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ORIGINAL ARTICLE

Clinical features affecting efficacy of immune checkpoint inhibitors in pretreated patients with advanced NSCLC: a Danish nationwide real-world study

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) are implemented as standard treatment for patients with advanced non-small cell lung cancer (NSCLC) in first-line and subsequent-line treatment. However, certain subgroups such as patients with older age, poor performance status (PS), and severe comorbidity are underrepresented in the randomized controlled trials (RCTs). This study aimed to assess overall survival (OS), treatment data, and clinical features affecting second- or subsequent-line ICI efficacy in an unselected, Danish, nationwide NSCLC population.

Methods: Patients with advanced NSCLC who started nivolumab or pembrolizumab as second-line or subsequent-line treatment between 1 September 2015, and 1 October 2018, were identified from institutional records of all Danish oncology departments. Clinical and treatment data were retrospectively collected. Descriptive statistics and survival analyses were performed.

Results: Data were available for 840 patients; 49% females. The median age was 68 years (19% were ≥75 years), 19% had PS ≥2, and 36% had moderate to severe comorbidity. The median OS (mOS) was 12.2 months; 15.1 months and 10.0 months in females and males, respectively. The median time-to-treatment discontinuation (mTTD) and median progression-free survival (mPFS) was 3.2 and 5.2 months, respectively. Patients with PS ≥2 had a mOS of 4.5 months, mTTD of 1.1 month, and mPFS of 2.0 months. In multivariable Cox regression analysis, male sex (HR = 1.35, 95% CI 1.11–1.62), PS >0 (PS 1, HR = 1.88, 95% CI 1.52–2.33; PS ≥2, HR = 4.15, 95% CI 3.13–5.5), liver metastases (HR = 1.72, 95% CI 1.34–2.22), and bone metastases (HR = 1.27, 95% CI 1.03–1.58) were significant poor prognostic OS factors.

Conclusions: Danish real-world patients with advanced NSCLC treated with second- or subsequent-line ICI had an OS comparable to results from RCTs. Women, frail and older patients constituted a higher proportion than in previous RCTs. Clinical features associated with poor OS were male sex, PS ≥1 (in particular PS ≥2), bone-, and liver metastases.

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Cancer immunotherapy; clinical prognostic factors; immune-checkpoint inhibitors; non-small cell lung cancer; real-world evidence

Background

Lung cancer is the leading cause of cancer-related mortality and morbidity worldwide, with a five-year survival rate ranging from 6% in advanced stages to 59% in early stages [1]. In the Nordic countries, the lung cancer mortality has declined since the 1980s, due to improved diagnostics and treatment strategies [2]. The latter include the implementation of immune checkpoint inhibitors (ICIs) as standard therapy, and despite the rapidly increasing use of first-line ICI as

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Supplemental data for this article can be accessed here.

monotherapy or in combination with chemotherapy, some patients are ineligible for these regimens and may still be offered second-line ICI treatment [3–11]. The pivotal randomized controlled trials (RCTs) had strict inclusion and exclusion criteria, not comparable to a real-world setting; thus, selecting patients for ICI treatment in a daily clinical setting remains challenging due to the lack of evidence in certain subgroups. These subgroups include patients with an old age, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), and severe comorbidity. Furthermore, the sex distribution in most international RCTs and real-world studies (RWS) is unequal, and thus less representative of the Nordic population, where NSCLC incidences are equal in men and women [2,12–14]. The median age of lung cancer patients in RCTs is 61 years; however, the median age in newly diagnosed Nordic patients with NSCLC is approximately 70 years [3–5,15,16]. Thus, older patients and particularly patients aged $\geq$75 years, are greatly underrepresented in RCTs [15,17]. Lung cancer patients with PS $\geq$2 also constitute a substantial proportion of patients receiving oncologic treatment in the daily clinical setting [18]. Nevertheless, frail patients with poor PS are typically underrepresented or not included in RCTs. Organ metastases are present in more than 50% of lung cancer patients at the time of diagnosis, and metastases to the brain, liver, and bone have been associated with impaired overall survival (OS) [1,19]. Moreover, comorbidity is frequent in lung cancer patients, and may affect their treatment and clinical outcome [20–22]. However, neither level of comorbidity nor location of metastatic sites are reported in the RCTs [3–5].

