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Two-year survival with nivolumab in previously treated advanced non–small-cell lung cancer: A real-world pooled analysis of patients from France, Germany, and Canada

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ABSTRACT

Objectives: Immune checkpoint inhibitors have become the standard of care for metastatic non–small-cell lung cancer (NSCLC) progressing during or after platinum-based chemotherapy. Real-world clinical practice tends to represent more diverse patient characteristics than randomized clinical trials. We sought to evaluate overall survival (OS) outcomes in the total study population and in key subsets of patients who received nivolumab for previously treated advanced NSCLC in real-world settings in France, Germany, or Canada.

Materials and methods: Data were pooled from two prospective observational cohort studies, EVIDENS and ENLARGE, and a retrospective registry in Canada. Patients included in this analysis were aged ≥18 years, had stage IIIB/IV NSCLC, and received nivolumab after at least one prior line of systemic therapy. OS was estimated

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand 1; TRAE, treatment-related adverse event.

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in the pooled population and in various subgroups using the Kaplan-Meier method. Timing of data collection varied across cohorts (2015–2019).
Results: Of the 2585 patients included in this analyses, 1235 (47.8 %) were treated in France, 881 (34.1 %) in Germany, and 469 (18.1 %) in Canada. Median OS for the total study population was 11.3 months (95 % CI: 10.5–12.2); this was similar across France, Germany, and Canada. The OS rate was 49 % at 1 year and 28 % at 2 years for the total study population. In univariable Cox analyses, the presence of epidermal growth factor receptor mutations in nonsquamous disease, liver, or bone metastases were associated with significantly shorter OS, whereas tumor programmed death ligand 1 expression and Eastern Cooperative Oncology Group performance status 0–1 were associated with significantly prolonged OS. Similar OS was noted across subgroups of age and prior lines of therapy.
Conclusion: OS rates in patients receiving nivolumab for previously treated advanced NSCLC in real-world clinical practice closely mirrored those in phase 3 studies, suggesting similar effectiveness of nivolumab in clinical trials and clinical practice.

1. Introduction

Immune checkpoint inhibitors of programmed death-1 (PD-1) or programmed death ligand 1 (PD-L1) have become the standard of care in North America and Europe for immunotherapy-naïve patients with metastatic non–small-cell lung cancer (NSCLC) who experience disease progression during or after treatment with platinum-based chemotherapy [1–4]. The approval of the PD-1 inhibitor nivolumab for this indication in the United States and Europe was based on the results of the global phase 3 studies CheckMate 017 [1] and CheckMate 057 [2], which demonstrated significantly longer overall survival (OS) with nivolumab versus docetaxel in patients with previously treated squamous and nonsquamous advanced NSCLC, respectively [1,2]. Long-term OS data from the combined study populations of CheckMate 017 and CheckMate 057 showed a hazard ratio for death of 0.68 (95 % CI, 0.59–0.78) in favor of nivolumab. Median OS with nivolumab was 11.1 months (95 % CI, 9.2–13.1), and the estimated 1-, 2-, 4- and 5-year OS rates were 48 %, 27 %, 14 %, and 13 %, respectively [5,6].

Patients receiving treatment in real-world clinical practice tend to be more heterogeneous in terms of clinical characteristics than participants of randomized clinical trials. For example, patients with poor performance status at screening are often excluded from clinical trials, as was the case with CheckMate 017 and 057. Furthermore, large real-world studies provide a sufficient sample size that enables a more robust estimation of effectiveness in clinical subgroups of interest.

In this large pooled data analysis, we evaluated OS of patients who received nivolumab for previously treated advanced NSCLC in France, Germany, and Canada. Data were pooled from prospective multicenter observational cohort studies conducted in France (EVIDENS, NCT03382496) and Germany (ENLARGE, NCT02910999) [7,8] and a retrospective registry of patients treated through expanded access to nivolumab in Canada [9]. The large analysis population of 2585 patients provided the opportunity to explore OS in patients of special interest, such as those with poor performance status, brain, liver, or bone metastases, or epidermal growth factor receptor (*EGFR)* mutations.

