0.1 %) and the V5 of the lung was 1.8 % (range 0–4 %). One patient received 10 Gy instead of 20 Gy, due to the central location the dose on the surrounding structures would otherwise be too high (supplementary Table 1). In one patient only the irradiated lesion could be used as a target lesion, in all other cases the primary tumors were non-target lesions.

3.1. Safety

There was one DLT in cohort 3 (durvalumab prior to SBRT followed by tremelimumab), occurring 7 days after the first dose of tremelimumab. This concerned a colitis CTC grade 3. irAEs are presented in Table 2. One CTC grade 2 pneumonitis occurred in cohort 1. In cohort 2 and 3, 6 (50 %) patients experienced low grade irAE [CTC 1–2] (3 colitis, 1 infusion related reaction, 3 pruritis, 2 rash), 2 (17 %) patients had CTC grade 3 irAE (2 colitis, 1 rash). One of these 2 patients discontinued treatment. There was one dose interruption and two delays. The dose interruption was due to a possible allergic reaction, after which the patient did not continue treatment due to progressive disease. In 1 patient, cycle 6 was delayed for 1 week due to an influenza infection. One patient skipped one dose, due to a colitis CTC grade 2, and continued the next cycle after 50 days. All AEs are presented in the supplementary, most common AEs were low grade anemia and aberrant laboratory findings (supplementary Table 2).

3.2. Exploratory data

3.2.1. Efficacy

All patients reached progressive disease, median progression free survival was 2 months (range: 1–20 months) (supplementary Table 3). At determination of OS, on June 1st 2022, three patients were still alive (Fig. 2). Median overall survival was 10 months (range: 1 month – not reached). Median duration of follow-up was 10 months (range: 1 month – 40 months).

A confirmed partial response was present in 2 patients. For both patients, the time to response was 2 months, their duration of response was 3 and 18 months. None of the patients obtained a complete response. In one patient the only target lesion was partly irradiated (patient 7, supplementary Table 1), and therefore non-evaluable by RECIST v1.1. The median duration of clinical benefit was 39 weeks (range: 25 weeks – 90 weeks). The objective response rate was 13 %. The disease control rate was 20 % at 6 months and 6 % at 12 months.

Table 2
Immune related adverse events to therapy.

Event	Durvalumab group (N = 3)	Doublet ICI groups (N = 12)	
	Grade 1–2	Grade 1–2	Grade 3
Subjects with an event	1 (33)	6 (50)	2 (17)
Event leading to discontinuation of therapy	–	–	1 (8)
Colitis	–	1 (8)	2 (17)
Diarrhea	–	2 (17)	–
Hyperthyroidism	–	1 (8)	–
Infusion related reaction	–	1 (8)	–
Pneumonitis	1 (33)	–	–
Pruritis	–	3 (25)	–
Rash	–	2 (17)	1 (8)

Overview of the treatment related adverse events in all cohorts, subdivided into severity based on NCI CTCAE version 4.03. Data is presented as n (%). There were no ≥ 3 grade 3 irAE in the durvalumab monotherapy group and no ≥ 4 irAE in the doublet ICI groups. *ICI: Immune Checkpoint Inhibition. N: Number.*

3.2.2. Exhaled breath

Twelve out of fifteen patients performed eNose measurements at baseline. No significant difference was observed in the eNose sensor signals between patients with a PFS below the median (n = 7) and those with a PFS above the median (n = 5). Subsequently, patients were divided in a group of seven patients with irAEs and five without. The irAE group had a significantly higher sensor 7 signal compared to those without irAEs (p =.042) (supplementary figure 2). The accuracy for detecting irAE with this sensor was 67 % and the area under the curve of the ROC analysis (ROC-AUC) was 0.857 [95 % confidence interval: 0.638–1] (supplementary figure 3).

4. Discussion

This phase 1 safety and tolerability study showed that our regimen combining durvalumab, tremelimumab and SBRT on a part of the primary tumor is feasible and safe. There was only 1 DLT in cohort 3 (starting with durvalumab).

The irAE profile was comparable with that observed in studies with double checkpoint inhibition [17,28–33]. In the MYSTIC Trial, the combination of durvalumab and tremelimumab has a higher grade 3 irAE incidence (22.9 %) than durvalumab alone (15.9 %), being mainly fatigue and diarrhea [17]. Most frequent irAEs observed in patients receiving double ICI are diarrhea, pruritis and rash. In the current study the only DLT encountered was a colitis after the first cycle of double immunotherapy. No increase in pneumonitis was observed, even though the primary lung tumor was irradiated with high dose radiotherapy (but small volume). This is in line with Theelen et al., who did not report an increase in immunotherapy related AE or pneumonitis combining ICI with irradiation [11]. Additionally, Schoenfeld et al. neither observed additional irAEs when combining double ICI and radiotherapy [33]. In contrast, the Pacific study shows a slight increase in any grade pneumonitis, but no difference in grade 3–4 pneumonitis comparing durvalumab with placebo subsequent to chemoradiotherapy [34].