The primary aim of the present study was to report on OS in a Danish, comprehensive, consecutive population with advanced NSCLC, treated with ICIs in second-line or subsequent-line treatment. This implies a special attention to, and a comparison with RCTs of, the potential predictive or prognostic clinical features characterizing the subgroups of patients who are underrepresented in RCTs. These include those with higher age, poor PS, and more comorbidity. The secondary aims were to assess reasons for ICI discontinuation (including immune-related adverse events (irAEs)), treatment duration, and progression-free survival (PFS).

Methods

Study design and patients

A retrospective, nationwide real-world study (RWS) approved by the Danish Patient Safety Authority was conducted. Consecutive patients with NSCLC who received nivolumab or pembrolizumab in second-line or subsequent-line of palliative treatment between 1 September 2015, and 1 October 2018, were identified from institutional records. Data were collected from all ($n = 11$) Danish oncology departments.

Data collection and data management

Data were manually extracted from the electronic health record (EHR) systems. Clinical data were collected and stored in local databases at every oncology department. Covariates from the local databases were aligned according to variable names, values, and labels, and data were gathered into one dataset. Furthermore, data quality control was performed for each covariate. If the PS was described as a range, such as PS 1–2, in the EHR, the highest value was captured [18]. Specific irAEs causing ICI discontinuation, and hospitalization and death due to irAEs were recorded. The disease stage and metastatic sites at ICI treatment initiation were retrospectively evaluated by reviewing baseline computed tomography (CT) scan reports.

Variables and endpoints

Baseline characteristics at ICI initiation included sex, age, PS, comorbidity according to Charlson Comorbidity Index Score (CCIS), smoking status, histopathological NSCLC subtype, TNM stage, metastatic locations, programmed death-ligand 1 (PD-L1) tumor proportion score (TPS), and epidermal growth factor receptor (EGFR) mutation status. When calculating the CCIS, the actual lung cancer diagnosis was excluded. Treatment data included the ICI drug, ICI start- and stop date, number of cycles administered (one cycle equals one administered dose), treatment line, and reasons for ICI discontinuation. These reasons were categorized as progressive disease (PD), poor PS, irAEs, and "other" reasons. Hospitalization and death due to irAEs were also recorded. The irAE types that were present at ICI discontinuation were recorded and classified as pneumonitis, hepatitis, skin toxicity, endocrinopathy, diarrhea/colitis, and 'other toxicity'. Treatment could be discontinued for more than one reason, and more than one type of irAE could be present at treatment discontinuation. Patients received either nivolumab 3 mg/kg every two weeks, pembrolizumab 2 mg/kg every 3 weeks, or pembrolizumab 200 mg every three weeks. Individual dose intensities (mg/kg/time) were not recorded [23]. The dates of progression and death were obtained from the EHRs. The progression date was defined as the date of the first clinical evidence of progressive disease (PD) (clinical examination leading to discontinuation of ICI) or radiological PD as verified by a CT and/or magnetic resonance imaging (MRI). The index date was the date of the first ICI administration, and the censoring date was 1 March 2020. The date of treatment discontinuation was the date of the last ICI administration. For living patients, the last follow-up date was defined as the date of the last patient contact in the EHRs. The primary aim was to asses OS, including investigation of predictive or prognostic clinical features. The secondary aims were to assess reasons for ICI discontinuation, treatment duration, and PFS.