2. Methods

2.1. Study design and patients

The current data analysis in patients with advanced NSCLC who were treated with nivolumab in real-world clinical practice after at least one prior line of systemic therapy used data pooled from two prospective observational cohort studies, EVIDENS and ENLARGE, and a retrospective registry in Canada. EVIDENS enrolled 1452 patients from 146 French centers between October 2016 and November 2017, with a planned follow-up of 3 years. ENLARGE enrolled 907 patients from 79 German centers between August 2016 and February 2019, with a planned follow-up of 5 years. Patients enrolled in EVIDENS and ENLARGE provided informed consent to participate in the study. The primary endpoint in both EVIDENS and ENLARGE was OS. The Canadian registry included 472 patients who received nivolumab through expanded access between May 2015 and February 2016 [9].

For the current pooled analyses, inclusion criteria were harmonized across all three studies. Patients were included if they were at least 18 years old at the time nivolumab treatment initiation was decided, had stage IIIB or IV NSCLC (with a pathologically confirmed diagnosis of NSCLC), and received nivolumab after at least one prior systemic therapy. Patients were excluded from the current analyses if they had other concurrent primary cancers, had received prior immunotherapy, or were participating in an interventional study for locally advanced/metastatic NSCLC.

2.2. Assessments and analyses

Baseline demographic and clinical characteristics were summarized using descriptive statistics. PD-L1 testing was not mandatory in any of the studies, and testing and reporting were not standardized across sites. In EVIDENS and ENLARGE, some sites reported PD-L1 status as positive or negative and some indicated a specific cut-off used to determine positivity. Patients in Canada were not routinely tested for PD-L1 status. In this analysis, PD-L1 status was grouped according to positivity or negativity, regardless of percent expression.

Follow-up time was calculated using the Schemper method [10]. OS from the time of nivolumab initiation until death or censoring was estimated in the total analysis population and in subgroups using the Kaplan-Meier method. Cox proportional hazards univariable models were used to explore factors associated with OS. Safety data were only available for EVIDENS and ENLARGE. Descriptive statistics were used to report the frequencies of treatment-related adverse events (TRAEs) of any grade, grade 3 or 4, and grade 5.

3. Results

3.1. Patients

Of the 2585 patients included in the current analyses, 1235 (47.8 %) were treated in France, 881 (34.1 %) in Germany, and 469 (18.1 %) in Canada. Patients' demographic and disease characteristics at baseline are shown in Table 1. Across all 3 countries, the median age was 66 years at treatment initiation and 18.4 % of patients were aged ≥75 years; 62.5 % of patients were male; 11.5 % had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2; and 67.7 % had nonsquamous tumor histology. The Canadian dataset had the highest proportion of women (45.4 % vs 30.4 % in France and 36.4 % in Germany), patients with nonsquamous NSCLC (73.6 % vs 69.7 % in France and 61.9 % in Germany), and patients with more than one prior line of therapy (55.9 % vs 27.0 % in France and 23.2 % in Germany). The majority of patients (96.4 %) received a prior platinum-based therapy. Overall, 18.5 % of patients had baseline brain metastases. No baseline information was available for disease stage, liver metastases, bone metastases, or PD-L1 expression for patients in Canada; in addition, PD-L1 expression status

Table 1
Patients' demographic and disease characteristics.

