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ORIGINAL ARTICLE

Association between treatment and improvements in overall survival of patients with advanced/metastatic non–small cell lung cancer since 2011: A study in the United States, Canada, and Germany using retrospective real-world databases

Frank Griesinger MD[1] | Sreeram Ramagopalan PhD[2] | Winson Y. Cheung MD[3,4] | Thomas Wilke PhD[5] | Sabrina Mueller MSc[6] | Alind Gupta PhD[7] | Dylan E. O'Sullivan PhD[3,4] | Paul Arora PhD[7,8] | Darren R. Brenner PhD[3,4] | Carolin Froelich PhD[9] | Jessica Inskip PhD[10] | Ulf Maywald PhD[11] | Vivek Subbiah MD[12]

[1]Department of Medical Oncology, Pius-Hospital Oldenburg, Oldenburg, Germany

[2]Global Access, F. Hoffmann-La Roche, Basel, Switzerland

[3]Department of Oncology, University of Calgary, Calgary, Alberta, Canada

[4]Oncology Outcomes Research Initiative, University of Calgary, Calgary, Alberta, Canada

[5]Institut für Pharmakoökonomie und Arzneimittellogistik e.V., University of Wismar, Wismar, Germany

[6]Cytel, Wismar, Germany

[7]Cytel, Toronto, Ontario, Canada

[8]Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[9]Roche Pharma AG, Grenzach-Wyhlen, Germany

[10]Hoffmann-La Roche Limited, Mississauga, Ontario, Canada

[11]AOK PLUS, Dresden, Germany

[12]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Correspondence

Thomas Wilke, Alter Holzhafen 19, Wismar, Germany.

Email: thomas.wilke@ipam-wismar.de

Abstract

Background: This study aimed to describe treatment patterns and overall survival (OS) in patients with advanced non–small cell lung cancer (aNSCLC) in three countries between 2011 and 2020.

Methods: Three databases (US, Canada, Germany) were used to identify incident aNSCLC patients. OS was assessed from the date of incident aNSCLC diagnosis and, for patients who received at least a first line of therapy (1LOT), from the date of 1LOT initiation. In multivariable analyses, we analyzed the influence of index year and type of prescribed treatment on OS.

Findings: We included 51,318 patients with an incident aNSCLC diagnosis. The percentage of patients treated with a 1LOT differed substantially between countries, whereas the number of patients receiving immunotherapies/targeted treatments increased over time in all three countries. Median OS from the date of incident diagnosis was 9.9 months in the United States vs. 4.1 months in Canada. When measured from the start of 1LOT, patients had a median OS of 10.7 months in the United States, 10.9 months in Canada, and 10.9 months in Germany. OS from the start of 1LOT improved in all three countries from 2011 to 2020 by approximately 3 to 4 months.

Conclusions: Observed continuous improvement in OS among patients receiving at least a 1LOT from 2011 to 2020 was likely driven by improved care and changes in the treatment landscape. The difference in the proportion of patients receiving a 1LOT in the observed countries requires further investigation.

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carcinoma, immune checkpoint inhibitors, lung neoplasms, non-small-cell Lung, protein-tyrosine kinases, retrospective studies, treatment outcome

INTRODUCTION

Accounting for 1.8 million of 10 million cancer deaths worldwide, lung cancer was the leading cause of cancer-related death in 2020, corresponding with 11.4% of new cancer cases around the world.[1] Lung cancer can be categorized into small cell lung cancer and non–small cell lung cancer (NSCLC), the latter accounts for 80% to 90% of lung cancers.[2,3] The treatment of advanced NSCLC (aNSCLC), defined as stage IIIb or higher disease, has changed substantially in recent years, from a "one chemotherapy fits all" approach to a more phenotype/mutation-targeted treatment strategy. Advanced NSCLC has emerged as one of the key areas for precision oncology, and this centers on the treatment of several key aNSCLC subgroups as defined by mutations of epidermal growth factor receptor (*EGFR*), BRAFV600E, or fusions/rearrangements of anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*), rearrangements of the rearranged during transfection (*RET*) gene, or neurotrophic tyrosine receptor kinase (*NTRK*) genes and/or PD-L1 expression, among others.[4–6] These newer treatments, mainly tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), have demonstrated improvement in overall survival (OS) in randomized clinical trials, typically in comparison to conventional chemotherapy.[2,7]

However, there is a paucity of analyses on treatment and outcomes in patients with aNSCLC over time using real-world data. This multicountry retrospective database study aimed to bridge this data gap by studying treatment patterns and OS in patients with aNSCLC in the United States, Canada, and Germany between 2011 and 2020.

METHODS

Study design and data sources

The study was based on three anonymized retrospective databases: the Canadian Oncology Outcomes (O2) Research Initiative database, the US Flatiron Health database, and the German AOK PLUS claims database. All data sets covered the period from January 1, 2010, to December 31, 2020, with the exception of the Flatiron database, which included data until September 30, 2020. The CAN O2 database includes all individuals diagnosed with aNSCLC at first diagnosis within the province of Alberta, a province in Western Canada with a population of approximately 4.5 million. It contains information from the Alberta Cancer Registry, which is linked by a unique lifetime identifier to data on hospital-related health events and mortality. The Flatiron Health database is a US nationwide longitudinal electronic health record real-world database comprising deidentified patient-level structured and unstructured data curated via technology-enabled abstraction.[8,9] Most patients in the Flatiron Health database are treated in community oncology settings. The AOK PLUS claims data set covers 3.4 million individuals insured by this statutory sickness fund in the eastern German regions of Saxony and Thuringia.

