Original Article

Trends in the prescription of immune checkpoint inhibitors for non-small cell lung cancer in the Netherlands from 2016 to 2020, a national cancer registry analysis

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Background: Lung cancer is the leading cause of cancer mortality globally, with a 5-year survival rate of 10–20%. In recent years, immune checkpoint inhibitors (ICIs) have significantly improved overall survival (OS) in patients with lung cancer. The approval of nivolumab in 2015 marked a milestone in non-small cell lung cancer (NSCLC) treatment, leading to ongoing trials and approvals of new ICI drugs that have reshaped treatment strategies and clinical outcomes for patients with lung cancer. This study aims to describe ICIs prescription trends for NSCLC in the Netherlands and their association with survival. We compared our results with data from randomized controlled trials (RCTs).

Methods: We analyzed ICIs prescription trends and their relationship with survival using national-level data from the Netherlands Cancer Registry (NCR) for first-line treatments from 2016–2020. Additionally, we performed a secondary analysis using data from the Oncological Life Study (OncoLifeS) for any-line treatments. Descriptive statistics and annual percentage change (APC) assessed trends in patient and treatment characteristics. OS analyses were performed.

Results: In the Netherlands (2016–2020), the proportion of first-line ICI-treated NSCLC patients significantly increased from 1.1% to 54.9% (APC =14.5%, P=0.002), replacing chemotherapy monotherapy. Stage III ICI-treated patients' proportion increased (APC =3.5%, P=0.034), while the proportion of ICI-treated patients with ≥50% programmed death-ligand 1 (PD-L1) expression decreased (APC =−13.82%, P=0.04). Two-year OS was 25.9%. Median OS remained stable, increasing from 2016 to 2018 (16.6 to 19.4 months) and declining slightly in 2019 and 2020 (17.3 and 16.6 months, respectively). In the secondary analysis, median OS varied by treatment line, being 18.8, 9.4 and 7.5 months for first-, second- and third-line treated patients respectively.

Conclusions: Using real-world data, we determined that ICI-based therapies replaced chemotherapy-only schemes as first-line treatment for NSCLC. Our survival data are comparable with data from RCTs on first-line ICI-treated NSCLC. Median OS of ICI treated patients has remained stable, with small decreases in recent years possibly attributed to the proportional decrease of individuals with high PD-L1 expressions in treatment regimens. Further-line treatments are associated with lower survival.

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Keywords: Lung cancer; immunotherapy; immune checkpoint inhibitors (ICIs); survival; trends

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Introduction

Background

Lung cancer is the leading cause of cancer death worldwide, with a low survival rate of 10% to 20% after 5 years of diagnosis (1). In recent years, the introduction of immune checkpoint inhibitors (ICIs) has offered new treatment options for patients with lung cancer. ICIs have shown to increase the overall survival (OS) of patients with lung cancer, especially those patients with better performance status (PS) and higher programmed death-ligand 1 (PD-L1) tumoral expression (2-4).

In 2015, the European Medicines Agency (EMA) approved the use of the first programmed cell death protein 1 (PD-1) inhibiting monoclonal antibody for non-small cell lung cancer (NSCLC) patients, nivolumab (5). Since then, several new ICI drugs for treating lung cancer have continued to be tested and are approved. Immunotherapy alone or in combinations with chemotherapy, as first- and further-line treatments have been implemented. As a result of the innovations in the use of ICIs to treat patients with lung cancer, tumor characteristics, treatment regimens and clinical outcomes have changed over recent years.

Highlight box

Key findings

- Immunotherapy-based schemes replaced chemotherapy as first-line lung cancer treatment in the Netherlands from 2016 to 2020.
- The use of immune checkpoint inhibitors (ICIs) in stage III lung cancer has increased compared to stage IV.
- The restricted use of immunotherapy to patients with ≥50% programmed death-ligand 1 (PD-L1) expression has decreased in favor of the inclusion of patients with lower PD-L1 expressions.
- The median overall survival (OS) remained stable, showing a tendency to increase from 2016 to 2018 and a slight decrease during 2019 and 2020.
- Median OS is associated with treatment line.