Characteristic, n (%)	France (n = 1235)	Germany (n = 881)	Canada (n = 469)	Pooled (N = 2585)
Age, years	n = 1235	n = 877	n = 469	n = 2581
Mean (SD)	65.4 (9.8)	66.2 (8.9)	65.1 (9.5)	65.6 (9.5)
Median (range)	65 (35–91)	66 (21–87)	66 (36–92)	66 (21–92)
Age category				
<65 years	570 (46.2)	381 (43.2)	212 (45.2)	1163 (45.0)
≥65 to <75 years	437 (35.4)	321 (36.4)	185 (39.4)	943 (36.5)
≥75 years	228 (18.5)	175 (19.9)	72 (15.4)	475 (18.4)
Unknown	0	4 (0.5)	0	4 (0.2)
Sex				
Male	859 (69.6)	556 (63.1)	201 (42.9)	1616 (62.5)
Female	376 (30.4)	321 (36.4)	213 (45.4)	910 (35.2)
Unknown	0	4 (0.4)	55 (11.7)	59 (2.3)
Smoking status				
Current/former	1112 (90.0)	722 (82.0)	251 (53.5)	2085 (80.7)
Never	120 (9.7)	129 (14.6)	32 (6.8)	281 (10.9)
Unknown	3 (0.2)	30 (3.4)	186 (39.7)	219 (8.5)
ECOG PS				
0–1	1078 (87.3)	644 (73.1)	401 (85.5)	2123 (82.1)
2	111 (9.0)	95 (10.8)	42 (9.0)	248 (9.6)
≥3	30 (2.4)	20 (2.3)	0	50 (1.9)
Unknown	16 (1.3)	122 (13.8)	26 (5.5)	164 (6.3)
Tumor histology				
Squamous	374 (30.3)	336 (38.1)	124 (26.4)	834 (32.3)
Nonsquamous	861 (69.7)	545 (61.9)	345 (73.6)	1751 (67.7)
Disease stage*				**N = 2116**
IIIB	79 (6.4)	39 (4.4)	NA	118 (5.6)
IV	1156 (93.5)	749 (85.0)	NA	1905 (90.0)
Unknown	0	93 (10.6)	NA	93 (4.4)
Brain metastases				
Yes	262 (21.2)	154 (17.5)	61 (13.0)	477 (18.5)
No	973 (78.8)	727 (82.5)	408 (87.0)	2108 (81.5)
Liver metastases*				**N = 2116**
Yes	210 (17.0)	148 (16.8)	NA	358 (16.9)
No	1025 (83.0)	733 (83.2)	NA	1758 (83.1)
Bone metastases*				**N = 2116**
Yes	390 (31.6)	259 (29.4)	NA	649 (30.7)
No	845 (68.4)	622 (70.6)	NA	1467 (69.3)
EGFR mutation status, nonsquamous histology	**N = 861**	**N = 545**	**N = 345**	**N = 1751**
Positive	39 (4.5)	28 (5.1)	24 (7.0)	91 (5.2)
Negative	705 (81.9)	370 (67.9)	214 (62.0)	1289 (73.6)
Unknown	117 (13.6)	147 (27.0)	107 (31.0)	371 (21.2)
ALK mutation status, nonsquamous histology	**N = 861**	**N = 545**	**N = 345**	**N = 1751**
Positive	4 (0.5)	2 (0.4)	3 (0.9)	9 (0.5)
Negative	683 (79.3)	338 (62.0)	218 (63.2)	1239 (70.8)
Unknown	174 (20.2)	205 (37.6)	124 (35.9)	503 (28.7)
PD-L1 expression status*,†				**N = 2116**
Positive	123 (10.0)	314 (35.6)	NA	437 (20.6)
Negative	58 (4.7)	218 (24.7)	NA	276 (13.0)
Unknown	1054 (85.3)	349 (39.6)	NA	1403 (66.3)
Number of prior lines of therapy				
1	902 (73.0)	662 (75.1)	207 (44.1)	1771 (68.5)
≥2	333 (27.0)	204 (23.2)	262 (55.9)	799 (30.9)
Unknown	0	15 (1.7)	0	15 (0.6)
Concurrent corticosteroid use				**N = 2116**
Yes	185 (15.0)	59 (6.7)	NA	244 (11.5)
No	1050 (85.0)	252 (28.6)	NA	1302 (61.5)
Unknown	0	570 (64.7)	NA	570 (26.9)
History of autoimmune disease				**N = 2116**

(*continued on next page*)

Table 1 (*continued*)

Characteristic, n (%)	France (n = 1235)	Germany (n = 881)	Canada (n = 469)	Pooled (N = 2585)
Yes	34 (2.8)	26 (3.0)	NA	60 (2.8)
No	1201 (97.2)	0	NA	1201 (56.8)
Unknown	0	855 (97.0)	NA	855 (40.4)

Data are n (%) unless otherwise indicated.

Abbreviations: *ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; NA, not available; PD-L1, programmed death ligand 1.

[*] Baseline data for disease stage, presence of liver or bone metastases, PD-L1 expression, corticosteroid use, and autoimmune disease were not available for patients treated in Canada.

[†] PD-L1 positive combines expression levels of 1–50 %, >50 %, and positive-unspecified; PD-L1 negative combines expression <1 % and negative-unspecified.