All three databases contain anonymized, patient-level information on medication prescriptions and outpatient/inpatient care. Moreover, information on key sociodemographic characteristics and all-cause mortality is available in the databases. Differences exist across databases with regard to available variables on clinical characteristics, including NSCLC stage and histopathological subtypes. Because of database regulations, all analyses were performed on a country-specific basis.

Patient selection

In all three databases, patients with a minimum age of 18 years on the date of an incident aNSCLC diagnosis from January 1, 2011 through December 31, 2019 (United States: September 30, 2019) were included. All patients were observed for a minimum of 12 months or until death, whichever came first (Figure S1). Patients who received any lung cancer diagnoses during the 12-month baseline period or who were not characterized as incident cases were excluded, leading to the omission of patients who progressed from earlier NSCLC stages to aNSCLC.

Because of database specifications, additional country-specific criteria for patient selection were applied. In Canada and the United States, aNSCLC disease stage was determined according to the most recent edition of the American Joint Committee on Cancer's Tumor-Nodes-Metastases staging criteria, available at the time of a patient's incident diagnosis. In the US Flatiron database, two database-specific exclusion criteria were applied. First, patients who were administered an unspecified "clinical study drug" at any point were excluded from the analysis. Second, patients with a gap of more than 90 days between the advanced diagnosis date and the start of systemic therapy were excluded in accordance with best practices to account for potentially incomplete historical treatment information.

In German claims data, staging information is not directly available. Therefore, a proxy applied in previous German claims data studies was used to identify patients with aNSCLC.[10] Patients with at least one inpatient or two outpatient specialist diagnoses of lung cancer (International Classification of Diseases, 10th revision [ICD-10] code: C34.-) and additional metastasis diagnoses (ICD-10 codes: C77.0/.1/.2/.3/.4/.5/.8, C78.X [excluding C78.0/C78.3], and C79.X) within 1 month leading up to or 3 months after the first observable incident lung cancer diagnosis (e.g., index date) were classified as advanced because this comes closest to the definition of stage IIIB/C

and IV NSCLC. Furthermore, diagnoses in the German claims data are based on the ICD-10, German modification, coding system. Because no ICD-10 code for NSCLC exists, a treatment proxy was used to identify the non–small cell subtype. Patients with an incident lung cancer diagnosis who received at least one prescription for a systemic therapy approved for NSCLC were included. Consequently, in Germany, this study only describes patients with aNSCLC who received at least one prescription for a systemic NSCLC treatment.

Outcomes and analysis

After the identification of target patients in the three databases, key sociodemographic and clinical characteristics such as age, gender, smoking status, stage of disease and its histology, as well as previous hospitalizations were summarized (at the date of the incident aNSCLC diagnosis and/or during the 12-month baseline period) for each country using descriptive statistics.

Reporting on treatment patterns included the percentage of patients receiving a first line of therapy (1LOT) and later lines of systemic treatments (exception Germany: all patients received a 1LOT), as well as the type/class of therapies in all treatment lines (e.g., ICI, ALK inhibitors, EGFR inhibitors, and other treatments [any non-ICI or nontargeted therapy, mainly chemotherapy]). Specific assumptions regarding the identification of treatment lines were made and are summarized in Table 1.

Absolute and relative frequencies of patients who received a 1LOT, second line of therapy (2LOT), and third line of therapy (3LOT) in each country were assessed, including the most frequently prescribed agent classes. Because of the limited follow-up time for patients who were included late in the study period, a sensitivity analysis analyzed patients with a minimum follow-up period of 24 months (in which death was the only exception).

In all analyses, time to all-cause death was analyzed by means of Kaplan–Meier estimations, with observations being censored at the end of data availability. For each country, OS of observed patients was additionally assessed per index year, starting in 2011.

OS was evaluated from the time of the incident aNSCLC diagnosis and, second, from the date of start of a 1LOT. We ran two multivariable models to interpret the change in OS in our patient populations. First, among patients who received at least a 1LOT, we analyzed whether the index year was associated with superior survival outcomes when comparing patients included in 2011 with those included in later years. Cox regression models were adjusted for age, gender, and time from incident diagnosis to initiation of 1LOT. Second, we explored whether treatment with specific agent groups (e.g., ICI, EGFR inhibitors, ALK inhibitors, other treatments [mainly chemotherapy]) was associated with a better OS in patients who received both a 1LOT and 2LOT and whether, after adjusting for these treatments, later index years (compared with 2011) were still associated with a superior OS since the start of 1LOT.

Regulatory aspects and general considerations

As the study addressed retrospective anonymized data sets, no informed consent was needed for Canada and Germany. Regarding the O2 data set, there was an expedited ethical review for this study.

TABLE 1 County-specific approaches for identifying treatment lines in the retrospective databases.

