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ORIGINAL ARTICLE

Immune checkpoint blockade in the treatment of advanced non-small cell lung cancer – predictors of response and impact of previous radiotherapy

Åsa Kristina Öjlert[a], Daniel Nebdal[a], Marius Lund-Iversen[b], Renée Åstrøm Ellefsen[a], Odd Terje Brustugun[a,c], Jon Michael Gran[d], Ann Rita Halvorsen[a,e] and Åslaug Helland[a,e,f]

[a]Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway; [b]Department of Pathology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway; [c]Section of Oncology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway; [d]Oslo Centre for Biostatistics and Epidemiology, University of Oslo and Oslo University Hospital, Oslo, Norway; [e]Department of Clinical Medicine, University of Oslo, Oslo, Norway; [f]Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway

ABSTRACT

Background: The implementation of immune checkpoint inhibitors (ICI) into the standard care of advanced non-small cell lung cancer (NSCLC) has improved prognosis for this group of patients. However, long-term survival is rare. The aim of the study was to identify predictors of response and, especially, to investigate the impact radiotherapy might have on duration of response.

Material and methods: The association between pretreatment patient/tumor characteristics and progression-free survival (PFS), overall survival (OS), and lung cancer-specific survival was investigated in 78 patients receiving an ICI as ≥2nd line treatment for advanced NSCLC, using Cox regression analysis. Due to competing risk, cause-specific deaths were also examined with cumulative incidence plots.

Results: Median OS was 12.6 months (95% CI 7.8–18.2) and median PFS 4.1 months (95% CI 3.0–6.2), after median follow-up time of 49.7 months (range 20.9–51.5). Increasing CRP and neutrophil/lymphocyte ratio (NLR), were associated with poor PFS (CRP: HR 1.49, 95% CI 1.12–1.98; NLR: HR 1.59, 95% CI 1.22–1.85) and OS (CRP: HR 1.94, 95% CI 1.47–2.56; NLR: HR 1.54, 95% CI 1.27–1.87). Radiotherapy prior to immunotherapy was not significantly associated with patient outcome. However, when the dataset was split at 6 months of follow-up, to be able to identify early and late predictors of prognosis, we found that patients receiving radiotherapy <6 months prior to immunotherapy had better PFS (HR: 0.27, 95% CI 0.09–0.84) and lung cancer-specific survival (HR: 0.41, 95% CI 0.18–0.95) after the first 6 months of follow-up, while increasing CRP (PFS: HR1.61, 95% CI 1.21–2.14; OS: HR2.04, 95% CI 1.51–2.74) and NLR (PFS: HR 1.57, 95% CI 1.29–1.91; OS: HR 1.63, 95% CI 1.35–1.97) were predictors of poor short-term prognosis.

Conclusions: Radiotherapy may be of importance to achieve a long-lasting response to immunotherapy, while indicators of systemic inflammation can help in identifying patients with poor short-term prognosis.

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Non-small cell lung cancer; immune checkpoint inhibitors; radiotherapy; prognosis; neutrophil-to-lymphocyte ratio

Introduction

The prognosis for localized lung cancer has slowly improved, but the 5-year survival rate for patients with metastatic disease remains poor [1]. With the implementation of immune checkpoint inhibitors in the treatment of non-small cell lung cancer (NSCLC), improvements have been made for subsets of patients. Among unselected patients with NSCLC, response rates to PD-1/PD-L1 inhibitors are around 20%, while some patients experience disease control for years [2–4]. Though the proportion of patients with progressive disease at 6 months was very similar for the nivolumab and docetaxel treatment groups in the CheckMate 017 and 057 trials, the 4-year OS rate was significantly better for patients receiving nivolumab (14%) than docetaxel (5%) [5]. A similar long-term OS rate was reported for pembrolizumab in the Keynote 001 trial, where 5-year OS for previously treated patients was 15.5%, while in the OAK trial 28% of patients treated with atezolizumab were alive at two years follow-up, as compared to 18% of those receiving docetaxel [6,7].