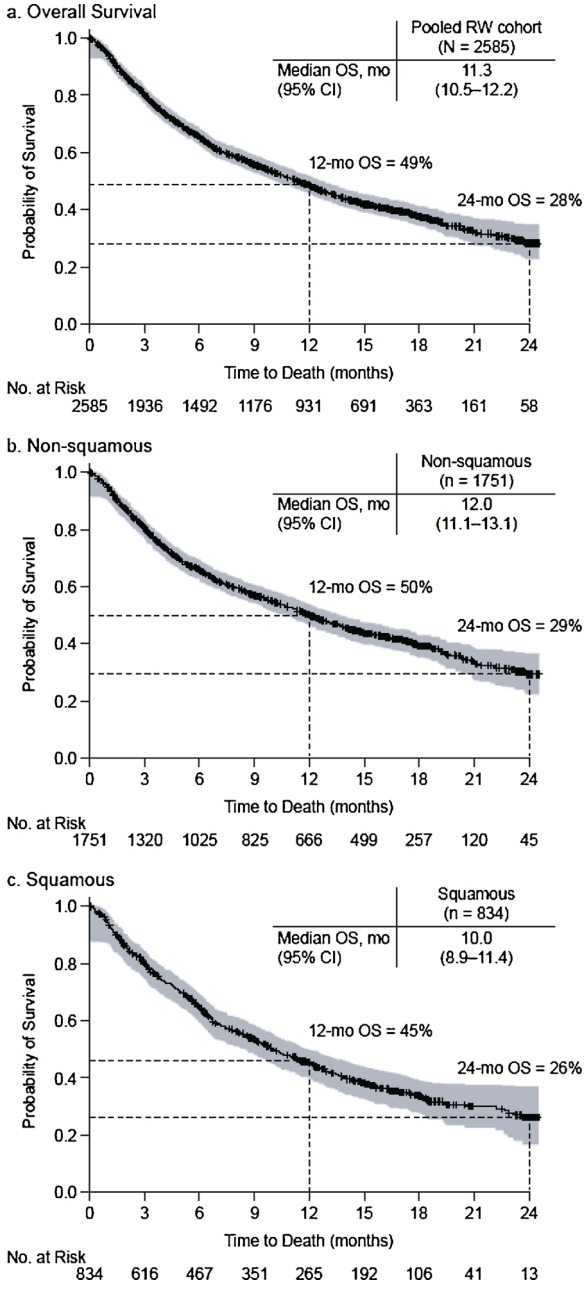

Fig. 1. Overall survival (OS) among all patients (A), patients with non-squamous NSCLC (B) and patients with squamous NSCLC (C). NSCLC, non–small-cell lung cancer; RW, real-world.

was unknown for 85.3 % of patients in France and 39.6 % of patients in Germany. In patients with nonsquamous histology, *EGFR* mutation status was 5.2 % positive and 21.2 % unknown; anaplastic lymphoma kinase (*ALK)* rearrangement status, was 0.5 % positive and 28.7 % unknown.

3.2. Overall survival

The median duration of follow-up was 17.5 months (range, 0–27) for the total study population, and 18, 12, and 16 months for patients treated in France, Germany, and Canada, respectively. Median OS was 11.3 months (95 % CI: 10.5–12.2) among all patients (Fig. 1A) and was similar among patients in France (11.3 months [95 % CI: 10.0–12.5]), Germany (11.1 months [95 % CI: 9.3–12.7]), and Canada (11.9 months [95 % CI: 10.7–13.5]). Overall, 1-year OS was 49 % and 2-year OS was 28 % from the time of nivolumab treatment initiation (Fig. 1A).