Step	Canada/Canadian Oncology Outcomes	United States/Flatiron	Germany/AOK PLUS
Step 1: identification of start of treatment line	First prescription for an agent after incident aNSCLC diagnosis is defined as start of 1L treatment	First eligible drug episode after an advanced diagnosis	First prescription of an agent after incident aNSCLC diagnosis defined as start of 1L treatment
Step 2: identification of agent(s) included as part of treatment line	Combination therapies are noted in the database	First eligible drug plus other eligible drugs given within 28 days are defined as a line of therapy	Any agents prescribed on the same day or within 21 days of starting a treatment line seen as a part of a combination therapy
Step 3: definition of the end of treatment line/start of new treatment line	End or discontinuation of a treatment line was assumed if there was a gap of at least 90 days between treatment initiation and completion dates; some exceptions were permitted to allow for switching	Line number is advanced when there is a gap of >120 days between any two sequential drug episodes, with exceptions (e.g., for oral drugs)	End or discontinuation of a treatment line assumed if: (1) there was a prescription for a new agent that had not been prescribed previously and/or the prescribed agent was not part of the combination therapy (start of a new treatment line), or (2) there was a gap in drug availability of at least 90 days Note: "Continuation" or "switch" maintenance therapies were not identified

Abbreviations: 1L, first line; aNSCLC, advanced non–small cell lung cancer.

Approval for the use of Flatiron Health data was granted by the WIRB-Copernicus Group institutional review board. Informed consent was waived because the data were deidentified in accordance with 45 CFR §46.

Statistical analyses were performed using STATA/MP 14 (StataCorp LLC, College Station, TX), R statistical programming language,[11] and Microsoft Excel.

RESULTS

Patient populations

We included 51,318 patients with an incident aNSCLC diagnosis in our study (Canade: 9380 [18%]; United States: 37,977 [74%]; Germany: 3961 [8%]); respective attrition charts are provided as Figures S2–S4. The mean age of patients ranged from 66 (Germany) to 71 years (Canada); 52.4% (Canada) to 68.6% (Germany) of patients were male (Table 2).

Systemic treatment patterns

The percentage of patients treated with at least a 1LOT differed substantially between countries. In Germany, because of the patient selection process, 100% of patients received systemic treatment. In the United States, 28,573 of 37,977 patients (75.2%; 95% CI, 74.8–75.6) received at least a 1LOT; treated patients were slightly younger than the overall sample (mean: 67 vs. 68 years). The percentage of treated patients (2847 of 9380 patients, or 30.3%; 95% CI, 29.4–31.2) was much lower in Canada. Treated patients were substantially younger than the overall sample (mean: 65 vs. 70 years).

Among patients who received a 1LOT, the percentage of patients receiving later lines during the follow-up was similar between the United States and Canada but significantly higher in Germany, with 47.2% (US/Canada: 95% CI, 46.6–47.8/45.4–49.0) to 58.7% (Germany: 95% CI, 57.1–60.1) initiating a 2LOT and 19.6% (Canada: 95% CI, 18.1–21.1) to 27.8% (Germany: 95% CI, 26.4–29.2) initiating a 3LOT (Figure 1). Results for subcohorts observable over 24 months are shown in Figure S5.

The frequency of specific agents observed within each respective treatment line varied across countries. Notably, a significantly higher percentage of patients were treated with ICI in the United States across all lines (1LOT/2LOT/3LOT: 18.5% [95% CI, 18.0–19.0]/38.8% [95% CI, 38.0–39.6]/28.5% [95% CI, 27.3–29.7]) compared with Canada (14.2% [95% CI, 13.3–15.5]/23.7% [95% CI, 21.4–26.0]/20.1% [95% CI, 16.8–23.4]) and Germany (14.4% [95% CI, 13.3–15.5]/26.6% [95% CI, 24.8–28.4]/24.1% [95% CI, 21.6–26.6]) (Figure S6). On the other hand, the proportions of patients who received targeted ALK/EGFR inhibitors were similar in the United States and Germany but significantly higher in Canada (for 1LOT/2LOT/3LOT, using the example of EGFR inhibitors: 9.5% [95% CI, 9.2–9.8]/12.3% [95% CI, 11.7–12.9]/12.4% [95% CI, 11.5–13.3] in the United States and 4.7% [95% CI, 4.0–5.4]/11.8% [95% CI, 10.5–13.1]/17.4% [95% CI, 15.2–19.6] in Germany versus 18.8% [95% CI, 17.4–20.2]/26.2% [95% CI, 23.9–28.5]/35.8% [95% CI, 31.8–39.8] in Canada). Prescription of these therapies mostly increased over time in all three countries, especially related to the number of patients receiving ICI. The percentage of patients receiving ICI at any line initially diagnosed in 2011/2016/2019 was 2.0% [95% CI, 1.1–2.9]/27.1% [95% CI, 24.4–29.8]/59.5% [95% CI, 56.5–62.5] in Canada, 2.8% [95% CI, 2.2–3.4]/45.3% [95% CI, 43.9–46.7]/77.0% [95% CI, 75.6–78.4] in the United States, and 2.1% [95% CI, 0.8–3.4]/36.3% [95% CI, 31.8–40.8]/79.9% [95% CI, 76.3–83.5] in Germany.