After the benefit of immune checkpoint inhibitors in the treatment of advanced NSCLC has been established, the current focus is mainly directed at identifying predictive biomarkers for better patient selection, and treatment combinations that might improve the outcome for more patients. The most studied predictive biomarkers are tumor mutational burden and PD-L1 expression on tumor cells. However, none of these are sufficient to predict response accurately [8–10]. Trials combining an immune checkpoint

CONTACT Åslaug Helland aslaug.helland@medisin.uio.no

Supplemental data for this article can be accessed here.

inhibitor with chemotherapy, targeted therapy, or with another immune checkpoint inhibitor have been performed. Results suggest higher response rates, although increased toxicity is also seen [11–15]. The proposed abscopal effect, where an immune-mediated response may be seen after radiotherapy in lesions not included in the radiation field, has inspired studies where immunotherapy and radiotherapy are combined [16]. Results are promising, both when it comes to response rates and toxicity, but completed clinical studies with this combination are few and the optimal timing and dosage of radiotherapy remain to be elucidated [17,18].

The aim of this study was to report the clinical outcome for patients with advanced NSCLC receiving an immune checkpoint inhibitor as ≥2nd line treatment and to identify patient- and tumor-related properties associated with prognosis. Especially, we wished to investigate the relationship between radiotherapy and long-lasting response to immunotherapy.

Material and methods

Patients

Patients treated with PD-1/PD-L1-inhibitors as ≥2 line therapy for stage IV NSCLC at Oslo University Hospital and Drammen hospital were included in the study between September 2013 and June 2019, and followed until October 2019. The evaluation was performed every 6–8 weeks. Clinical information, including details on any previous or concomitant radiotherapy, cause of death, and results on blood tests at the start of immunotherapy, was collected from the patient records. Where available, information on EGFR mutation status and ALK rearrangements was also collected from the patient records. Of 78 patients included 39 (50%) were female. The median age was 65 years. Forty-five patients (58%) had adenocarcinoma (AD), 29 (37%) had squamous cell carcinoma (SCC), 1 patient (1%) had large cell neuroendocrine carcinoma (LCNEC) and 3 patients (4%) had mixed histology. The majority of patients (78%) had ECOG performance status 0–1. Smoking status was known for 65 of the patients and these 8 were never-smokers. For further details on patient characteristics, see Table 1.

The study has been approved by the regional ethics committee (South East REC) on 21 September 2015 (ethic code: 2015/1587), and was performed in accordance with the standards of The Helsinki Declaration. All patients signed a written informed consent.

Table 1. Patient, tumor, and treatment characteristics.

Age	
Median (range)	64.7 (41–88)
Sex	
Female	39 (50.0%)
Male	39 (50.0%)
Previous systemic therapies	
1	32 (41.0%)
2	29 (37.2%)
3	13 (16.7%)
4	4 (5.1%)
Immune checkpoint inhibitor	
Nivolumab	63 (80.8%)
Atezolizumab	7 (9.0%)
Pembrolizumab	8 (10.3%)
Smoking status	
Never	8 (10.3%)
Current	19 (24.4%)
Previous	38 (48.7%)
NA	13 (16.7%)
Histology	
Adenocarcinoma	45 (57.7%)
Squamous cell carcinoma	29 (37.2%)
LCNEC	1 (1.3%)
Mixed NSCLC histology	3 (3.8%)
Molecular alterations (n)	
EGFR mutation (43)	3 (7.0%)
ALK translocation (38)	0
Radiotherapy	
Before immunotherapy	59 (75.6%)
<6 months before immunotherapy	38 (48.7%)
<3 months before immunotherapy	25 (32.1%)
Concomitant	10 (12.8%)
PD-L1 expression	
Negative	33 (42.3%)
≥1 and <50%	13 (16.7%)
≥50%	12 (15.4%)
NA	20 (25.6%)
ECOG	
0	15 (19.2%)
1	46 (59.0%)
2	12 (15.4%)
3	4 (5.1%)
NA	1 (1.3%)
Albumin ($n = 61$)	
Median (range)	39 (22–46)
Lymphocytes ($n = 75$)	
Median (range)	1.2 (0.3–3.26)
CRP ($n = 59$)	
Median (range)	19 (0–269)
WBC ($n = 77$)	
Median (range)	7.0 (3.0–24.0)
N/L ratio ($n = 75$)	
Median (range)	4.09 (1.27–30.00)
LD ($n = 61$)	
Median (range)	190 (109–591)
Neutrophils ($n = 76$)	
Median (range)	4.9 (1.7–20.4)
Hemoglobin ($n = 76$)	
Median (range)	11.9 (8.1–16.3)
Thrombocytes ($n = 77$)	
Median (range)	300 (113–744)
Creatinine ($n = 77$)	
Median (range)	74 (38–151)

N/L ratio: neutrophil/lymphocyte ratio; WBC: white blood cells.