Median OS was 12.0 months (95 % CI: 11.1–13.1) in patients with nonsquamous NSCLC and 10.0 months (95 % CI: 8.9–11.4) in those with squamous NSCLC (Fig. 1B and C). Patients with an ECOG PS 0–1 at treatment initiation had a median OS of 12.2 months (95 % CI: 11.3–13.0) and an estimated 1- and 2-year OS of 51 % and 30 %, respectively, whereas patients with an ECOG PS $\geq$ 2 had a median OS of 5.8 months (95 % CI: 5.0–6.9) and an estimated 1- and 2-year OS of 32 % and 18 %, respectively (Supplemental Fig. 1 and Table 2). Additional subgroup analyses are summarized in Table 2. Patients with positive PD-L1 expression status had a median OS of 12.1 months (95 % CI: 10.0–14.0) and an estimated 1- and 2-year OS of 51 % and 33 %, respectively; whereas patients with negative PD-L1 expression status had a median OS of 8.6 months (95 % CI: 6.5–11.0) and an estimated 1- and 2-year OS of 43 % and 21 %, respectively. Patients without liver metastases had a median OS of 12.3 months (95 % CI: 11.3–13.5) and an estimated 1- and 2-year OS of 51 % and 29 %, respectively. Patients with liver metastases had a median OS of 6.1 months (95 % CI: 4.9–7.9) and an estimated 1- and 2-year OS of 36 % and 21 %, respectively. Patients without bone metastases had a median OS of 12.5 months (95 % CI: 11.5–14.0) and an estimated 1- and 2-year OS of 52 % and 30 %, respectively. Patients with bone metastases had a median OS of 7.9 months (95 % CI: 6.5–9.4) and an estimated 1- and 2-year OS of 40 % and 22 %, respectively. Furthermore, median OS was similar in patients using corticosteroids or not (11.3 [95 % CI: 8.4–14.5] vs 11.2 months [95 % CI: 10.0–12.2]) with an estimated 1-year OS of 48 % for both groups, and 2-year OS of 29 % and 28 %, respectively (Table 2 and Supplemental Fig. 2). Patients with autoimmune disease had a median OS of 11.3 months (95 % CI: 8.3–16.4) and those without had 11.2 months (95 % CI: 10.0–12.2), with an estimated 1-year OS of 47 % and 49 % respectively as well as 2-year OS of 23 % and 28 % respectively (Table 2 and Supplemental Fig. 3).

In univariable Cox analyses, presence (vs absence) of liver or bone metastases was associated with significantly shorter OS ($P < 0.0001$), as were the presence of *EGFR* mutations among patients with nonsquamous disease ($P = 0.0199$), whereas prolonged OS was significantly associated with tumor PD-L1 expression ($P = 0.019$) and ECOG PS 0–1 (vs $\geq$2;

$P < 0.0001$) (Fig. 2). Interestingly, presence of brain metastases, age, and prior line of therapy were not associated with differences in OS ($P > 0.05$) (Fig. 2).

3.3. Safety

Safety was only assessed in the prospective EVIDENS and ENLARGE studies. Approximately one third of patients reported TRAEs, including 7.5 % who reported grade 3 or 4 TRAEs (Table 3). There were eight Grade 5 TRAEs. Most TRAEs occurred during the first year of follow-up. The median time to onset of any TRAE was 29 days (interquartile range, 15–85). In patients using corticosteroids (n = 244), 36.9 % reported any grade TRAEs compared to 31.4 % in those not using corticosteroids (n = 1872, Supplemental Table 1). Rates of any grade TRAEs in patients with autoimmune disease (n = 60) were 35.0 % and without (n = 2056) were 31.9 % (Supplemental Table 2).

4. Discussion

OS outcomes in this real-world analysis of patients who received nivolumab for previously treated advanced NSCLC were similar to those in the pivotal phase 3 studies for this indication. The median OS was 11.3 months in this analysis and 11.1 months in CheckMate 017/057 [5]. Furthermore, the estimated 1- and 2-year OS were 49 % and 28 %, respectively, in this analysis, very similar to 48 % and 27 %, respectively, in CheckMate 017/057 [5,6]. It is important to note that the 2-year estimates of OS were primarily driven by patients in the French and German data sets, as they had the longest follow-up time. However,

Table 2
OS in subgroups of the total study population.