Statistical methods

To compare baseline characteristics between sexes and PS groups, chi-square tests were used for the categorical variables, while the distributions of age were compared using Wilcoxon rank-sum test. No correction for multiple testing was performed. Kaplan–Meier (KM) estimates stratified by

baseline variables and log-rank tests were used to assess OS, time to treatment discontinuation (TTD) and PFS. The median follow-up time was calculated using the reverse KM estimate. To adjust for multiple covariates and potential confounders, a multivariable Cox regression analysis was performed. Initially, the assumption of proportional hazard functions was assessed for each of the baseline categorical variables by visual inspection of the log-minus-log survival curves and formally tested using the Grambsch-Therneau proportional hazard test with survival times transformed by the KM estimate. PS, bone-, liver-, adrenal- and distant lymph node metastases, histopathology, and EGFR mutation status violated the proportional hazards assumption. Therefore, average hazard ratios were estimated by weighted Cox regression [24]. Weighted univariable and multivariable Cox regression models were used for analysis of the association between OS and all the baseline categorical variables (except for TNM stage). Comorbidities that were present in >5% of the cases, were included in the weighted univariable Cox regression analysis. For the KM estimate and Cox regressions, CCIS was categorized as CCIS 0–1 and CCIS ≥2 [25].

A *p*-value of 0.05 was defined as the threshold of statistical significance. All analyses were performed using R version 4.0.2 (R Core Team, Vienna, Austria) [26]. The survival package was used to assess the assumption of proportional hazard functions, the ggsurvplot package for visualizing KM estimates, and the coxphw package for the weighted Cox regression analyses.

Results

Baseline characteristics

We identified 841 consecutive patients. No patients were lost to follow up. A single patient harboring an ALK translocation was excluded, leaving 840 patients with a median follow-up time of 34.7 months (95% confidence interval (CI) 33.2–35.9) eligible for analysis.

The median age was 68 years, with 19% ≥75 years, and 5% ≥80 years. A total of 19% of the patients ($n = 158$) had PS ≥2, 57% ($n = 479$) had PS 1, and 22% ($n = 182$) had PS 0. PS was missing in 2% of the patients ($n = 21$). Distant metastases were present in 86% of the patients. CCIS ≥2 was observed in 36% ($n = 301$) of the patients. The prevalence of specific comorbidities according to CCIS is summarized in Supplementary Table 1. The baseline characteristics of the patients are summarized in Table 1.

Male patients had a higher age ($p = 0.001$) and more comorbidities ($p < 0.0001$) than females. Squamous cell carcinomas were more frequent among male (49%) than female patients (23%) ($p < 0.0001$). Brain metastases were more prevalent in women than in men ($p < 0.0001$) (Supplementary Table 2).

Patients with baseline PS ≥2, compared to PS 0–1, consisted of more male patients (58%, $p = 0.046$), and received fewer nivolumab/pembrolizumab cycles (2/3 vs. 7/8) (Supplementary Table 2).

Table 1. Baseline characteristics.

Baseline characteristics	*n* (%)
All patients	840 (100)
Sex	
Male	432 (51)
Female	408 (49)
Age, median; range	68; 22−89
Age	
<75 years	677 (81)
≥75 years	163 (19)
ECOG PS	
0	182 (22)
1	479 (57)
≥2	158 (19)
Missing	21 (2)
Charlson Comorbidity Index Score (CCIS)	
0 (no)	332 (40)
1 (mild)	207 (25)
2 (moderate)	154 (18)
≥3 (severe)	147 (17)
Smoking status	
Current	238 (28)
Former	535 (64)
Never	46 (6)
Unknown	21 (2)
TNM stage	
III	116 (14)
IV	724 (86)
Metastatic sites[a]	
Brain	95 (11)
Bone	221 (26)
Liver	133 (16)
Adrenal	127 (15)
Distant lymph nodes	233 (28)
NSCLC histopathology	
Adenocarcinoma	485 (58)
Squamous cell carcinoma	303 (36)
Other[b]	52 (6)
EGFR mutation	
No	537 (64)
Yes	25 (3)
Unknown	278 (33)
PD-L1 status	
Negative	72 (9)
≥1% and < 50%	233 (28)
≥50%	290 (35)
Unknown	245 (29)

[a]Patients may be registered with more than one metastatic site.
[b]'Other' includes NSCLC NOS (not otherwise specified) and adenosquamous carcinoma.
n: number of patients; ECOG PS: Eastern Cooperative Oncology Group performance status; NA: not available; TNM: tumor-node-metastasis classification of malignant tumors; NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; PD-L1: programmed death-ligand 1.