Gene expression assessment

Formalin-fixed paraffin-embedded (FFPE) tissue from needle biopsies or surgical specimens were available for 39 of the participants. RNA was isolated using the miRNeasy FFPE kit from Qiagen. The quantity was controlled using the Qubit 2.0 Fluorometer, while Agilent 2100 Bioanalyzer microfluidic gel electrophoresis system was used for quality control. The expression of 395 immune-related genes was assessed using the Oncomine immune response research assay (Ion Torrent).

Quality control of the data was performed using the Torrent Suite immuneResponseRNA plug-in in the Torrent Suite software. Of 39 samples assessed for expression of immune-related genes, 8 were excluded due to low RNA concentration, read counts, or library concentration.

Statistics

Gene expression values were log2 transformed and then normalized by subtracting the mean expression of the housekeeping genes and adding $\log_2 10^6$. Of the 11 housekeeping genes two, *G6PD* and *HMBS,* were not used for normalization because these were not well correlated with the other genes and had a disproportionally large effect on the normalization output. The cytolytic score was calculated as the geometric mean of *GZMA* and *PRF1* [19].

Cox regression analyses were performed to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for the primary outcome of progression-free survival (PFS), overall survival (OS) and lung cancer-specific survival. Note that cause-specific survival is subject to competing risk and should be interpreted with caution [20]. A result was defined as significant if its 95% CI did not include one. OS was calculated based on the time from when the patients started with immunotherapy to the time of death. If the patients were still alive when data was collected they were censored on that date. Blood values and cytolytic score were first divided by the interquartile range (IQR) and thus the HRs are for an IQR increase. In addition, the patient outcome was visualized using Kaplan–Meier plots, and a log-rank test used to compare the survival curves. Due to competing risk, cause-specific deaths were examined with cumulative incidence plots, using the cmprsk package in R [21]. In these, Gray's test was used to compare the curves. Note that no correction for multiple testing has been performed and the results must be interpreted thereafter. Laboratory results and gene expression data were not available for all patients. For these measures information on the number of patients included in the analyses is shown in Table 1. All statistical analyses were performed using R version 3.6.3 (http://www.r-project.org).

Results

Seventy-eight patients were included in the analysis. Median follow-up time, calculated as median observation time after initiation of immunotherapy for patients still alive at the end of follow-up, was 49.7 (range 20.9–51.5) months. Median survival time was 12.6 (95% CI 7.8–18.2) months and median PFS 4.1 (95% CI 3.0–6.2) months. ECOG, sex, histology, age, smoking history and number of previous lines of therapy did not affect PFS or lung cancer-specific survival, while men (HR 1.74, 95% CI 1.07–2.84) and patients with squamous histology (HR 1.65, 95% CI 1.01–2.71) had poor OS. Note that the estimated hazard ratios for lung cancer-specific survival are subject to competing risk and must be interpreted thereafter [20]. In our dataset, 10 out of a total of 66 deaths were from other causes, mostly pneumonia. PD-L1 status was known for 58 (74.4%) of the patients and was not significantly associated with the outcome for these patients. Gene expression data from pretreatment tumor biopsies were available for 31 of the patients. In these, the cytolytic score was used as a marker for an ongoing adaptive immune response in the tumor. Increasing cytolytic score was found to be associated with better lung-cancer specific survival (HR 0.56, 95% CI 0.33–0.95), but not with better PFS (HR 0.74, 95% CI 0.46–1.18) or OS (HR 0.63, 95% CI 0.38–1.06). For details, see Supplementary Table S1 and the Kaplan–Meier plots and, for cause-specific survival, cumulative incidence plots in Supplementary Figure S1.