Overall Survival

Median OS from the date of the incident aNSCLC diagnosis (regardless of treatment initiation) was 9.9 months in the United States, 4.1 months in Canada, and 13.2 months in Germany; note that only patients who received an aNSCLC treatment were observed in Germany. If, instead, OS was measured from the date of therapy initiation among those who received at least a 1LOT, patients had a median OS of 10.7 months in the United States, 10.9 months in Canada, and 10.9 months in Germany (Figure 2, Table 3). OS from the start of a 1LOT improved substantially in all three countries from 2011 onward: (1) in Canada, median OS improved from 8.7 to 10.3 months for patients diagnosed in 2011/12 to from 11.8 to 12.4 months for patients diagnosed in 2018/19; (2) in the United States, median OS improved from 8.9 to 9.1 to from 12.4 to 13.4 months; and (3) in Germany from 8.7 to 9.3 months to from 11.4 to 12.1 months in patients with incident aNSCLC diagnosis in the respective index years. When adjusting for sociodemographic and other patient characteristics available in all databases (age, gender, time from incident diagnosis until start of treatment), OS was significantly higher in later index years compared with 2011 (Table 3). In line with that, the 1-year survival rates were lower in patients initiating 1LOT in 2011 (Canada/United States/Germany: 37%/41%/44%) compared with those starting the 1LOT in 2019 (Canada/United States/Germany: 52%/53%/51%). In an additional multivariable model that only featured patients who received a 1LOT and 2LOT and included the type of 1LOT/2LOT treatment, we observed that ICI and targeted treatments were associated with a better OS in all countries (Figure 3). ICI was significantly associated with better OS in the United States (HR [95% CI], 0.84 [0.79–0.88], $p < .001$) and Germany (HR [95% CI], 0.80 [0.71–0.91], $p < .001$), and a positive trend toward better OS was observed in Canada (HR [95% CI], 0.85 [0.68–1.02], $p = .080$). In the case of targeted treatments, this was significant for ALK inhibitors in all three countries. A significant impact of EGFR inhibitors on OS could only be observed in the United States. In all three countries, patients who received other systemic treatment (mainly chemotherapy) had a significantly lower OS (HR [95% CI] Canada/United States/Germany, 2.47 [1.99–3.06]/1.47 [1.34–1.61]/

TABLE 2 Patient characteristics.

Baseline characteristics reported at index or within 12 months before index date:	Incident aNSCLC CAN (O2) Diagnosis date	1LOT aNSCLC CAN (O2) Treatment start	Incident aNSCLC US (Flatiron) Diagnosis date	1LOT aNSCLC US (Flatiron) Treatment start	Incident aNSCLC GER (AOK PLUS) Diagnosis date	1LOT aNSCLC GER (AOK PLUS) Treatment start
Sample size (*n*)	9380	2847	37,977	28,573	3961	3950[a]
Age at index date, mean (SD) | Median	70.4 (11.3) | 71	65.2 (10.5) | 66	68.0 (10.0) | 69	67.0 (10.0) | 68	66.1 (10.3) | 66	66.2 (10.0) | 66
Male, *n* (%)	4917 (52.4)	1387 (48.7)	20,467 (53.9)	15,369 (53.8)	2717 (68.6)	2710 (68.6)
Smoking status, *n* (%)						
Current smoker	2804 (29.9)	1012 (35.6)	32,904 (86.6)	24,533 (85.9)	-	-
Former smoker	2425 (25.9)	868 (30.5)			-	-
Never smoked	611 (6.5)	397 (13.9)	4655 (12.3)	3797 (13.3)	-	-
Missing	3540 (37.7)	570 (20.0)	418 (1.1)	243 (0.9)	-	-
Stage of aNSCLC at index date, *n* (%)						
IIIB/IIIC	965 (10.3)	387 (13.6)	5918 (15.6)	4827 (16.9)	-	-
IV	8415 (89.7)	2460 (86.4)	32,059 (84.4)	23,746 (83.1)	-	-
Histology of aNSCLC at index date, *n* (%)						
Squamous	1495 (15.9)	391 (13.7)	9051 (23.8)	6692 (23.4)	-	-
Nonsquamous	6108 (65.1)	2361 (82.9)	26,700 (70.3)	20,359 (71.3)	-	-
Not otherwise specified	1777 (18.9)	95 (3.3)	2226 (5.9)	1522 (5.3)	-	-
Index LC diagnosis (ICD-10-GM subcodes), *n* (%)						
C340 - Main bronchus (including Carina tracheae & lung)	-	-	-	-	308 (7.8)	307 (7.8)
C341 - Upper lobe	-	-	-	-	949 (24.0)	947 (24.0)
C342 - Middle lobe	-	-	-	-	113 (2.8)	112 (2.8)
C343 - Lower lobe	-	-	-	-	483 (12.2)	481 (12.2)
C348 - Overlapping lesion of bronchus and lung	-	-	-	-	288 (7.3)	287 (7.3)
C349 - Bronchus or lung, unspecified	-	-	-	-	1820 (45.9)	1816 (46.0)
All-cause hospitalizations (in the 12-month baseline period)						
Number of hospitalizations, mean (SD) | median	-	-	-	-	0.7 (1.5) | 1	2.4 (2.0) | 2
Number of patients with at least one hospitalization, *n* (%)	-	-	-	-	1456 (36.8)	3574 (90.5)
LOS, mean (SD) | median	-	-	-	-	13.4 (18.6) | 8	20.3 (19.0) | 16

Abbreviations: 1LOT, first line of therapy; 2LOT, second line of therapy; aNSCLC, advanced non–small cell lung cancer; LOS, length of stay; O2, Canadian Oncology Outcomes.

[a]11 patients were excluded from the treatment line analysis because of insurance gaps of >30 days in the follow-up.