What is known and what is new?

- Immunotherapy offers survival benefits over chemotherapy-based treatments. Observational studies in European countries with large sample sizes have found median OS ranging from 11 to 16 months.
- In our study, using a data from a Netherlands Cancer Registry we found a median OS of 17.4 months.

What is the implication, and what should change now?

- Real-world data are relevant for complementing randomized controlled trial (RCT) evidence on therapy effectiveness in clinical settings.
- The median OS data found in this national cancer registry are similar to the one reported in RCT in patients with lung cancer treated with ICIs.

Rationale and knowledge gap

Most data on ICI treatment effectiveness are obtained through randomized controlled trials (RCTs), being tested in selected patients with clinical characteristics such as favorable PS and mild symptomatology. RCTs usually provide good internal validity and control for bias. However, real-world observational studies are necessary to complement RCTs evidence, providing better external validity and information on the performance of ICIs in a wider range of patients with different clinical characteristics (6,7).

Insight in the evolution of ICI therapy and its outcomes for lung cancer in a real-world setting will be informative to various stakeholders including clinicians, patients, and policy makers. National level data allow for the analysis of effectiveness in large populations with diverse clinical characteristics.

Objective

The aim of this study is to provide a description of the trends in patient and disease characteristics, treatment patterns, and survival in NSCLC patients treated with ICIs in the Netherlands from 2016 to 2020, using a national registry and an in-depth local cohort. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-264/rc).

Methods

Netherlands Cancer Registry (NCR)

The NCR is a database containing national-level information about the characteristics and prevalence of cancer, and it is administered by the Netherlands Comprehensive Cancer Organisation (IKNL). This database gathers information cancer patient's first-line treatment, including patients treated with ICIs inside and outside RCT settings. After being informed of the new diagnosis by either the patient's healthcare provided or the Dutch Nationwide Pathology Databank (PALGA), patients' clinical and treatment-related data is collected. Dutch law allows the medical centers to collect data from patients when this is used for scientific and statistical purposes, without the need of informed consent. This data was provided to us anonymized. Patients included from the NCR in this study were adults over the age of 18 diagnosed with NSCLC and treated with ICIs in the Netherlands, between January 2016 and December 2020. Data on the number of NSCLC patients that received anti-cancer systemic therapies in the form of chemotherapy or ICIs were received as well.

Oncological Life Study (OncoLifeS)

The OncoLifeS is a hospital-based data-biobank including patients referred to the University Medical Center Groningen (UMCG), a tertiary-level hospital offering healthcare services to the northern part of the Netherlands, for cancer treatment, which links clinical and socio-economic characteristics with a biological specimens' repository (8). OncoLifeS is approved by the Medical Ethical Committee of UMCG, and all included patients gave written informed consent to join OncoLifeS. Data from OncoLifeS was used for a secondary analysis of ICIs as first- and further-line NSCLC treatment. For this sub-analysis, we included adults over 18 years of age diagnosed with NSCLC who received treatment with ICIs between January 2016 and December 2020.

Data collection

The national data for ICI treatment requested from NCR included sex, age, PS, institution of cancer diagnosis and ICI treatment, date of diagnosis, TNM stage, PD-L1 expression, ICI type, start and stop dates, and the date of death/last contact. This information was gathered by trained IKNL employees from clinical records. Date of death is collected by IKNL through the linkage with the municipal personal records database, insuring complete survival follow-up data.

Regarding the information gathered from OncoLifeS, data on patients' age, sex, education, and smoking status was collected through the OncoLifeS questionnaires, filled in by the patients around the start of their immunotherapy treatment. Furthermore, data was retrieved from electronic medical records, providing information on PS, TNM stage, date of diagnosis, PD-L1 expression, treatment line, as well as chemotherapy and ICI type, start and stop dates, and date of death. Details on variable definition can be found in Table S1.