Increasing CRP, leukocytes, neutrophils and neutrophil/lymphocyte ratio (N/L ratio), and decreasing hemoglobin, were associated with poor PFS (CRP: HR 1.49, 95% CI 1.12–1.98; WBC: HR 1.61, 95% CI 1.26–2.06; neutrophils: HR 1.72, 95% CI 1.33–2.21; N/L ratio: HR 1.5, 95% CI 1.22–1.85; hemoglobin: HR 0.68, 95% CI 0.47–0.99), OS (CRP: HR 1.94, 95% CI 1.47–2.56; WBC: HR 1.56, 95% CI 1.25–1.95; neutrophils: HR 1.66, 95% CI 1.33–2.07; N/L ratio: HR 1.54, 95% CI 1.27–1.87; hemoglobin: HR 0.59, 95% CI 0.4–0.85) and lung cancer-specific survival (CRP: HR 1.88, 95% CI 1.41–2.52; WBC: HR 1.55, 95% CI 1.23–1.96; neutrophils: HR 1.65, 95% CI 1.3–2.09; N/L ratio: HR 1.55, 95% CI 1.26–1.9; hemoglobin: HR 0.51, 95% CI 0.34–0.77). High albumin and low thrombocytes were associated with better OS (albumin: HR 0.52, 95% CI 0.36–0.76; thrombocytes: HR 1.37, 95% CI 1.05–1.79), though not with better PFS (albumin: HR 0.85, 95% CI 0.58–1.26; thrombocytes HR 1.18, 95% CI 0.92–1.53). When prognosis according to pretreatment blood counts was visualized in Kaplan–Meier plots, defining low as below median and high as median or higher, signs of systemic inflammation were mostly associated with poor prognosis the first months of follow-up and had a greater impact on survival than on PFS (Figure 1 and Supplementary Figure S1).

Radiotherapy prior to immunotherapy was not significantly associated with patient outcome when assessed by univariable Cox regression analysis (Supplementary Table S1). In Figure 2, PFS is plotted against time from the last dose of radiotherapy to the first dose of immunotherapy. Patients who did not receive radiotherapy, and patients who received radiotherapy >6 months before immunotherapy, are similarly distributed along the *y*-axis. Among those who received radiotherapy <6 months before immunotherapy we find all but one of the long-term responders (defined as PFS > 2 years), but also many patients with very poor prognosis. Figure 3 gives an overview of patient outcome, PD-L1 status and whether the patient received radiotherapy <6 months before immunotherapy or not for all patients. The Kaplan–Meier curves for radiotherapy <6 months before immunotherapy are crossing, indicating that this variable affects prognosis differently over time.

With long follow-up time the hazards are often not proportional, and Cox regression analysis therefore not an optimal method to investigate the impact of different variables on prognosis [22]. To be able to identify short-term and long-term predictors of PFS and survival, we decided to split the dataset and look at the first 6 months of follow-up and the time after 6 months separately. When this was done it became clear that markers of systemic inflammation, as high CRP, leukocytes, neutrophils, and N/L ratio were strong predictors of poor prognosis the first 6 months of follow-up (PFS: CRP HR 1.61, 95% CI 1.21–2.14; WBC HR 1.72, 95% CI 1.34–2.19; neutrophils HR 1.82, 95% CI 1.42–2.35; N/L ratio