ICI Treatment

At the censoring date, 99% ($n = 831$) had discontinued ICI. ICI treatment characteristics are demonstrated in Table 2.

The median TTD (mTTD) was 3.2 (95% CI 2.8–3.6) months. In patients with PS ≥2, the mTTD was 1.1 (95% CI 0.7–1.4) month compared to 3.3 (95% CI 2.8–3.8) and 6.0 (95% CI 5.1–7.8) months in PS 1 and PS 0 patients, respectively.

Clinical outcomes

The mOS was 12.2 (95% CI 10.8–13.8) months, and the 1- and 2-year OS rates were 50% (95% CI 47–54) and 30% (95% CI 27–33), respectively (Table 3). The estimated three-year OS rate was 20% (95% CI 17–23). The mOS was 15.1 and 10.0 months in female and male patients, respectively. The

Table 2. ICI treatment characteristics.

Treatment characteristics	*n* (%)
All patients	840 (100)
Treatment line	
2	536 (64)
3	205 (24)
4	68 (8)
≥5	31 (4)
Treatment	
Nivolumab	444 (53)
Pembrolizumab	396 (47)
Median number of ICI cycles[a]; range	
Nivolumab	6; 1–64
Pembrolizumab	6; 1–37
ICI treatment duration[a];	
Median days; range	98; 1–961
mTTD months; 95% CI	3.2; 2.8–3.6
Ongoing ICI treatment[b]	10 (1)
ICI discontinuation due to[c]:	
PD	461 (56)
Poor PS	126 (15)
irAEs[d]	179 (22)
Pneumonitis	47 (6)
Hepatitis	19 (2)
Skin toxicity	27 (3)
Endocrinopathy	15 (2)
Diarrhea/colitis	40 (5)
Other toxicity	51 (6)
irAEs only[e]	150 (18)
Other reasons[f]	145 (17)
Hospitalization due to irAEs	135 (16)
Death due to irAEs	8 (1)

[a]Patients with ongoing ICI treatment ($n = 10$) not included.
[b]At date of censoring.
[c]Each patient could be registered with more than one cause of treatment-discontinuation.
[d]Each patient could be registered with more than one type of irAE as a cause of treatment-discontinuation.
[e]Proportion of patients with irAE as the only cause of treatment discontinuation.
[f]'Other reasons' are not specified irAEs.
n: number of patients; ICI: immune checkpoint inhibitor; mTTD: median time to treatment discontinuation; PD: progressive disease; PS: performance status; irAEs: immune-related adverse events.

mOS for patients with PS ≥2 was 4.5 months compared to 12.2 and 22.1 months in patients with PS 1 and PS 0, respectively (Table 3). The mPFS was 5.2 (95% CI 4.5–6.9) months (Table 3), and 2.0 months in patients with PS ≥2.

Prognostic clinical features

Kaplan-Meier estimates demonstrated that OS was reduced in men ($p < 0.0001$), in patients with PS >0 ($p < 0.0001$), and in patients with bone ($p = 0.003$) and/or liver metastases ($p < 0.0001$) (Figure 1).

Age ≥75 years, comorbidity according to CCIS, and the presence of brain metastases at ICI initiation were not significantly associated with impaired OS (Supplementary Table 3).