In early-stage NSCLC, combining durvalumab with radiotherapy (3 × 8 Gy) to the primary tumor led to significantly more patients with a major pathological response compared to durvalumab alone, even after adjustment for PD-L1 expression [35]. This is – to the best of our knowledge – the only in human study combining double ICI with high dose radiotherapy specifically targeting the primary tumor to address the trunk mutations in advanced NSCLC [6]. Several studies with different radiotherapy strategies address mostly the metastases [11,33,36]. Theelen et al. and the MDACC trial combined anti PDL-1 monotherapy with metastasis directed radiotherapy and Schoenfeld et al. treated patients who were progressive on PD-L1 monotherapy with durvalumab and tremelimumab with either low dose or hypo fractionated radiotherapy on different tumor sites (lung, lymph node, liver, adrenal gland) [11,33]. Theelen et al. did observe a two times higher ORR combing pembrolizumab with SBRT compared to SBRT alone, but did not reach a clinical relevant increase in ORR [11]. The MDACC trial did not find an advantage of adding radiotherapy (conventional or hypofractionated) to pembrolizumab [36]. A pooled analysis of both studies showed a significantly longer PFS and OS for ICI combined with radiotherapy compared to ICI alone [37]. The study of Schoenfeld et al. showed no benefit and was terminated due to futility [33]. The combination of ipilimumab, nivolumab and SBRT on several metastases as first line treatment showed promising results [38]. Furthermore, in case of oligometastatic disease local ablative therapy as SBRT to all metastases appears to prolong progression free survival as well [39]. Probably, a reduced tumor load due to the ablative therapy might contribute to this response. Developments to direct SBRT to the most active metastases, might further improve the response to the combination of irradiation of metastases and ICI [40]. However, we specifically chose to irradiate a constant volume (9 cm^3) of the primary tumor to address the added value of SBRT to checkpoint inhibition. By addressing 9 cm^3 of tumor (i.e. about $4x10^9$ cells), there should be sufficient release of tumor antigens

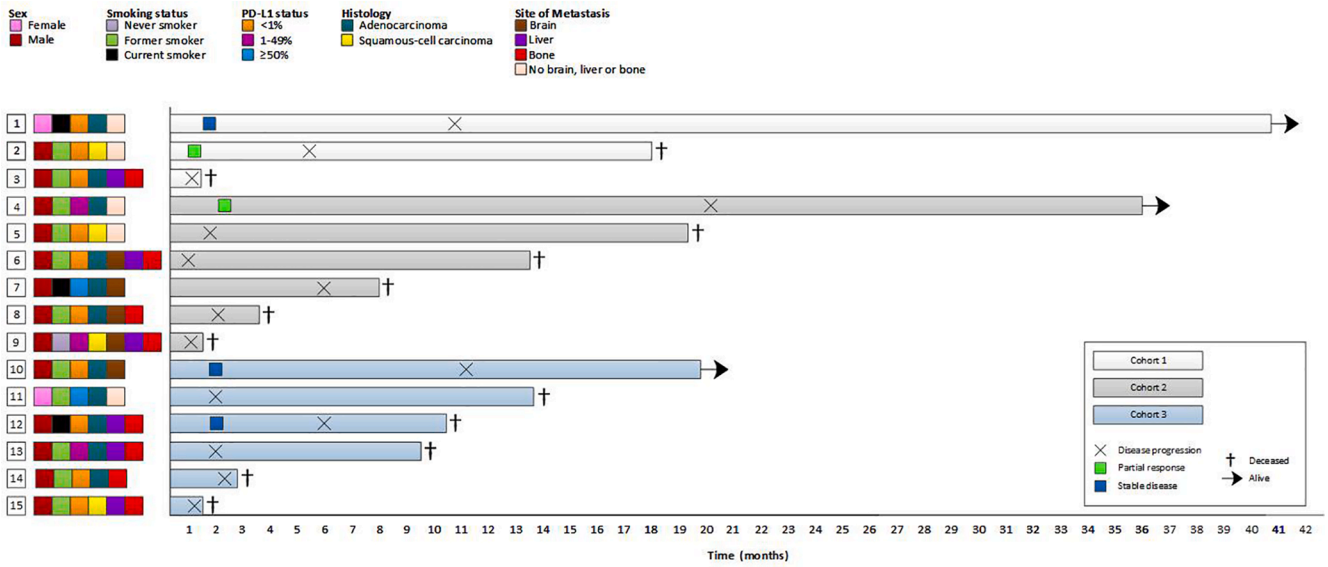

Fig. 2. ***Swimmer plot of response.*** Swimmer plot showing response and duration of follow-up (in months) after the start of the first treatment with either durvalumab or tremelimumab. All individual patients with some of their characteristics are displayed on the y-axis, ordered by cohort and overall survival. Disease progression is indicated in each plot and vital status presented at the end of each plot. Cohort 1: durvalumab monotherapy. Cohort 2: Tremelimumab and durvalumab. Cohort 3: Durvalumab and tremelimumab. *PD-L1: programmed cell death-ligand 1.*

without a confounding treatment effect of radiotherapy itself [41].