Variable	n	Median OS (95 % CI), months	1-year OS rate (SE), %	2-year OS rate (SE), %
Age category				
<65 years	1163	11.7 (10.6–13.2)	50 (2)	30 (2)
≥65–<75 years	943	11.5 (9.9–12.6)	49 (2)	25 (2)
≥75 years	475	10.2 (8.8–11.9)	45 (2)	30 (3)
Sex				
Male	1616	11.2 (10.1–12.2)	48 (1)	27 (2)
Female	910	12.4 (11.0–13.7)	51 (2)	30 (3)
Smoker				
Current/former	2085	11.6 (10.5–12.5)	49 (1)	29 (2)
Never	281	9.6 (6.9–11.8)	44 (3)	20 (7)
ECOG PS				
0–1	2123	12.2 (11.3–13.0)	51 (1)	30 (2)
≥2	298	5.8 (5.0–6.9)	32 (3)	18 (4)
Unknown	164	14.6 (7.9–18.5)	51 (4)	26 (8)
Disease stage*				
IV	1905	11.0 (9.8–12.2)	48 (1)	29 (2)
IIIB	118	11.3 (7.0–15.7)	49 (5)	10 (5)
Brain metastases				
Yes	477	9.7 (7.5–11.2)	44 (2)	29 (3)
No	2108	11.9 (10.8–12.5)	50 (1)	28 (2)
Liver metastases*				
Yes	358	6.1 (4.9–7.9)	36 (3)	21 (3)
No	1758	12.3 (11.3–13.5)	51 (1)	29 (2)
Bone metastases*				
Yes	649	7.9 (6.5–9.4)	40 (2)	22 (2)
No	1467	12.5 (11.5–14.0)	52 (1)	30 (2)
EGFR mutation, nonsquamous histology				
Yes	91	6.2 (4.8–11.3)	37 (6)	10 (8)
No	1289	12.5 (11.2–14.0)	51 (1)	30 (2)
ALK mutation				
Yes	12	10.6 (1.4–NE)	47 (18)	NA
No	1371	11.9 (10.8–13.2)	50 (1)	28 (2)
PD-L1 expression*,†				
Positive	437	12.1 (10.0–14.0)	51 (3)	33 (3)
Negative	276	8.6 (6.5–11.0)	43 (3)	21 (4)
Prior lines of therapy				
≥2	799	12.6 (11.3–13.8)	52 (2)	29 (3)
1	1771	10.6 (9.6–11.9)	47 (1)	28 (2)
Corticosteroid use*				
Yes	244	11.3 (8.4–14.5)	48 (0.03)	29 (0.04)
No	1872	11.2 (10.0–12.2)	48 (0.01)	28 (0.02)
Autoimmune disease*				
Yes	60	11.3 (8.3–16.4)	47 (0.07)	23 (0.08)
No	2056	11.2 (10.0–12.2)	49 (0.01)	28 (0.02)

Abbreviations: *ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand 1; SE, standard error.

* Baseline data for disease stage, presence of liver or bone metastases, PD-L1 expression, corticosteroid use, and autoimmune disease status were not available for patients treated in Canada.

† PD-L1 positive combines expression levels of 1–50 %, >50 %, and positive-unspecified; PD-L1 negative combines expression <1% and negative-unspecified.