In multivariable Cox regression analysis, male sex (HR = 1.35; 95% CI 1.11–1.62), liver metastases (HR = 1.72; 95% CI 1.34–2.22), and bone metastases (HR = 1.27; 95% CI 1.03–1.58) remained statistically significant poor prognostic factors. Likewise did PS ≥2 (HR = 4.15; 95% CI 3.13–5.50) and PS 1 (HR = 1.88; 95% CI 1.52–2.33) compared to PS 0. Age ≥75 years (HR = 0.99; 95% CI 0.8–1.23), and the presence of brain metastases at ICI initiation (HR = 1.1; 95% CI 0.82–1.47) did not significantly affect OS (Figure 2). EGFR mutation status and PD-L1 TPS were unknown in 33% and 29% of cases, respectively. PD-L1 ≥ 50% was associated with an improved OS (HR = 0.69; 95% CI 0.48–0.98).

Extension of the multivariable Cox regression with interaction between sex and histopathology demonstrated a significantly poorer OS in patients with adenocarcinoma, if they were male rather than female, while no difference in OS were seen between sexes for patients with squamous cell carcinoma (Supplementary Table 5).

Kaplan-Meier estimates demonstrated that factors associated with a poor PFS were male sex ($p = 0.006$), ECOG PS >0 ($p < 0.0001$), no history of smoking ($p = 0.03$), liver metastases ($p < 0.0001$), a positive EGFR mutation status ($p = 0.004$), and PD-L1 < 1% ($p < 0.0001$) (Supplementary Table 4).

Discussion

Several subgroups have been underrepresented in RCTs, and therefore, focus is increasingly placed on the importance of gathering clinically relevant data from RWS, which typically represent a more unselected treatment population. However, different global health care systems affect the populations included in RWS. In Denmark, according to the Danish Health Care Act, all patients are offered treatment according to national treatment guidelines, irrespective of their income, education, and residential and socioeconomic status, which minimizes the risk of selection bias in Danish studies [27]. Treatment with ICIs is expensive and holds a potential risk of causing severe irAEs. Thus, characterizing a large cohort of real-life patients in detail may contribute with important knowledge helping clinicians make more evidence-based decisions on whether to offer patients ICI or not.

In this large nationwide NSCLC study of real-world ICI efficacy, the mOS and the 1-year OS rate were comparable to results from previous anti-PD-1 clinical trials of pretreated patients [3–5,28,29]. An improved mPFS compared to results from the RCTs, could be explained by differences in PFS definition [3–5].

Lung cancer incidence and mortality remain higher in males than females in some countries [30,31]. However, in agreement with the narrowing gap in the lung cancer incidence between sexes in Nordic countries, half of the patients in our study were females, as opposed to a lower proportion reported in comparable RCTs and RWS [2,13,14]. In RCTs, ICI significantly improved OS in both men and women compared to chemotherapy, however, the benefit seemed to be higher in men [7,13]. In this study, PS ≥2, higher CCIS, and squamous cell carcinomas were more frequent in males as compared to females. Despite adjusting for these factors, male patients with adenocarcinomas had a worse OS than female patients with adenocarcinomas.

In our study, the median age was 68 years, which is 5–7 years older than patients included in the anti-PD-1 RCTs, and more comparable to the age of real-world lung cancer patients [3–5,15,16]. Especially data on patients aged ≥75 years is lacking in RCTs. However, in our study they constituted 19% of patients, compared to only 7%–8% in previous RCTs [3,4]. Even with this greater proportion of older patients, the mOS was comparable to results from previous clinical trials and RWS,

Table 3. Overall and progression-free survival according to sex and performance status.

Survival	mOS months (95% CI)	mPFS months (95% CI)	one-year OS rate % (95% CI)	Two-year OS rate % (95% CI)
All patients	12.2 (10.8–13.8)	5.2 (4.5–5.9)	50 (47–54)	30 (27–33)
Male	10.0 (9.0–11.7)	4.4 (3.7–5.3)	44 (40–49)	25 (21–30)
Female	15.1 (13.4–17.2)	6.4 (5.2–8.1)	57 (53–62)	34 (30–39)
PS 0–1	15.3 (13.5–16.8)	6.3 (5.4–7.5)	57 (53–61)	35 (31–38)
PS ≥2	4.5 (3.2–5.7)	2.0 (1.7–2.6)	26 (20–34)	11 (7–17)

mOS: median overall survival; mPFS: median progression-free survival; CI: confidence interval; PS: performance status.

