Outcomes of first-line pembrolizumab monotherapy for PD-L1-positive (TPS $\geq 50\%$) metastatic NSCLC at US oncology practices

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Aim: To determine real-world outcomes with first-line pembrolizumab monotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor expression $\geq 50\%$. **Methods:** This retrospective study included adults with ECOG 0–1 initiating first-line pembrolizumab monotherapy on/after 24 October 2016 (EHR cohort) or from 1 December 2016 through 30 November 2017 (spotlight cohort) with ≥ 6 -month follow-up. We estimated Kaplan–Meier overall survival (OS, both cohorts), and, for spotlight, real-world progression-free survival (rwPFS) by Kaplan–Meier and real-world tumor response (rwTR). **Results:** For 423 patients in the EHR cohort and 188 in spotlight, median OS was 18.9 months (95% CI: 14.9–25.5) and 19.1 months (12.6-not reached), respectively. For spotlight, median rwPFS was 6.8 months (5.3–8.1); rwTR of complete/partial response was 48% (41–56%). **Conclusion:** Observed OS, rwPFS and rwTR were consistent with clinical trial findings.

Lay abstract: This study analyzed electronic health record data to determine outcomes for patients who received first-line pembrolizumab monotherapy for metastatic non-small-cell lung cancer. These patients received treatment at oncology clinics, not in a clinical trial, and had lung tumors with $\geq 50\%$ expression of the protein PD-L1. Although patients were older, on average, and included fewer men than in clinical trials, overall survival and tumor response rates resembled those recorded in the Phase III pivotal clinical trials, KEYNOTE-024 and -042, with median overall survival of 19 months, 12-month survival rate of 60% and tumor response rate of 48%.

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Randomized controlled trials (RCTs) provide important drug efficacy data because of high internal validity resulting from well-characterized, selective patient populations, random treatment assignment and protocol-defined clinical management [1]. In routine clinical practice, however, oncologists provide care for a heterogeneous patient population in an environment influenced by time constraints, socioeconomic factors, patient preferences and adherence. Moreover, observational data suggest that there are differences from RCTs in real-world patient characteristics [2–5] and potentially in outcomes as well [1,6]. Clinical questions thus arise regarding the effectiveness of therapies in real-world settings, as well as for patient populations under-represented in RCTs. The increased availability of high-quality observational data in the form of electronic health records (EHRs) can facilitate the study of real-world patient characteristics and outcomes to answer clinical questions, identify patient populations needing further study and develop hypotheses for further investigations [1,7–10].

Evidence from RCTs illustrates important advances in therapy for non-small-cell lung cancer (NSCLC) with the development of targeted therapies and immune checkpoint inhibitors of PD-1 and PD-L1 [11]. First-line monotherapy with the anti-PD-1 agent pembrolizumab for metastatic NSCLC (stage IV) was first approved by the US FDA in October 2016, based on KEYNOTE-024 (KN024) Phase III pivotal trial results, for tumors with

PD-L1 tumor proportion score (TPS) $\geq 50\%$ and no *EGFR* mutation or *ALK* rearrangement [12]. In a recently published update of KN024, median overall survival (OS) was 30.0 months (95% CI: 18.3–not reached [NR]) in the pembrolizumab arm (median treatment duration, 7.9 months) [13]. The KN042 pivotal trial further examined the use of pembrolizumab monotherapy for patients with locally advanced NSCLC or metastatic NSCLC and PD-L1 TPS $\geq 1\%$. In that trial, patients with PD-L1 TPS $\geq 50\%$ experienced median OS of 20.0 months (95% CI: 15.4–24.9) [14].

Anti-PD-(L)1 therapy for advanced NSCLC has been rapidly adopted in clinical practice in the USA [15]. Recently published observational studies of anti-PD-(L)1 therapy for NSCLC tend to be small [16–19] and/or to include a majority of patients receiving anti-PD-(L)1 therapy in second-line or later [5,20–22], likely because first-line pembrolizumab approval is so recent. In addition, few studies report tumor PD-L1 expression levels for all or a majority of studied patients [16–18]. Our aim was to describe clinical outcomes of first-line pembrolizumab monotherapy administered at US oncology practices for PD-L1-expressing (TPS $\geq 50\%$) metastatic NSCLC without *EGFR/ALK* aberrations, thus with the goal of studying a patient population clinically similar, with good performance status, to that enrolled in KN024 and the subpopulation of KN042 with locally advanced or metastatic NSCLC and PD-L1 TPS $\geq 50\%$.

Methods

Data source & patients

The datasets used for these retrospective analyses were drawn from the Flatiron Health longitudinal database comprising EHR data of patients with cancer in the USA [23]. At the time of the study, this database included 280 participating cancer clinics and over 2.1 million patients with active EHRs. The deidentified patient-level information derived from EHRs includes structured data, such as test results and prescribed drugs, and unstructured data, such as physicians' notes and radiology reports, collected via technology-enabled chart abstraction, as previously described [3,15,20]. Lines of therapy are identified using oncologist-defined, rule-based extraction, and the data are refreshed each month.