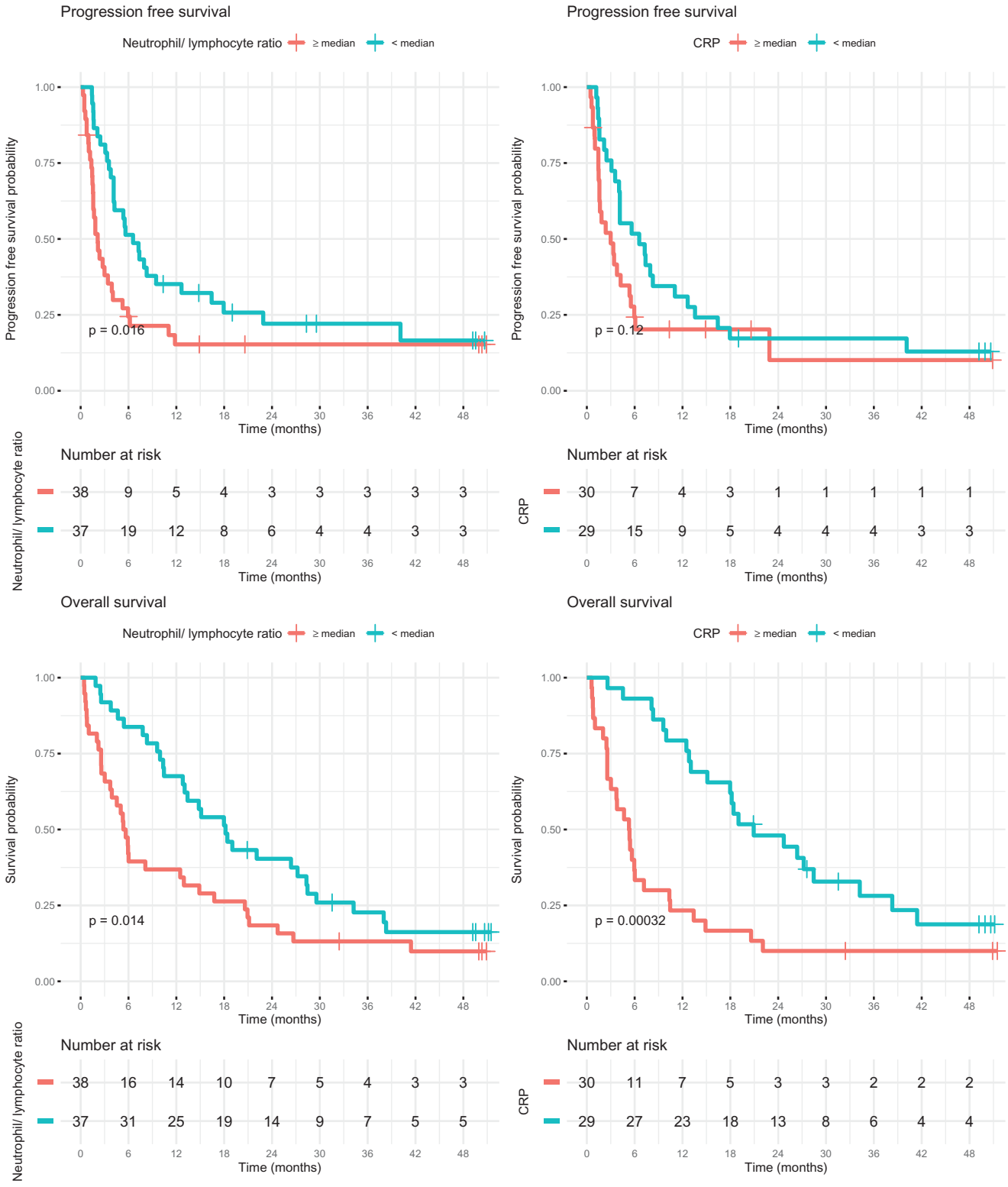

Figure 1. Kaplan–Meier plots showing PFS and OS according to CRP and neutrophil/lymphocyte ratio at the start of treatment with an immune checkpoint inhibitor.

HR 1.57, 95% CI 1.29–1.91), but not after 6 months (PFS: CRP HR 0.44, 95% CI 0.09–2.1; WBC HR 0.64, 95% CI 0.23–1.77; neutrophils HR 0.64, 95% CI 0.22–1.89; N/L ratio HR 0.41, 95% CI 0.11–1.51). Low albumin and hemoglobin are often seen in patients with more advanced cancer, and these were also correlated to poor prognosis in the first months of follow-up (PFS: albumin HR 0.61, 95% CI 0.41–0.92; hemoglobin HR 0.6, 95% CI 0.4–0.92). For further details including results for OS and lung cancer-specific survival, see Supplementary Tables S2A and S2B.

Radiotherapy <6 months before immunotherapy was associated with poor OS the first 6 months of follow-up (HR