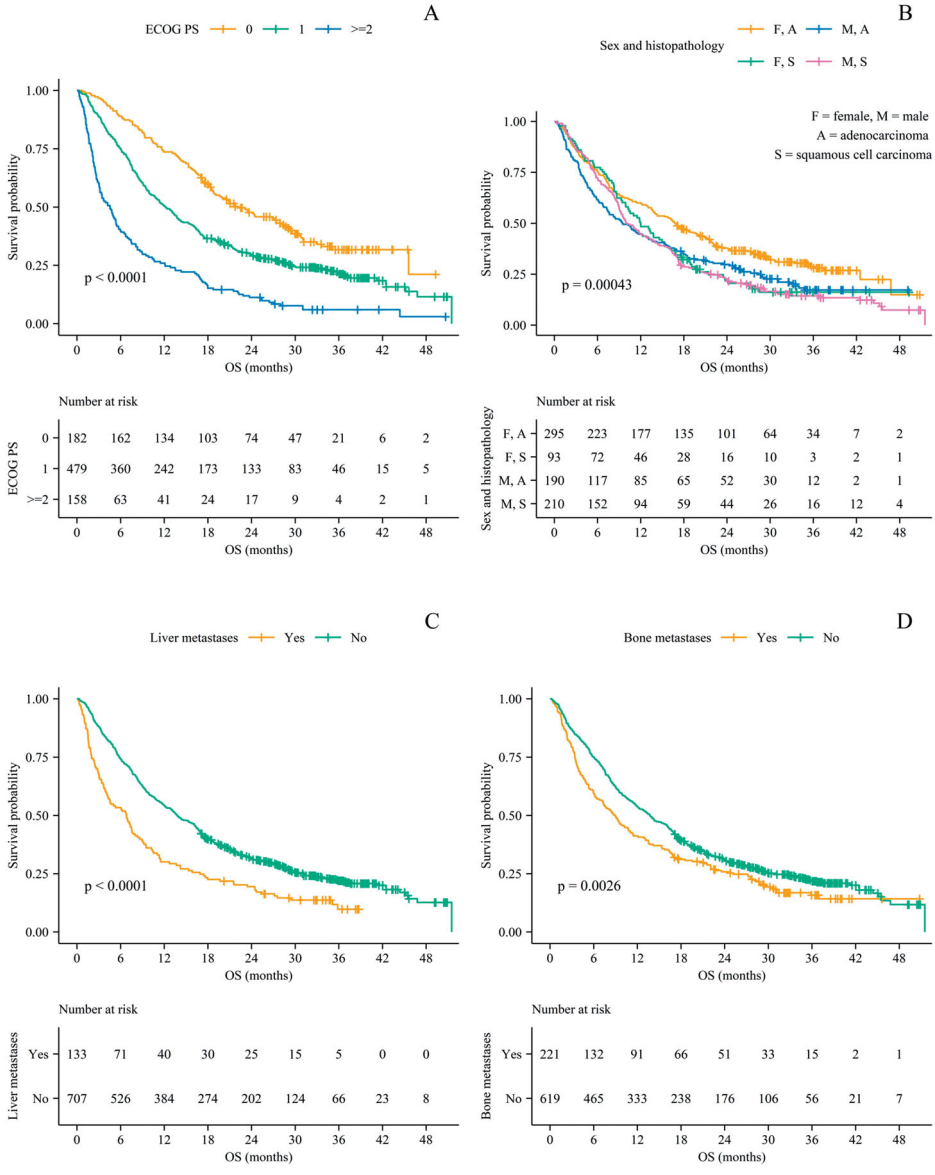

Figure 1. OS stratified by ECOG PS, sex and histopathology, liver metastases and bone metastases. OS: overall survival; ECOG PS: Eastern Cooperative Oncology Group performance status; F: female; M: male; A: adenocarcinoma; S: squamous cell carcinoma.

as age did not significantly affect OS [3,4,28,29,32,33]. Our data demonstrate that ICI should not be excluded as a treatment option because of high chronological age.