This study was carried out conformed to the provisions of the Declaration of Helsinki (as revised in 2013) (9). Regarding the data from the NCR provided by IKNL, according to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymized data for this study. Furthermore, the OncoLifeS study has been approved by the medical ethics committee of the UMCG (no. 2010/109) and has been International Organization for Standardization (ISO) certified (9001:2008 Healthcare). It has been also registered in the Dutch Trial Register under the number: NL7839. All the participants in OncoLifeS have signed informed consent.

Statistical analysis

A complete case analysis was carried out. Descriptive statistics were used to present the national level data regarding the first-line treatment with ICI (source: NCR) and the any-line treatment (source: OncoLifeS). Frequency and percentages were used to present categorical variables. Means and standard deviations (SDs) were used to present continuous variables. These statistical analyses were performed using SPSS 25. Annual percentage change (APC) was calculated to present the changes in patient and tumor characteristics, as well as treatment regimens from 2016 to 2020. APC was calculated using Joinpoint 4.9.1.0 software.

Survival analysis was performed to observe changes in median OS over the years. The Kaplan-Meier method, with 95% confidence intervals (CIs), was used to calculate median OS. To ensure each individual had the opportunity for at least two years of follow-up, the censoring date was set at two years after the treatment initiation date of the last patient included in the study (December 31st, 2022). Consequently, survival time was defined as the interval

between the ICI treatment start date until either death or the censoring date. To account for individual and group differences in follow-up times, we calculated hazard ratios (HRs) using four Cox proportional hazards regression models. Model 1 was an univariable model, model 2 was adjusted for age and gender, model 3 included model 2 plus adjusting for stage and PS, and model 4 included model 3 plus adjustment for tumor PD-L1 expression. These analyses were carried out in Stata 14.

Results

Patients treated with first-line ICI

From January 2016 to December 2020, 22,665 NSCLC patients received anti-cancer systemic therapies in the form of chemo or immunotherapy in the Netherlands, of whom 6,816 (30.1%) were treated with ICI as first-line treatments. The mean age of the patients was 65 years (SD =9.2) and were mostly male (n=3,707, 54.4%). The majority of patients were treated with PD-1 inhibitors as monotherapy (63.2%). The most commonly prescribed ICI was pembrolizumab as monotherapy (43.9%), followed by pembrolizumab as a combination with two chemotherapeutic agents (34.7%). At the start of ICI treatment, 75% of the patients had stage IV NSCLC. Regarding the PS, the largest proportion of patients were classified as 0–1 (91.3%) (*Table 1* and Table S2).

Patients treated with any-line ICI

In the years 2016 to 2020, a total of 449 NSCLC patients were treated with ICIs in the UMCG and signed informed consent to join OncoLifeS. These patients had a mean age of 64.7 years (SD =9.4) and were predominantly male (60.1%). From these patients, the majority were treated with ICIs as second-line treatment (n=253, 56.3%). The majority of patients received immunotherapy treatment for a stage IV NSCLC, especially as second and third lines (94.1% and 100% respectively). PD-1 inhibitors were the most commonly used drugs as first-, second- and third-lines of treatment (48.1%, 90.1% and 71.4% respectively). The most commonly prescribed ICI was nivolumab as monotherapy (53.2%), and pembrolizumab as monotherapy (20.3%).

Changes over the years in the prescription of ICI in the Netherlands as first-line treatment

The proportion of NSCLC patients treated with ICI as first-line treatment increased from 1.1% in 2016 to 54.9% in 2020 (APC =14.5%, P=0.002), compared to the chemotherapy-only treated patients (98.8% to 45.1%, APC =−14.5%, P=0.002) (NCR data, *Figure 1*). Patients with a stage III disease treated with ICI grew in proportion, from 11.9% to 25.6% (APC =3.5%, P=0.03), whilst the proportion of stage IV patients declined from 88.1% to 72.4% (APC =−3.9%, P=0.03, *Table 2*). The administration of ICIs to patients with a tumor PD-L1 expression of ≥50% decreased steady from 2016 to 2020 [APC of −13.82% (P=0.04)] (*Table 2*).