1.82 [1.29–2.56]), which was mainly driven by patients who received receive chemotherapy only without any ICI or targeted therapy. In line with the increasing number of patients receiving ICI, as reported further previously, the number of patients receiving chemotherapy only decreased over the years.

In Canada and the United States, after adjusting for treatments mentioned previously, we could no longer observe a significant association between index year and OS. In Germany, the index years 2014 to 2017 were still significantly associated with a better OS compared with 2011.

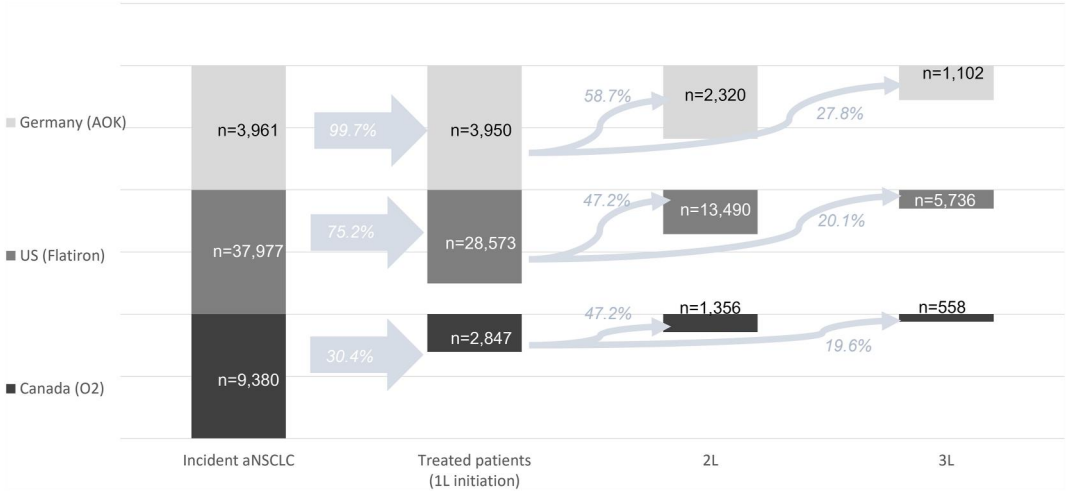

FIGURE 1 Number of patients in different lines of therapy based on the overall sample of incident patients with aNSCLC. aNSCLC indicates advanced non–small cell lung cancer.

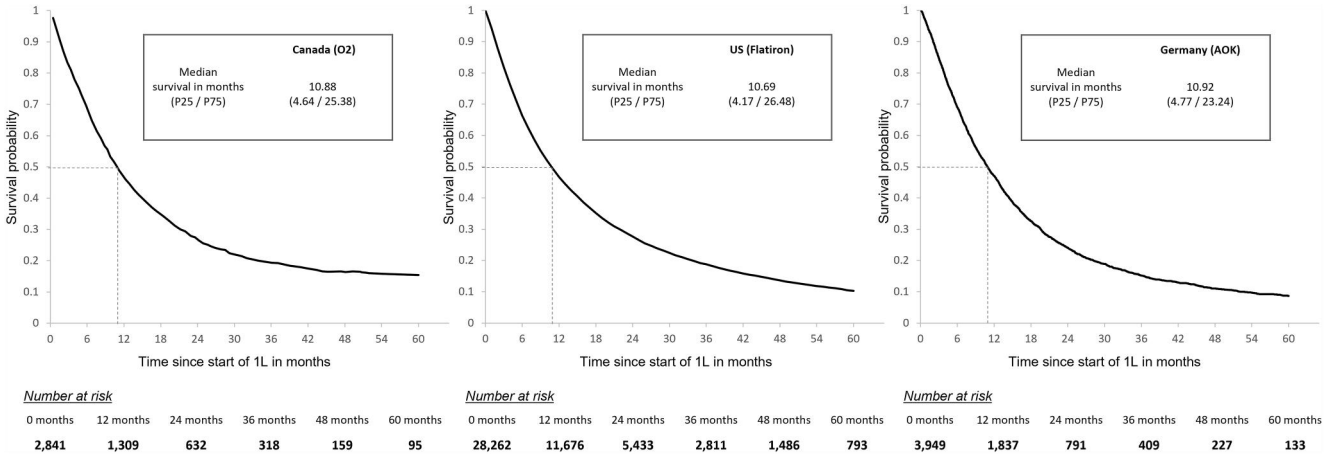

FIGURE 2 OS after start of first-line therapy (1LOT). OS indicates overall survival.

DISCUSSION

Through the use of unique and large data sets from Canada, the United States, and Germany, this multinational study described the real-world treatment of patients with aNSCLC and evaluated the development of OS in the given patient population in these data sets from 2011 to 2020.

In Germany, all documented patients received at least a 1LOT by the nature of how they were identified. However, we observed substantial differences in the percentage of patients who received a 1LOT between the United States and Canada. Although approximately 75% of US patients received a 1LOT, only approximately 30% of Canadian patients did. Because the Canada O2 database features population-level data, this number seems to be generalizable and suggests that a substantial percentage of patients do not receive a systemic treatment; a previous population-based study in Ontario presented similar numbers.[12] One of the main explanations for this is that many patients with aNSCLC obviously are never referred to an oncologist, whereas, as an example, the US Flatiron database only includes patients who are referred to these specialists. Our reported US numbers may therefore overestimate the percentage of treated patients because no patients with fewer than two oncology visits are included in the Flatiron database, and patients with a gap of >90 days between their initial physician visit and the start of a systemic treatment have been excluded. In a comparison of Canada and the United States, differences in the percentage of treated patients directly translated into differences in observed median OS: from the time of the incident aNSCLC diagnosis, median OS was 4.1 months in Canada compared with 9.9 months in the United States.