As opposed to the RCTs, the proportion of PS ≥2 patients in our study (19%) reflects the overall fraction of patients with NSCLC and PS ≥2 [18]. Thus, compared to the RCTs, our study included more frail and heavily pretreated patients, with more than one third receiving third-line or further subsequent-line ICI treatment [3–5]. Nevertheless, the mOS of patients with PS ≥2 was comparable to results from clinical trials, pooled analyses and other RWS [28,29,34]. In contrast to this, the PePS2 study assessed the efficacy of pembrolizumab in 60 patients with PS ≥2, and reported a mOS of 12.1 months in previously treated patients [35]. However, since the mPFS was only 2.0 months and the mTTD was only 1.1 month in our study, the clinical benefit of ICIs is very limited in most of these patients. On the other hand, we report a mOS of 22.1 months in patients with PS 0, which is comparable to the mOS of PS 0–1 patients treated with first-line ICI in RCTs [6,36]. This illustrates that PS 0 patients may benefit particularly from ICIs, even when

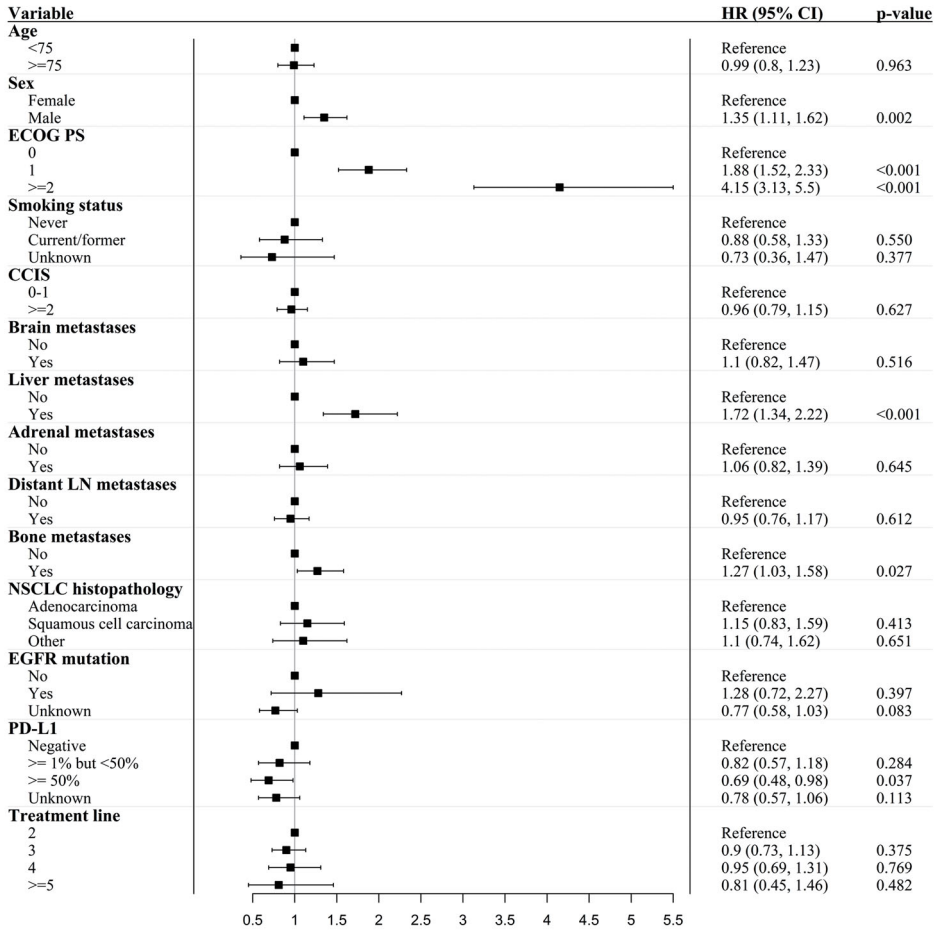

Figure 2. Weighted multivariable Cox regression analysis, with forest plots showing average hazard ratios (HR). CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; CCIS: Charlson Comorbidity Index Score; NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; PD-L1: programmed death-ligand 1

administered in subsequent lines. However, the mOS of PS 0 and PS 1 patients, has not been compared in RCTs and rarely in RWS of second-line ICI [3–5,37,38].

A large proportion of the patients in our study had metastatic disease (86%), which is representative of the palliative NSCLC population. However, in most RCTs, information regarding metastatic sites is rarely available, despite the known prognostic impact [3–5,28,29]. In the present study, bone- and liver metastases were significant poor prognostic factors for OS, whereas brain metastases did not affect OS. This is comparable to results from other RWS [19,39–42]. In most patients, brain metastases are stable at ICI initiation due to previous local therapy with radiotherapy or neurosurgery. In our study, not all patients had a MRI of the brain prior to ICI initiation, thus the actual number of patients with brain metastases, as opposed to those with liver metastases, were not known at baseline. These factors may explain the lack of impact on OS of brain metastases. Poor PS, liver and bone metastases er known poor prognostic factors, and based on our results, it is difficult to assess whether these patients actually could benefit from ICI compared to best supportive care or subsequent line chemotherapy. However, our results imply that careful consideration should be made before administering ICI to particularly patients with PS $\geq$2.