Changes over the years in the prescription of ICI in the Netherlands as all-line treatment

In our secondary analysis using OncoLifeS data on ICIs prescribed as all-line ICI treatment, the age of the patients at the start of the treatment increased with an APC of 0.61% during this time period (P=0.02). Patients with a stage III NSCLC grew in proportion (APC =5.4%, P=0.04). The proportion of combination therapy increased with an APC of 12.4% (P=0.049), as well as use of ICI as first line treatments (APC of 17.1%, P<0.001) during the study period (Table S3).

Survival analysis

The mean follow-up time for the national level was 13.8 months. The median OS for the NCR cohort was 17.4 months (95% CI: 16.4–18.1, *Figure 2*), the 1-year OS was of 59.0% (95% CI: 57.8–60.2%) and the 2-year survival was 25.9% (95% CI: 24.8–26.9%, *Table 3*). When analyzing the OS per year of ICI treatment start, the median OS for 2016 was 16.6 months (95% CI: 9.1–19.5) and peaked in 2018: 19.4 months (95% CI: 17.0–22.0) and slightly decreasing to reach 16.5 (95% CI: 15.3–17.9) in 2020 (*Figure 2*). Regarding the Cox regression model 1, the hazard ratio for death due to any cause was higher for patients who received treatment in a more recent year (HR =1.04; 95% CI: 1.00–1.07). However, after adjustment for tumor's PD-L1 expression (model 4), this association became non-significant (HR =0.99; 95% CI: 0.95–1.03) (*Figure 3*).

In our secondary analysis, using data from OncoLifeS in the UMCG including all lines of treatment, we found that the median OS is highly determined by treatment line, varying from 18.8 months (95% CI: 13.8–24.4) for first-line, 9.4 months (95% CI: 7.3–11.2) for second-line treated patients, and 7.5 months (95% CI: 6.0–9.3) third and

Table 1 Characteristics of patients with lung cancer treated with immunotherapy in the Netherlands from 2016 to 2020: NCR (first-line treatment) versus dedicated hospital (UMCG, all lines of treatment)

Variables	NCR[†]	UMCG[‡]		
	First line (n=6,816)	First line (n=161)	Second line (n=253)	Third and further line (n=35)
Age (years), mean (SD)	65 (9.2)	65.2 (9.0)	64.4 (9.6)	64 (9.6)
Sex, n (%)				
Men	3,707 (54.4)	105 (65.2)	145 (57.3)	20 (57.1)
Women	3,109 (45.6)	56 (34.8)	108 (42.7)	15 (42.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment regimen, n (%)				
Durvalumab monotherapy	1,208 (17.7)	40 (24.8)	3 (1.2)	0 (0.0)
PD-1 combination therapy[§]	2,420 (35.5)	42 (26.1)	8 (3.2)	0 (0.0)
PD-1 monotherapy[¶]	3,084 (45.2)	77 (47.8)	228 (90.1)	25 (71.4)
Other[#]	81 (1.2)	2 (1.2)	14 (5.5)	10 (28.6)
Missing	23 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical tumor stage, n (%)				
II	136 (2.0)	3 (1.9)	0 (0.0)	0 (0.0)
III	1,564 (22.9)	41 (25.5)	15 (5.9)	0 (0.0)
IV	5,110 (75.0)	117 (72.7)	238 (94.1)	35 (100.0)
Missing	6 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PD-L1 expression, n (%)				
<1%	1619 (23.8)	39 (24.2)	86 (34.0)	9 (25.7)
≥1–<50%	1,270 (18.6)	30 (18.6)	40 (15.8)	7 (20.0)
50%	3,091 (45.3)	71 (44.1)	35 (13.8)	5 (14.3)
Unknown/not tested	836 (12.3)	21 (13.0)	92 (36.4)	14 (40.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECOG performance status, n (%)				
0–1	5,282 (77.5)	141 (87.6)	228 (90.1)	6 (17.6)
2	431 (6.3)	13 (8.1)	20 (7.9)	25 (73.5)
3	73 (1.1)	3 (1.9)	3 (1.2)	2 (5.9)
Missing	1,030 (15.1)	4 (2.5)	2 (0.8)	1 (2.9)