If OS was measured from the date of start of 1LOT, it was very similar in all three countries (median OS: 10.7–10.9 months in all countries; 1-year OS: 46.9%/46.5%/47.0% in Canada/United States/Germany). Therefore, it seems that once patients get access to systemic treatment typically prescribed by oncologists, health care structures in all three countries provide a similar quality of health care when considering OS outcomes. Among treated patients,

TABLE 3 Kaplan–Meier estimates of the overall survival by year of index and country.

	Canada (O2)			United States (Flatiron)			Germany (AOK)		
	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)
All patients with an incident diagnosis of aNSCLC (2011–2019) (index date = date of incident diagnosis)									
	9380	7534.9	4.1 (1.5/11.7)	37,977	44,414.0	9.9 (4.0/24.5)	3961	6148.6	13.3 (6.8/26.5)
By the year of incident diagnosis of aNSCLC (index date = date of incident diagnosis)									
2011	981	800.0	4.2 (1.4/10.4)	2562	3651.7	9.9 (4.2/23.0)	467	760.3	12.7 (6.6/22.7)
2012	998	896.8	4.3 (1.6/12.0)	3320	4293.0	9.1 (4.2/20.6)	408	621.2	11.0 (6.2/20.9)
2013	1006	819.5	3.9 (1.5/11.5)	4087	5263.2	9.5 (4.0/21.6)	363	644.1	13.2 (7.1/24.0)
2014	1126	917.7	3.7 (1.5/09.9)	4664	5894.1	9.1 (3.9/21.8)	410	722.5	12.7 (6.0/25.1)
2015	1024	821.0	4.1 (1.5/10.9)	4900	6246.1	9.7 (4.0/24.4)	439	722.5	13.4 (6.9/26.2)
2016	1073	914.3	4.6 (1.7/12.4)	4898	5802.4	9.5 (4.0/24.2)	435	771.8	14.8 (7.2/32.5)
2017	1081	884.2	4.1 (1.4/12.0)	5028	5722.3	10.3 (3.8/27.7)	444	700.5	13.3 (7.2/30.7)
2018	1046	793.0	4.1 (1.5/13.9)	4942	4857.0	11.3 (4.1/28.6)	521	694.8	13.9 (7.0/28.2)
2019	1045	688.5	4.6 (1.5/14.1)	3576	2684.4	11.6 (4.2/–)	474	511.0	14.5 (6.2/–)

By the year of the start of 1LOT (index date = date of start 1LOT)

	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Adjusted HRs[a] (95% CI)	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Adjusted HRs[b] (95% CI)	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Adjusted HRs[c] (95% CI)
2011	204	276.7	8.7 (4.7/17.1)	Reference	1460	1916.8	8.9 (3.8/20.4)	Reference	398	555.6	9.9 (4.4/18.5)	Reference
2012	263	377.7	10.3 (4.6/20.9)	0.90 (0.75-1.09)	2310	2997.1	9.1 (3.9/20.6)	1.04 (0.97–1.12)	407	526.4	8.7 (4.5/18.3)	1.02 (0.89–1.18)
2013	254	409.0	11.9 (4.9/24.9)	0.85 (0.71–1.03)	2,819	3,831.1	9.4 (3.9/22.5)	1.02 (0.95–1.09)	375	559.9	11.2 (5.0/20.2)	0.91 (0.79–1.06)
2014	301	447.9	9.4 (3.6/20.7)	0.88 (0.73–1.06)	3377	4480.3	9.2 (4.1/22.9)	1.01 (0.95–1.08)	399	622.7	10.0 (4.3/22.1)	0.91 (0.79–1.05)
2015	297	429.5	10.1 (5.0/25.1)	0.83 (0.69–0.99)*	3650	4964.2	10.1 (4.2/25.3)	0.99 (0.93–1.06)	419	593.5	10.9 (4.8/20.7)	0.94 (0.82–1.09)
2016	354	497.1	10.6 (4.7/25.9)	0.82 (0.68–0.98)*	3839	4990.4	10.6 (4.2/26.8)	0.97 (0.91–1.04)	432	670.1	12.4 (5.3/27.7)	0.82 (0.71–0.94)**
2017	357	529.7	11.8 (4.1/34.6)	0.66 (0.55–0.80)***	3933	4869.2	11.7 (4.1/32.1)	0.92 (0.86–0.98)*	450	665.8	11.8 (4.6/29.9)	0.77 (0.66–0.89)***

TABLE 3 (Continued)

By the year of the start of 1LOT (index date = date of start 1LOT)										
	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Adjusted HRs[a] (95% CI)	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Adjusted HRs[b] (95% CI)	Patients (*n*)	Time at risk in years	Survival time Median in months (P25/P75)	Adjusted HRs[c] (95% CI)
2018	400	481.1	11.8 (4.4/29.7)	0.74 (0.61–0.88)***	3810	4058.6	12.4 (4.4/30.9)	0.88 (0.82–0.95)**	511	602.6	11.4 (5.3/24.8)	0.84 (0.72–0.96)*
2019	417	409.6	12.4 (5.6/–)	0.68 (0.56–0.83)***	3334	2605.2	13.4 (4.7/–)	0.87 (0.80–0.93)***	558	516.3	12.1 (4.7/–)	0.78 (0.68–0.91)**

Abbreviations: 1LOT, first line of treatment; aNSCLC, advanced non–small cell lung cancer; CCI, Charlson Comorbidity Index; HR, hazard ratio; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; O2, Canadian Oncology Outcomes; P25/P75, Percentile 25/75.