In accordance with another RWS, no association between comorbidity and OS was observed [42]. However, comorbidities are rarely reported in RWS of ICI-treated patients with advanced NSCLC.

Strengths and limitations

The strengths of this study are the inclusion of a nationwide unselected population of all Danish patients with NSCLC treated with ICI in second-line or further subsequent line, the completeness of follow-up for all patients, and the large sample size, allowing for strong subgroup analyses. The study had some limitations. The retrospective nature of the study, reduced the validity of the comorbidity data, which preferably should be prospectively collected. Likewise for smoking status, ECOG PS, grade of toxicity by the Common Toxicity Criteria (CTC), and tumor response evaluation according to Response Evaluation Criteria in Solid Tumors [43,44]. Laboratory data and data regarding potential confounders such as prior or concomitant glucocorticoid and antibiotic administration and body mass index were also not obtained [44–46].

Conclusion

The OS of ICI-treated patients in our study, was comparable to the OS demonstrated in RCTs [3–5]. Women accounted for half of the patients in this Danish cohort, making the results from this cohort especially comparable to other countries (including Nordic countries) with a high proportion of female NSCLC patients eligible for ICI. Furthermore, our results showed that older age did not affect ICI efficacy, and ICIs should not be excluded as a treatment option, due to high chronological age. Patients with PS $\geq$2 had only very limited effect of ICI with a very poor prognosis, thus careful consideration should be made on an individual basis when offering ICIs to this subgroup. Data on metastatic sites should be available in future RCTs, because of the prognostic impact on OS and in order to improve the comparison between future RCTs and RWS.

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Ethics approval and consent to participate

Approved by the Danish Patient Safety Authority and reported to The Danish Data Protection Agency.

Consent for publication

Patient consent was waived by the Danish Patient Safety Authority, due to the retrospective design of the study, and the use of routinely collected data.

Disclosure statement

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Data availability statement

The study data may be available on request from the corresponding author, Mette T Mouritzen. The data are not publicly available due to the General Data Protection Regulation.

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