Although baseline characteristics of our patients are comparable between the different cohorts, there was a broad range in primary tumor size and therefore also in the percentual part of the primary tumor that was irradiated. This might implicate that, due to tumor heterogeneity, not all most relevant neoantigens were potentially released during radiotherapy, although radiotherapy was aimed at the most FDG-avid lesions on a Positron Emission Tomography scan. Also, the dose of 20 Gy might be too high, inducing DNA degeneration of the tumor microenvironment and attenuating the immune response [42]. There are suggestions that lower doses of radiotherapy might be more effective than higher doses, however the literature is very heterogenous in this respect and a recent study by Schoenfeld et al. combining double ICI with low dose and hypo-fractionated radiotherapy was terminated due to futility in an interim analysis [33,43].

We wanted to study what was the best regimen: starting with anti-CTLA4 or anti-PD-L1. Verma et al. showed that introducing anti-PD-L1 before optimal priming of CD8 + *T*-cells led to increased resistance to immunotherapy. Theoretically, administering tremelimumab and radiotherapy before durvalumab, as we did in cohort 2, should therefore be the best regimen. Yet, we were not able to show this in our safety cohort. The current study design was on patients in 2nd and later treatment line, but naïve for immunotherapy. Due to the fact that immunotherapy became available as first line treatment in NSCLC patients we were unable to extend the current study into a phase 1B trial to study efficacy of the combination of double ICI with SBRT [44–46]. Recently, ipilimumab/nivolumab combined with chemotherapy was approved as first line treatment in patients with NSCLC as well [13]. Additionally, the Poseidon trial showed a benefit of combining durvalumab/tremelimumab with chemotherapy over chemotherapy alone in first line setting [15]. A phase 2 study for our regimen could be performed as first line treatment with that strategy.

Our cohorts existed of pretreated metastasized patients with a high tumor burden at baseline. Ten (66 %) of them had liver, brain and/or bone metastasis, associated with a poor prognosis [47]. In this small safety cohort, we did not find any advantage of combining ICI and SBRT in terms of ORR or survival data. Interestingly, some patients had a long treatment response and three of them are still alive currently. This may indicate that selected patients do benefit from this treatment. However, based on our study there are no clear markers to select those patients.

As part of the exploratory analyses, we investigated whether exhaled breath analysis by eNose technology was able to predict treatment response. The results showed no significant differences between patients with PFS below and above the median, indicating prediction of treatment response based on eNose was not successful. This could be expected due to the very limited sample size. Previously performed studies with the same technology used RECIST to assess efficacy at 3 months follow up and showed that eNose is able to predict response to anti-PD-1 therapy in NSCLC patients at baseline [20,21]. Furthermore, combining eNose data at baseline and after six weeks of anti-PD-1 therapy resulted in even more accurate prediction of treatment response [21]. In malignant pleural mesothelioma eNose has also been shown to accurately discriminate between responders and non-responders to immune checkpoint inhibitor treatment after 6 months of treatment based on RECIST [22].

Additional exploratory analysis assessed the ability of eNose to predict irAEs at baseline. The results showed a significantly higher eNose signal for sensor 7 at baseline measurements in patient with irAEs compared to patients without irAEs. This might be an indication that the eNose can predict irAEs at baseline, although these results may be overfitted due to the limited sample size. Therefore, this result needs to be validated in a larger cohort. The sensors in the SpiroNose are cross-reactive nonspecific sensors, meaning multiple VOCs competitively interact with the sensors and multiple sensors interact with the same volatile. This is comparable to the mammalian olfactory system and results in a pattern of sensor signals driven by the complete mixture of VOCs without the identification of individual components [20]. There are no other studies that analyzed the role of eNose in predicting irAEs.

In conclusion, combining durvalumab and tremelimumab with low volume, high dose radiotherapy to the primary tumor is safe and feasible in patients with advanced NSCLC.

Conflict of interest statement

HK reports a research grant from Roche (paid to the institute) and support for attending a meeting by Mundipharma. MBM reports a support for attending a meeting, provided by the American Association of Cancer Research and Bristol Myers Squibb. GS reports personal fees from Breathomix BV. RdV receives personal fees and has a substantial interest in Breathomix BV. HJMG reports grants from Eli Lilly and Novartis (all

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.02.004.

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