[a]Adjusted for age, sex, stage (IIIB/C versus IV), subtype (adenocarcinoma, squamous cell carcinoma, NOS), CCI, treatment facility (academic versus community).

[b]Adjusted for age, sex, stage (IIIB/C versus IV), subtype (nonsquamous cell carcinoma, squamous cell carcinoma, NSCLC histology NOS), history of smoking (yes versus no), metastases (yes versus no), mutation testing (yes versus no), duration between diagnosis, and start of therapy.

[c]Adjusted for age, sex, diagnosis subcode (C340 - Main bronchus, C341 - Upper lobe, C342 - Middle lobe, C343 - Lower lobe, C348 - Overlapping lesion), CCI, number of hospitalizations in the 12-month preindex period, mutation testing (yes versus no), duration between diagnosis and start of therapy.

*$p < .050$, **$p < .010$, ***$p < .001$.

treatment patterns slightly differed between countries. The percentage of patients receiving ICI during any observed LOT was substantially higher in the United States compared with Germany and specifically Canada. This may be explained by several factors, but one might be a later approval for newer treatments in Canada and Germany, compared with the United States. In addition, the proportion of patients of Asian descent as well as nonsquamous subtype might be higher in Canada if compared with Germany and community US sites. This might explain the higher percentage of Canadian patients receiving EGFR-targeted treatments.

Our analysis shows that OS, measured from the date of 1LOT initiation, improved over the observed time period in all three countries. We hypothesize that most of these improvements can be attributed to the introduction of new treatments, mainly first- and second-generation TKIs and ICI.

Most previous observational studies reported median OS for aNSCLC subpopulations based on specific treatment classes. A Swedish study addressing TKI users only reported a median OS of 18.6 months,[13] whereas 19.4 months was reported in a Polish study.[14] A wide variety of observational research has investigated the impact of ICIs. A review of observational studies on patients with aNSCLC treated with this agent class reported a median OS of 7.9 to 24.3 months, with the majority of studies reporting an OS range of 10 to 18 months.[15] A recent US study showed a median OS of 16.5 months for patients treated with pembrolizumab plus pemetrexed-carboplatin.[16] Previous Flatiron analyses reported a median OS of up to 12 months.[17,18] A meta-analysis of observational studies using nivolumab reported a median OS of 9.6 months.[19] In observational studies, which addressed a broader population of patients with aNSCLC (both treated and untreated patients, all types of systemic treatments included), reported OS numbers were very similar to ours. An Italian study of 1673 patients with aNSCLC reported a 1-year OS of 36.9%,[20] whereas a US study of 9656 patients with aNSCLC showed a median OS of 10.1 months.[21] A Canadian study based on 12,159 patients with stage IV NSCLC in Ontario reported a median OS of 4.6 months for squamous patients and 4.9 months for nonsquamous patients. Ultimately, these figures corroborate the below-average OS numbers for Canada, which have been reported in this study.[22] A large multicountry observational study in non-Western countries concluded that the median OS of 3151 patients from 19 countries was 12.5 months.[23] The results of our multivariable analyses are also in line with those outlined in a recent US analysis based on the Surveillance, Epidemiology, and End Results data, which concluded that the majority of observed OS gains are attributable to the usage of newer treatments.[24]

Limitations

We acknowledge some limitations of our analysis. First, because of the structural differences between databases, we could not directly compare our findings between countries.