[†], including University Medical Center Groningen data from the NCR; [‡], data from the Oncological Life Study with all-line treatments; [§], nivolumab + chemotherapy or pembrolizumab + chemotherapy; [¶], nivolumab or pembrolizumab; [#], atezolizumab + bevacizumab + chemotherapy, or durvalumab + tremelimumab, or durvalumab + chemotherapy, or atezolizumab, or avelumab. NCR, Netherlands Cancer Registry; UMCG, University Medical Center Groningen; SD, standard deviation; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ECOG, Eastern Cooperative Oncology Group.

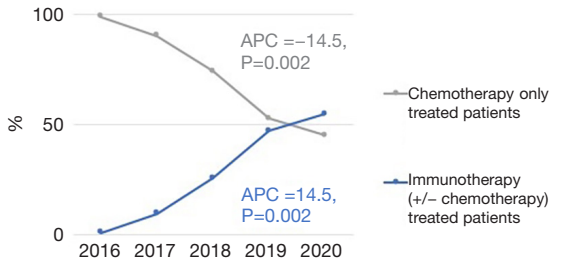
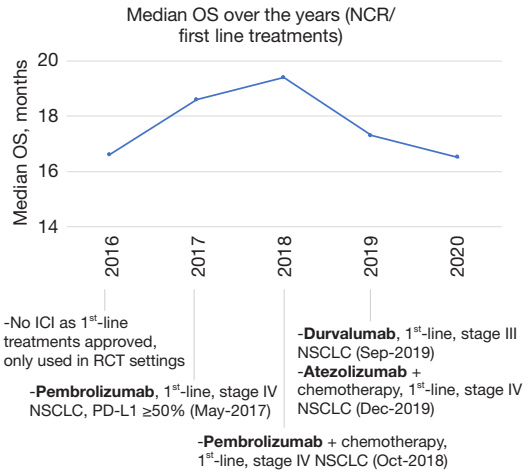


Figure 1 Proportion of non-small cell patients with lung cancer treated with immunotherapy and/or chemotherapy in the Netherlands 2016–2020. APC, annual percentage change.

Table 2 Patients with non-small cell lung cancer treated with first-line immunotherapy from the Netherlands Cancer Registry, patient and treatment characteristics: APC and SE

Variables	Category	APC (%)	SE	P value
Age (years)	Mean age	0.6	0.3	0.19
Sex	Men	0.4	0.4	0.43
	Women	−0.4	0.4	0.43
Stage	II	0.4	0.2	0.18
	III	3.5	0.9	0.03*
	IV	−3.9	1.0	0.03*
PD-L1 expression	<1%	9.35	2.2	0.05
	≥1–<50%	6.37	1.6	0.055
	≥50%	−13.82	2.8	0.04*
	Unknown/not tested	−1.86	2.0	0.45
ECOG performance status	0–1	−1.1	0.7	0.18
	2	1.0	0.4	0.10
	≥3	0.1	0.3	0.73
Treatment combination	Combination therapy	10.4	3.4	0.056
	Mono therapy	−10.4	3.4	0.056

*, significantly different from no change. APC, annual percentage change; SE, standard error; PD-L1, programmed death-ligand 1; ECOG, Eastern Cooperative Oncology Group.



	Participants	Median OS (months)	Lower 95% CI	Upper 95% CI	Log rank test P value
Total	6815	17.4	16.4	18.1	
Year					0.02
2016	43	16.6	9.1	19.5	
2017	395	18.6	14.5	24.5	
2018	1223	19.4	17.0	22.0	
2019	2437	17.3	15.6	18.5	
2020	2717	16.5	15.3	17.9	

Figure 2 Median overall survival for patients with NSCLC who were treated with immune checkpoint inhibitors as first-line treatment (data from the NCR)a; as well as approval dates of first-line treatments in the Netherlands*. a, includes data from the University Medical Center Groningen on patients with lung cancer treated with immune checkpoint inhibitors as first line of treatment; *, no missing data in date of death or loss of follow-up was found. OS, overall survival; NCR, Netherlands Cancer Registry; ICI, immune checkpoint inhibitor; RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; CI, confidence interval.

further-line treatments.