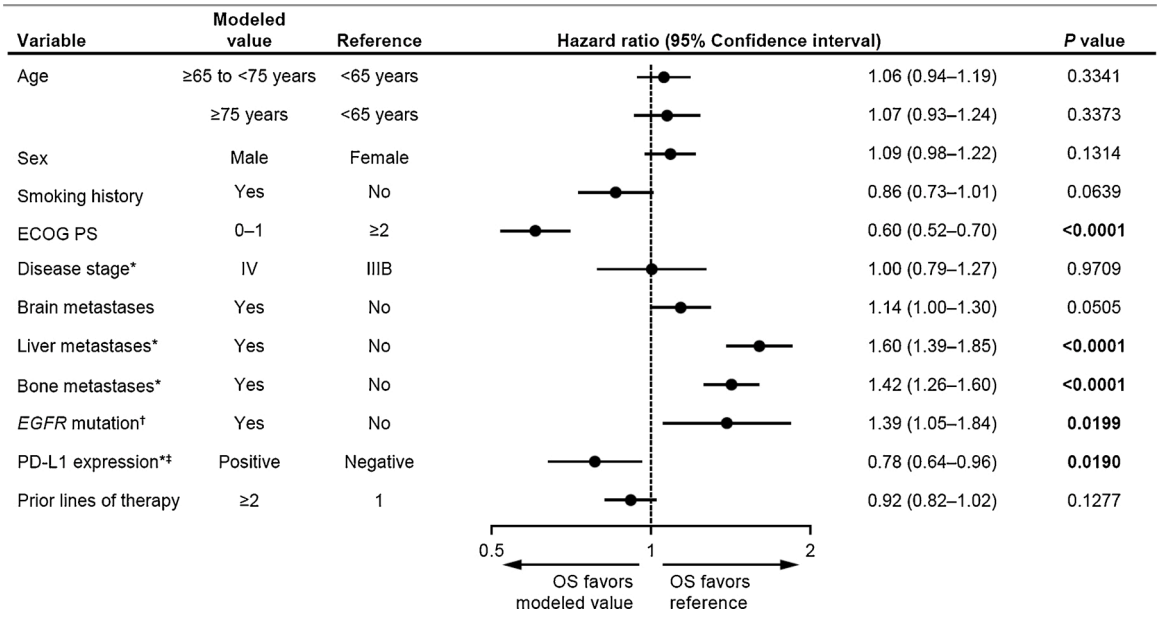

Fig. 2. Univariable Cox analyses for OS in the total study population.
P values less than 0.05 are shown in bold font. *Baseline data for disease stage, presence of liver or bone metastases, and PD-L1 expression were not available for patients treated in Canada. †Among patients with nonsquamous histology. ‡PD-L1 positive combines expression levels of 1–50 %, >50 %, and positive-unspecified; PD-L1 negative combines expression <1 % and negative-unspecified. ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; OS, overall survival; PD-L1, programmed death ligand 1.

as the kinetics of response across the three data sets were similar, these results can likely also be extrapolated to the Canadian patients. As in CheckMate 017/057 [1,2,5], OS estimates in this real-world analysis tended to be more favorable for nonsquamous histology than squamous tumor histology. This was also observed in a French nationwide retrospective study of nivolumab in 10,452 patients with previously treated advanced NSCLC [11].

As expected for a real-world population, there were higher proportions of patients with poor PS and baseline metastases compared with clinical trials. The Cox analyses demonstrated significant associations of ECOG PS ≥ 2, liver metastases, bone metastases, negative PD-L1 expression, and *EGFR* mutations in patients with nonsquamous disease with shorter OS. Importantly, in groups with poor prognosis defined by ECOG PS, liver or bone metastases, the 2-year OS rate was approximately 20 %, suggesting a subset of patients with these clinical characteristics experience long-term survival. Poor PS is known as a negative prognostic factor in patients with NSCLC [12], including those who receive nivolumab for previously treated advanced NSCLC [13–17]. Similarly, presence of liver metastases is a negative prognostic factor in NSCLC, and resulted in shorter OS with nivolumab compared with patients without baseline metastases [18,19]. Evidence from prior real-world studies shows that the presence of *EGFR* mutations is associated with shorter OS and PFS in patients with advanced NSCLC receiving immunotherapy [20–22]. Further in line with our findings, studies in the US and Japan demonstrated that *EGFR*+ patients with nonsquamous NSCLC receiving nivolumab monotherapy after prior systemic therapy had a significantly shorter OS relative to patients with EGFR wild-type disease [23,24]. Heterogeneity of *EGFR*+ mutations in NSCLC may drive differences in efficacy outcomes in patients receiving immune checkpoint inhibitor alone or in combination with other agents [25], but larger-cohort studies are needed to identify the optimal sequence of treatment and strategies for the long-term survival of patients with these mutations.