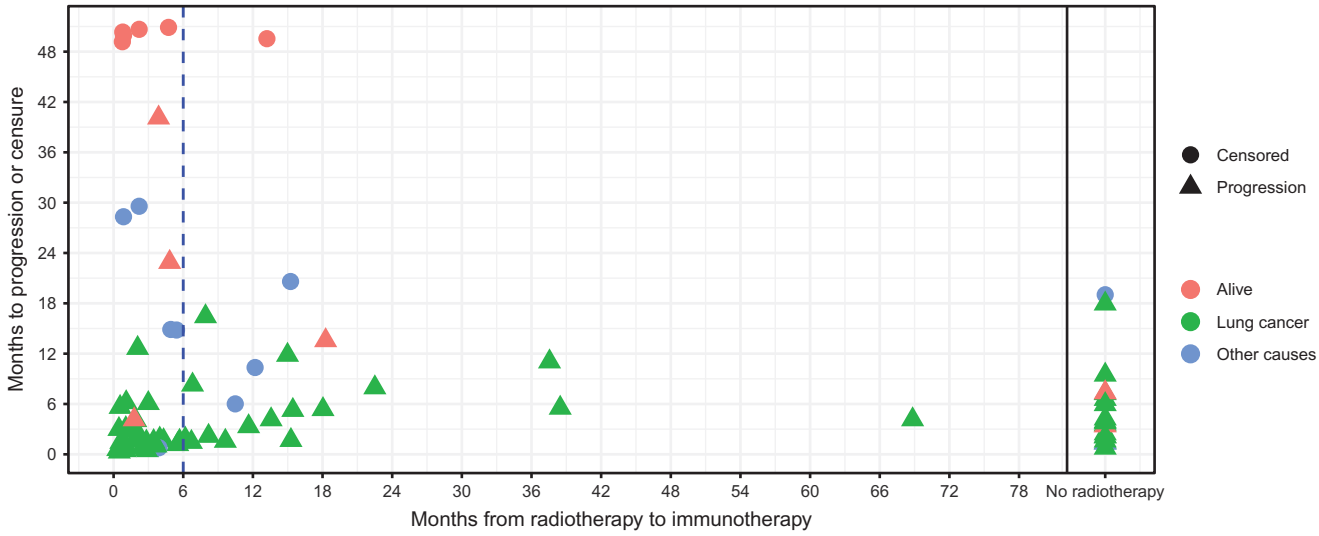

Figure 2. Time from last dose of radiotherapy to first dose of immunotherapy plotted against time to progression or censure. PFS for patients who did not receive any previous radiotherapy is shown to the right. In addition, cause of death is indicated by the color of the dots.