Discussion

Key findings

Using real world data, we showed how ICIs, alone or combined with chemotherapy, were replacing therapeutic schemes based only on chemotherapy as first-line treatment of NSCLC in the Netherlands, from 2016 to 2020. Also, we found changes in the treatment schemes and patients' profiles at national-level when ICIs were used as first-line treatments, such as the increasing use for stage III NSCLC and in patients with lower PD-L1 expression. Furthermore, on population-based level, we found a stable OS, with an increase in survival from the years 2016 to 2018, followed by a small non-significant decrease in in the years 2019 and 2020.

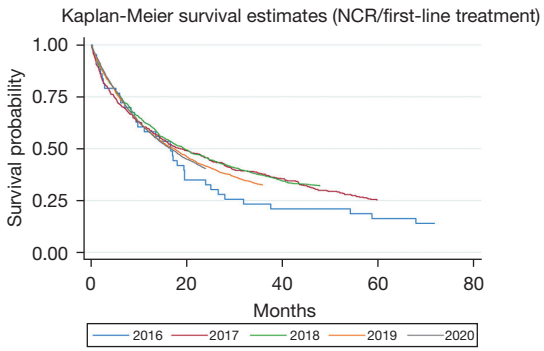
Strengths and limitations

Our study has strengths and limitations. We had access to a comprehensive national level data regarding the use

Table 3 Overall survival per timepoint for patients with non-small cell lung cancer who were treated with immune checkpoint inhibitors as first-line treatment (data from the Dutch Cancer Registry)[†]

Time	N	Deaths	Survival (%)[‡]	95% lower CI (%)[‡]	95% upper CI (%)[‡]
6 months	6,815	1,725	74.7	73.6	75.7
12 months	5,090	1,069	59.0	57.8	60.2
18 months	4,021	686	48.9	47.7	50.1
24 months	3,335	1,572	25.9	24.8	26.9

[†], no missing data in date of death or loss of follow-up were found; [‡], calculated using Kaplan-Meier survivor function. CI, confidence interval.



	HR	Lower 95% CI	Upper 95% CI	P value
Time period (1 year increase)	1.04	1.00	1.07	0.03
Time period (1 year increase)[a]	1.03	1.00	1.07	0.051
Time period (1 year increase)[b]	1.05	1.01	1.09	0.006
Time period (1 year increase)[c]	0.99	0.95	1.03	0.66

Figure 3 Factors associated with overall survival for patients with non-small cell lung cancer who were treated with immune checkpoint inhibitors as first-line treatment (data from the NCR); Cox regression models with HR and 95% CI*. [a], model 2: adjusted by age and gender; [b], model 3: adjusted by age, gender, stage, and performance status; [c], model 4: adjusted by age, gender, stage, and performance status and PD-L1 expression; *, includes patients treated with immune checkpoint inhibitors as first-line in the University Medical Center Groningen. NCR, Netherlands Cancer Registry; HR, hazard ratio; CI, confidence interval; PD-L1, programmed death-ligand 1.