Although PD-L1 expression is known to affect OS with PD-1 inhibitors in patients with advanced NSCLC [20], pooled results from CheckMate 017 and 057 demonstrated longer 5-year OS with nivolumab versus docetaxel in patients with both positive (hazard ratio [HR], 0.61) and negative (HR, 0.76; [95 % CI: 0.61–0.96]; OS rate: 8.0 % vs 2.0 %) PD-L1 expression [1,2,6]. Central nervous system metastases have been associated with shorter OS of patients receiving nivolumab in previously treated NSCLC [19]. However, in the present analysis, the association of brain metastases with shorter OS was not statistically significant. Baseline corticosteroid use for palliative care and/or brain metastases, but not for mitigation of AEs in patients treated with immune checkpoint inhibitors, has been associated with poor survival outcomes [26,27]. In this study, OS was similar regardless of concomitant corticosteroid use, but the reason for use could not be identified from available data. The efficacy of immune checkpoint inhibitors in patients with autoimmune disease appears to be comparable to the general oncologic population, and is associated with a higher but manageable incidence of immune-related AEs [28]. In this study, patients with and without autoimmune disease had a similar rate of TRAEs and median OS, although the estimated 1-year and 2-year OS rates were numerically slightly lower in the subgroup with autoimmune disease. Interestingly, OS was numerically longer among patients with ≥2 relative to <2 prior therapies and was similar regardless of age. Median OS and OS rates in the ≥75-year-old age group are encouraging. Notably, the proportion of elderly patients with poor performance status (ECOG PS ≥ 2) was similar to that in the <75-year-old group (data not shown), indicating that elderly patients with good performance status were not more likely selected to receive treatment compared with the younger patients.

There are a few key limitations of this pooled analysis of data from three real-world studies. First, study populations are not analogous, as

Table 3
Safety summary for patients treated with nivolumab in France and Germany.

Event, n (%)	All follow-up (N = 2116)			1-Year follow-up (N = 2116)		
	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5
Any TRAE	677 (32.0)	158 (7.5)	8 (<1)	662 (31.3)	150 (7.1)	6 (<1)
TRAE leading to discontinuation	162 (7.7)	NA	8 (<1)	89 (4.2)	NA	6 (<1)

Abbreviations: NA, not assessed; TRAE, treatment-related adverse event.

this is a combination of prospective and retrospective data. As such, patients from France and Germany consented to the collection of data that were not collected in the retrospective Canadian dataset, particularly PD-L1 expression and *EGFR* and *ALK* mutation status. The low rate of PD-L1 testing may be related to the approval of nivolumab for NSCLC regardless of PD-L1 status. As a result, the characteristics of patients at treatment initiation are reported only for patients who have these data recorded, and this may not reflect characteristics of the total population included in this study. The inconsistency in reporting across datasets also hampered the possibility of performing a multivariable analysis of characteristics identified as significant in the univariable analysis. Additionally, small sample sizes in some of the subgroups, including the never-smokers and patients with stage IIIB disease, may have impacted the OS rates, particularly at later time points when fewer patients were available for analysis. Lastly, in this real-world study, safety data were not as robustly collected as in clinical trials. It is therefore possible that safety data were underreported. However, rates of grade 3–4 TRAEs and TRAEs leading to discontinuation in this analysis were similar to reports from clinical trials, suggesting that the underreporting may be largely confined to lower-grade events. Appropriate management of adverse events associated with nivolumab is essential, particularly immune-mediated adverse events.

Different methods of determining follow-up time have other limitations. For example, use of observation time or censoring times to determine follow-up tends to underestimate follow-up time, whereas use of time to end-of-study, or known-function time methods, tend to overestimate actual follow-up. The median follow-up time for OS analysis was determined using Kaplan-Meier estimated potential follow-up or "reverse Kaplan-Meier", suggested by Schemper and Smith (1996) [10]. Because follow-up time is not consistently calculated across studies, it is difficult to make any cross-study comparisons even in cases in which reported follow-ups appear very similar.

Overall, this analysis demonstrated that OS outcomes in patients receiving nivolumab for previously treated advanced NSCLC in real-world clinical practice closely mirrored those in the pivotal global phase 3 studies, suggesting similar effectiveness of nivolumab in clinical study and real-world populations. Poor PS, presence of liver or bone metastases in the overall population, and *EGFR* mutations in patients with nonsquamous disease were associated with poor prognosis, whereas PD-L1 expression was associated with longer OS. These analyses contribute to the overall body of data regarding patients more likely to derive benefit from treatment with nivolumab.

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CRediT authorship contribution statement

All authors contributed to study conception, data acquisition, data interpretation, and drafting and revising the manuscript. Ariadna Juarez-Garcia, John R Penrod, and Victoria Allan contributed to study conception, data interpretation, drafting and revising the manuscript, and were responsible for data analysis.

Declaration of Competing Interest

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Appendix A. Supplementary data

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