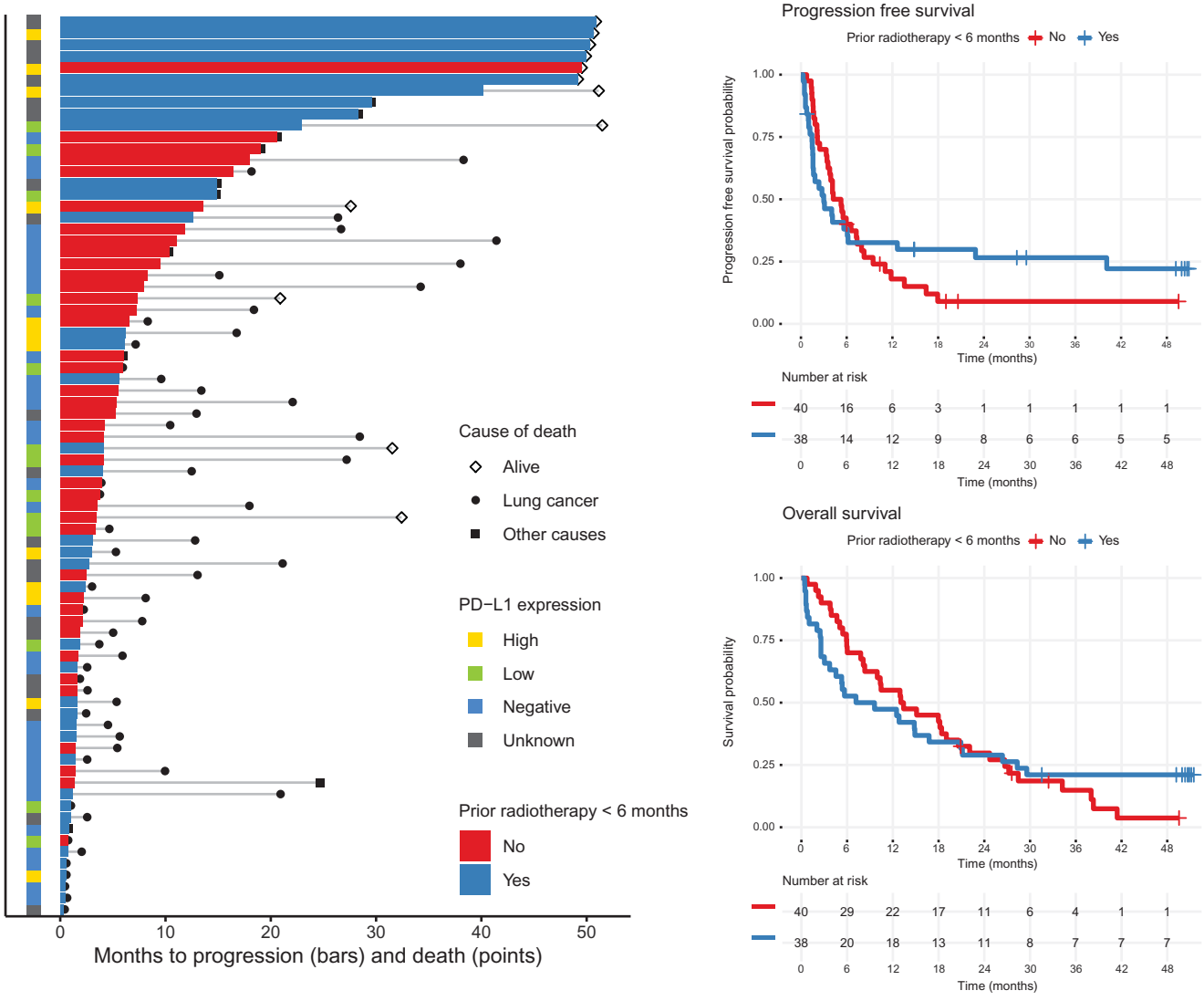

Figure 3. Bar plot illustrating PFS, OS, PD-L1 status and whether the patient received radiotherapy <6 months prior to immunotherapy or not, for all patients. Kaplan–Meier plots showing PFS and OS in patients who received radiotherapy <6 months prior to immunotherapy, compared to those who did not.

2.17, 95% CI 1.02–4.59), and with better PFS (HR 0.27, 95% CI 0.09–0.84) and lung cancer-specific survival (HR 0.41, 95% CI 0.18–0.95) after the first 6 months of follow-up. We hypothesized that the reason why no beneficial effect was recorded for radiotherapy <6 months before immunotherapy in patients who died or progressed shortly after inclusion was that patients with more advanced/aggressive disease were more likely to have had recent radiotherapy for symptom relief. Of the 38 patients who received radiotherapy <6 months prior to immunotherapy, only two received this treatment with curative intent. A high N/L ratio is known to be associated with poor prognosis in advanced NSCLC, regardless of treatment [23]. We found the N/L ratio to be higher in patients who had received radiotherapy <6 months prior to immunotherapy than in those who had not (Wilcoxon rank-sum test $p = 0.005$). In addition, these patients had higher CRP (Wilcoxon rank-sum test $p = 0.01$) and ECOG (Wilcoxon rank-sum test $p = 0.02$). When the association between previous radiotherapy and clinical outcome was investigated only in patients with N/L ratio below median, those who had received radiotherapy <6 months before immunotherapy had better PFS (HR 0.42, 95% CI 0.18–0.99) and lung cancer-specific survival (HR 0.33, 95% CI 0.12–0.88), though not significantly better OS (HR 0.46, 95% CI 0.20–1.04).

We were interested in whether the radiotherapy dose and target volume were related to patient outcome. In some studies, stereotactic radiotherapy (SRT) has been found to be superior to conventional radiotherapy, when combined with immunotherapy. Only two of the patients received SRT <6 months prior to immunotherapy, so this was not possible to investigate in our material. The first 6 months of follow-up radiotherapy given with a small dose per fraction was more beneficial (PFS: HR 2.38, 95% CI 1.02–5.57; OS: HR 3.78, 95% CI 1.33–10.72). After 6 months the only significant association found was between a higher total dose and poor OS (HR 5.01, 95% CI 1.15–21.79). These results are also shown in Supplementary Table S2A and S2B and visualized by Kaplan–Meier plots in Supplementary Figure S2.

Discussion

With advanced NSCLC being a disease with poor prognosis, the potential of immunotherapy to give long-lasting disease control has gained much enthusiasm. Though we do not yet understand all aspects of how immune checkpoint inhibitors function, including why we often encounter primary and acquired resistance, knowledge in this field is steadily increasing. Our results indicate that radiotherapy may pave the road for a durable response to immunotherapy.

We found markers of systemic inflammation, as high CRP and high N/L ratio, to be significantly associated with poor prognosis. Though these measures have been shown to predict prognosis in patients treated with immunotherapy [24,25] they are also known to be associated with poor survival in NSCLC regardless of treatment [23,26]. Our findings indicate that elevated markers of systemic inflammation are mainly markers of advanced disease, and thereby poor short-term prognosis, while they do not appear to be well suited to identify long-term responders to immunotherapy. Though patients with lung cancer are at increased risk of bacterial infections, for example pneumonia, this does not seem to explain the relationship between inflammation and poor prognosis as elevated CRP, N/L ratio, neutrophils, and leukocytes were significantly associated with poor lung cancer-specific survival, as well as OS.