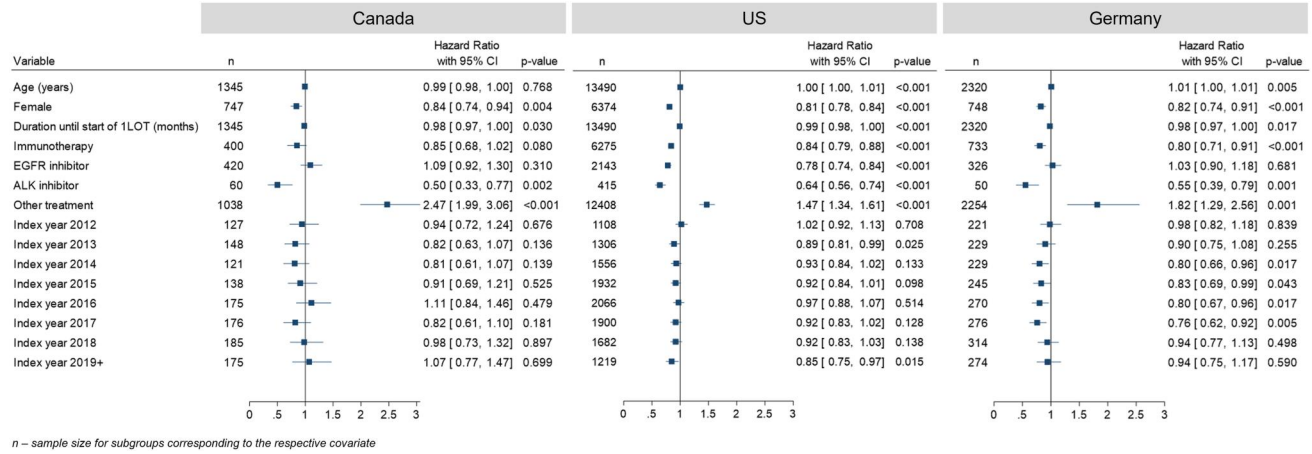

FIGURE 3 Results of the Cox regression model estimating OS from start of 1LOT among patients who initiated 2LOT+. 1LOT indicates first line of treatment; 2LOT, second line of treatment; OS, overall survival.

Second, each database has some specific aspects to consider concerning the representativeness of each country. Flatiron data are related to a specific setting with integral access to oncologists and care and, therefore, are not representative of the overall US care environment. In addition, the criteria and definition used to identify US patients (i.e., at least two oncologist visits, no data gaps >90 days) selected for those who received an oncologist treatment and, therefore, probably survived longer. German and Canadian databases are population-based. However, both databases are regional, and, therefore, the applicability of the results to the whole of the countries could be limited. In Germany, identifying patients with NSCLC was only feasible by using treatment proxies. Furthermore, it was not feasible to distinguish between stage IIIB/C and stage IV patients in the German claims database, leading to the inclusion of stage IIIB/C and stage IV patients in the study analysis samples.

Third, some important patient characteristics, such as race/ethnicity, for which disparities in cancer survival are particularly well documented in lung cancer, were not available in each database and could only be approximated by other covariates to a small extent.[25] The same applies to clinical information such as Tumor-Nodes-Metastases status, driver mutations, or performance status. Thus, our multivariable models estimating the impact of factors on OS over time were limited to those variables available in all databases. Fourth, only patients who received a 2LOT were considered in our multivariable analysis when adjusting for treatments the patients received. We did this because the inclusion of 1LOT treatments only would not have measured the impact of newer treatments because these are often prescribed as 2LOT. However, if 2LOT treatments are included as independent variables, observation needs to focus on patients who received at least a 2LOT as otherwise an immortal time bias (i.e., newer treatments are more likely to be applied in later lines of therapy, and therefore patients who survived until the 2LOT initiation have a higher chance of getting these treatments) would influence the results. Fifth, our assignment of treatments might have led to misclassifications because a patient was assigned to one treatment group if he or she received at least one dosage of treatment, independent of whether the patient received that treatment in a 1LOT or 2LOT setting. If a patient received other treatments as part of a combination treatment and/or at earlier/later LOT, he or she was assigned to these treatment groups as well (i.e., a double or even triple assignment was possible). Furthermore, only systemic treatments have been taken into account. Any change in the frequency of other therapies (e.g., radiation therapy) might have also been an influencing factor of the OS development over the years. Finally, the limitation related to the different lengths of follow-up available when comparing OS over the course of the years needs to be mentioned. Even if a minimum follow-up of 1 year was ensured for every patient included in the analysis and the majority of events were observed in the first year after diagnosis, observing more deaths over a longer follow-up than a shorter one leads to a more precise estimate for patients with an index in the more previous years (e.g., 2011) than in the more recent years (e.g., 2019).

CONCLUSIONS

To our knowledge, this study is the first multicountry database study reporting an improvement of OS in patients with aNSCLC over time. Our data show an improvement in OS over the past 10 years, which is most likely attributable to the introduction of new treatments. The dramatic differences in OS since incidence diagnosis in Canada compared with the other countries, with observing quite similar results across the countries for the OS after initiation of therapy, highlight the importance of access to systemic treatment for patients' prognosis. The reasons for the difference in the proportion of patients who received at least a 1LOT after an incident aNSCLC diagnosis across the countries and also evaluation of real-world outcomes in other countries (outside Europe and the United States/Canada) to better understand cancer treatment equity should be a subject of future research.

AUTHOR CONTRIBUTIONS

Frank Griesinger: Funding acquisition, supervision, and validation. **Sreeram Ramagopalan:** Funding acquisition, project administration, supervision, and validation. **Winson Y. Cheung:** Investigation, resources, supervision, and validation. **Thomas Wilke:** Funding acquisition, project administration, and writing - original draft preparation. **Sabrina Mueller:** Data curation, formal analysis, investigation, project administration, software, visualization, and writing - original draft preparation. **Alind Gupta:** Data curation, formal analysis, investigation, software, and visualization. **Dylan E. O'Sullivan:** Data curation, investigation, formal analysis, software, and visualization. **Paul Arora:** Supervision and validation. **Darren R. Brenner:** Investigation, resources, supervision, and validation. **Ulf Maywald:** Investigation, resources, supervision, and validation. **Vivek Subbiah:** Resources, supervision, and validation. **All authors:** Conceptualization, Methodology, and Writing - review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed that support the findings of this study are available within this article and its supplementary materials.

ORCID

Thomas Wilke https://orcid.org/0000-0001-8932-6426
Vivek Subbiah https://orcid.org/0000-0002-6064-6837

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