of ICIs in the Netherlands. However, a limitation of this dataset is the collection of only first-line treatment in the NCR national-level data, which leads to the inclusion of only patients enrolled in RCTs in the early years of the immunotherapy (2016–2017), since these therapies as first-line treatments were not authorized for their use in routine clinical care. This did not allow us to observe the performance of ICI as second- and further-line treatments, which in return can lead to an overestimation of the median OS, as well as a lower survival in the years 2019–2020. This might be due to a higher selection of patients with better clinical profiles and higher survival expectations included in RCTs in the early years of ICI implementation (2016–2017). Nevertheless, incorporating data from patients treated in more recent years (2021–2022) could provide a more comprehensive assessment of real-world evidence. However, due to the annual update process of the survival data sourced from the NCR, accessing more recent survival data to ensure patients were followed for at least 2 years was not possible at the time of completing this work. Furthermore, in our secondary analysis using a local, center-specific dataset (OncoLifeS cohort) granted us access to patient information for all-lines of treatment, allowing us to observe how survival decreased in patients treated with ICIs as second and further lines of treatment. Moreover, we lacked information on variables known to be indicative of treatment efficacy, such as tumor mutation burden (TMB) and tumor-infiltrating lymphocytes (TILs). This limitation impeded our ability to account for these crucial tumor characteristics, thereby hampering our ability to limit confounding biases (10,11). Finally, we were unable to adjust the OS by deaths due to coronavirus disease 2019 (COVID-19), since the survival of patient being treated during 2020 might have been reduced, given that COVID-19 was particularly aggressive with patients with lung cancer and increased their mortality rate (12,13). In addition, we did not have access to updated survival data for patients with lung cancer who underwent chemotherapy-only treatments between 2019 and 2020. This limitation hampered our ability to test this hypothesis in patients treated with systemic therapies other than ICIs.

Comparison with similar research

Previous evidence provided by RCTs has shown beneficial effects in the clinical outcomes of patients with lung cancer treated with ICIs, such as increased OS and more favorable treatment response (14-16). The main survival results from our study are, depending on the specific ICI prescribed, comparable to the ones provided by previous relevant RCTs evaluating the use of ICIs as first-line for NSCLC treatment; finding a median OS of 17.4 months in the NCR, compared to a range between 17.1–23.2 months in RCTs. Regarding the 1-year survival rate, in our study we found a survival rate of 59% *vs.* 53.1–73% from RCTs, and a lower 2-year survival rate (25.9% *vs.* 34–45.5% from RCTs) (17-21). Furthermore, similar with the findings presented in our study, Griesinger *et al.* conducted an observational study that assessed the nationwide utilization of ICIs in Germany and France. Their work yielded results comparable to our own, showing generally similar median OS and 1- and 2-year survival rates (22). Details on this comparison can be found in Table S4.

Explanations of findings

In our study we observed an initial increase in OS during the early years of monotherapy adoption as a first-line treatment for NSCLC, followed by a subsequent small decrease in recent years (2019–2020); this can be explained by factors such as the approval of ICIs as first-line treatments by the Dutch authorities at the end of 2018, which led to the availability of these therapies to patients outside RCT settings with broader clinical characteristics. Additionally, the inclusion in 2019 in Dutch national guidelines of combined chemo-immunotherapy treatment schemes administered to patients with <50% PD-L1, which has been shown to be a predictor of survival (23), further contributed to these trends. Furthermore, in our secondary analysis evaluating any-line treatment with ICIs in the UMCG from 2016 to 2020 that, median OS was determined by treatment line, being highest in first-line treatments, and decreasing in second and third treatment-lines. However, when comparing this data to the one from RCTs, we can observe a lower survival, explained by the inclusion of a majority patients treated with ICIs as second-line, with lower OS expectations. Similar real-world data analysis on melanoma patients have found an increase in median OS following the introduction of ICIs, especially after the incorporation of combined chemo-immunotherapy treatments (24). These changes in patients' outcome can be a result of the use of ICI-based therapies in patients that, in the past, would have received chemo-radiotherapy treatments available at the time, only to be left with no further treatment options after these failed.

Implications and actions needed

Currently, new immunotherapy-based treatments continue to be developed and approved for the treatment of lung cancer with a view on reducing the burden of the disease in the world. Real-world data will continue having an important role in complementing RCT evidence on the effectiveness of these therapies in real clinical settings. Future research is needed in the evaluation of the clinical outcomes of ICI-based therapies as they are becoming a standard for treatment in early stages of lung cancer, as adjuvant and neo-adjuvant therapies, as well as first-line treatment combinations with chemotherapy in late-stage lung cancer.