The effect of previous radiotherapy on response to immune checkpoint inhibition has been assessed both retrospectively and prospectively for the PD-1 inhibitor pembrolizumab [27,28]. In both studies radiotherapy was found to be associated with better patient outcome, but the positive effect on PFS was larger in the prospective study. Similar to the findings in this study the Kaplan–Meier curves for PFS fell steeply, both for patients who received radiotherapy and for those who did not, the first months of follow-up, before a positive effect of radiotherapy became apparent. Early progression on immunotherapy is probably due to a combination of host and tumor characteristics [29]. In cases with rapidly progressing disease, there might also not be enough time to mount an immune response. With a retrospective design, it is possible that a higher proportion of patients with aggressive disease received radiotherapy because they had more symptoms. In this study, this hypothesis was supported by those patients who had received radiotherapy the last 6 months before immunotherapy had a higher N/L ratio, and that previous radiotherapy was associated with better PFS and lung cancer-specific survival when only patients with N/L ratio below median were included in the analyses.

There is still a large degree of uncertainty when it comes to the optimal dose and fractionation of radiotherapy when combined with immunotherapy. In pre-clinical studies, results have generally been better when a larger dose per fraction has been used [16]. This study was not large enough to achieve conclusive results on the most beneficial radiotherapy characteristics for a long-lasting response to immunotherapy. In the first months of follow-up, a small dose per fraction was more beneficial. This is probably explained by that patients thought to have better prognosis usually receive more fractionated treatment regimes than patients with more advanced disease and shorter life expectancy. When radiotherapy has been combined with immunotherapy to gain a better response it has been given right before, or during, immunotherapy. Our results indicate that radiotherapy can be administered several months prior to immunotherapy, and still increase the likelihood of durable response. This is in accordance with the findings from a secondary analysis of the KEYNOTE-001 trial [28], and might be explained by factors such as the release of tumor neoantigens during radiotherapy, sustained inflammation in tumor and permanent changes to the tumor immune microenvironment [30,31].

Especially in studies with long follow-up, the varying impact of a variable on prognosis over time can pose a problem when analyzing the data [22]. The proportional hazards assumption is then not met, making Cox regression analysis a suboptimal choice. Though the problem by no means is

new, an increasing number of studies on immune checkpoint blockade has given the issue new actuality [32]. When immunotherapy is compared to traditional treatment a large proportion of patients might progress and die in both groups shortly after inclusion, while with longer observation time a small group of long-term responders can be identified among those who received immunotherapy. This can be visualized in a Kaplan–Meier plot, but often does not come out as a significant difference when a log-rank test or Cox regression analysis are used, as the majority of patients in both groups progress shortly after inclusion. Still, most would agree that the possibility of long-term survival is of clinical relevance. Common ways to handle variables with non-proportional hazards include weighted log-rank tests, restricted mean survival times (RMSTs) and to split the dataset by time [22,33,34]. In addition to showing how variables affect prognosis over time in Kaplan–Meier plots, we decided to split the dataset to be able to have a closer look at predictors of durable response.

The greatest limitations of the study are its retrospective design and the limited number of patients. PD-L1 status was not available for all patients, which made it difficult to control for this when investigating the effect of radiotherapy. On the other hand, there are indications that PD-L1 status might be of less importance when immunotherapy is combined with radiotherapy [27,35]. The study supports the combination of radiotherapy and immune checkpoint inhibition in advanced NSCLC, especially in those who have not received radiotherapy recently, and several ongoing clinical trials will help us to identify the best strategies for these patients, in the years to come [36].

Conclusions

The results of this study indicate that radiotherapy may increase the likelihood of lasting response to immunotherapy, while indicators of systemic inflammation can help in identifying patients with poor short-term prognosis. The role of radiotherapy in combination with immune checkpoint blockade needs to be further clarified in prospective clinical trials.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Åsa Kristina Öjlert http://orcid.org/0000-0002-2888-8406
Marius Lund-Iversen http://orcid.org/0000-0002-2025-4062

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