Conclusions

With this analysis until 2020, we found that ICI-based therapies have substituted chemotherapy-only schemes as first-line treatment in NSCLC patients in the Netherlands since their introduction. OS increased in patients until 2018 followed by a small decrease from 2019, likely due to the decrease in the proportion in recent years of individuals with ≥50% PD-L1 expressions included in treatment regimens. New evaluations using real-world data will have to be carried out to document the changes consequence of the introduction of ICIs as first-line treatments in the national guidelines, as they become the standard of care for lung cancer in all stages.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was carried out conformed to the provisions of the Declaration of Helsinki (as revised in 2013). Regarding the data from the NCR provided by IKNL, according to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the Netherlands Cancer Registry approved the use of anonymized data for this study. Furthermore, the OncoLifeS study has been approved by the medical ethics committee of the UMCG (no. 2010/109) and has been ISO certified (9001:2008 Healthcare). It has been also registered in the Dutch Trial Register under the number: NL7839. All the participants in OncoLifeS have signed informed consent.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63.
2. Haragan A, Field JK, Davies MPA, et al. Heterogeneity of PD-L1 expression in non-small cell lung cancer: Implications for specimen sampling in predicting treatment response. Lung Cancer 2019;134:79-84.
3. Arbour KC, Riely GJ. Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA 2019;322:764-74.
4. Ahmed T, Lycan T, Dothard A, et al. Performance Status and Age as Predictors of Immunotherapy Outcomes in Advanced Non-Small-Cell Lung Cancer. Clin Lung Cancer 2020;21:e286-93.
5. European Medicines Agency. New treatment option for patients with advanced lung cancer. 2015. Available online: https://www.ema.europa.eu/en/news/new-treatment-option-patients-advanced-lung-cancer
6. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014;110:551-5.
7. Tang M, Pearson SA, Simes RJ, et al. Harnessing Real-World Evidence to Advance Cancer Research. Curr Oncol 2023;30:1844-59.
8. Sidorenkov G, Nagel J, Meijer C, et al. The OncoLifeS data-biobank for oncology: a comprehensive repository of clinical data, biological samples, and the patient's perspective. J Transl Med 2019;17:374.
9. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
10. Li F, Li C, Cai X, et al. The association between CD8+ tumor-infiltrating lymphocytes and the clinical outcome of cancer immunotherapy: A systematic review and meta-analysis. EClinicalMedicine 2021;41:101134.
11. Wan L, Wang Z, Xue J, et al. Tumor mutation burden predicts response and survival to immune checkpoint inhibitors: a meta-analysis. Transl Cancer Res 2020;9:5437-49.
12. Rogado J, Pangua C, Serrano-Montero G, et al. Covid-19 and lung cancer: A greater fatality rate? Lung Cancer 2020;146:19-22.
13. Várnai C, Palles C, Arnold R, et al. Mortality Among Adults With Cancer Undergoing Chemotherapy or Immunotherapy and Infected With COVID-19. JAMA Netw Open 2022;5:e220130.
14. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J

Med 2022;386:1973-85.
15. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
16. Shen X, Huang S, Xiao H, et al. Efficacy and safety of PD-1/PD-L1 plus CTLA-4 antibodies ± other therapies in lung cancer: a systematic review and meta-analysis. Eur J Hosp Pharm 2023;30:3-8.
17. Nishio M, Barlesi F, West H, et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMpower132 Trial. J Thorac Oncol 2021;16:653-64.
18. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.
19. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol 2021;32:881-95.
20. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:1919-29.
21. Socinski MA, Nishio M, Jotte RM, et al. IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC. J Thorac Oncol 2021;16:1909-24.
22. Griesinger F, Pérol M, Girard N, et al. Impact of immune checkpoint inhibitors on the management of locally advanced or metastatic non-small cell lung cancer in real-life practice in patients initiating treatment between 2015 and 2018 in France and Germany. Lung Cancer 2022;172:65-74.
23. Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. Transl Lung Cancer Res 2019;8:413-28.
24. Rigo R, Doherty J, Koczka K, et al. Real World Outcomes in Patients with Advanced Melanoma Treated in Alberta, Canada: A Time-Era Based Analysis. Curr Oncol 2021;28:3978-86.

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