To be eligible for this study, adult patients (age ≥ 18 years) had received at least one dose of pembrolizumab as first-line therapy after pathological confirmation, recorded on or after 1 January 2011, of stage IV or recurrent metastatic NSCLC with PD-L1 TPS $\geq 50\%$ and no documented *EGFR* mutation or *ALK* or *ROS1* rearrangement. Patients included in the study had at least two clinic visits for NSCLC on or after 1 January 2011, recorded in the Flatiron Health database (as International Classification of Diseases [ICD]-9 code 162.x or ICD-10 code C34x or C39.9). Patients with <6 months of follow-up after pembrolizumab initiation or participating in a clinical trial were excluded, as were those with no EHR structured activity recorded within 90 days from the metastatic NSCLC diagnosis. We restricted all analyses to patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

Two datasets were used for this study. The EHR cohort included all patients from the Flatiron Health advanced NSCLC database meeting the above-listed eligibility criteria who initiated pembrolizumab on or after 24 October 2016 through 30 September 2018 (data cutoff 31 March 2019). The spotlight cohort included a random sample of patients in the database meeting the above-listed eligibility criteria who were selected for enhanced manual chart review to investigate outcomes of pembrolizumab monotherapy in greater detail. Patients in the spotlight cohort initiated pembrolizumab on or after 1 December 2016 through 30 November 2017, with data cutoff on 30 September 2018, to enable almost a full year of potential follow-up.

Ethical approval was obtained before study initiation from the Copernicus Group Institutional Review Board, including a waiver of informed consent for working with deidentified data. The data remained deidentified throughout the analyses to protect patient confidentiality. Flatiron Health, Inc. did not participate in the analysis of the data.

Study end points

For both study cohorts, we determined OS, defined as (date of death – start date of pembrolizumab [index date]) + 1 day, and censoring patients with no recorded date of death at the last contact date or end of the dataset, whichever occurred first. The Flatiron Health mortality 2.0 end point, a composite of structured and unstructured data from EHRs, external commercial sources, and the US Social Security Death Index, was used to identify the date of death [24,25]. Subsequent lines of systemic anticancer therapy were also determined in both study cohorts.

In addition, for patients in the spotlight cohort, enhanced manual chart review was used to capture real-world progression (rwP), real-world tumor response (rwTR) and reasons for pembrolizumab discontinuation. We defined rwP as a distinct episode in which the treating clinician concluded that there had been growth or worsening of NSCLC, as previously described [26,27]. In brief, to identify rwP episodes, the chart abstractors reviewed clinician notes chronologically beginning at the date of metastatic diagnosis to find notes describing progression either directly or indirectly (e.g., ‘the patient’s disease burden is worse’) and notes referring to source evidence describing progression, such as a radiology report describing new lesions, and including suspected pseudoprogression. Patients could have multiple progression records on different dates, and for each of these episodes of progression, abstractors reviewed relevant chart documentation to identify the first date on which progression was observed, as well as all source evidence. The rwP was then used to determine real-world progression-free survival (rwPFS), defined as the time from pembrolizumab initiation to the first documented rwP event or death from any cause, whichever occurred first and excluding events within 14 days after pembrolizumab initiation. Patients with no rwP were censored at their last clinic date, and those with no rwP starting a new line of therapy were censored at initiation of the new treatment.

We defined rwTR as an assessment of change in NSCLC tumor burden as indicated by radiology reports and occurring at least 30 days after pembrolizumab initiation. Chart abstractors captured the treating clinician’s assessment or interpretation of radiographic scans, directly or indirectly (e.g., ‘adenopathy is stable’), and mapped each assessment as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and other (pseudoprogression, indeterminate, not documented), as follows:

- CR: Complete resolution of all visible disease;
- PR: Disease still present, with partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease;
- SD: No change in overall size of visible disease or mixed response (some lesions increased, some lesions decreased);
- PD: Increase in visible disease and/or presence of any new lesions;
- Pseudoprogression: Increase in tumor size interpreted by the clinician as possible effect of immunotherapy;
- Indeterminate response: Explicit statement by clinician of inability to determine response;
- Not documented: Record of a radiology scan with no record of a clinician’s assessment of the scan.

The rwTR rate (rwTRR) was defined as the number and proportion of patients who had a CR or a PR, based on the rwTR assessment(s). For patients with multiple rwTR assessments during pembrolizumab therapy, the best response was used for rwTRR classification.

For patients who discontinued pembrolizumab, abstractors identified one or more reasons for pembrolizumab discontinuation from the following list: progression, adverse effect of therapy, disease-related symptoms not due to therapy, completed treatment, financial, patient request, no evidence of disease, unknown and other (the latter includes patients who remained on pembrolizumab until death in accordance with the need to maintain anonymized data).

To provide context to the retrospective database findings, we also report per-protocol OS and investigator-assessed PFS and tumor response estimates from clinical trials KN024 and KN042, restricting the KN042 findings to those for patients with PD-L1 $\geq 50\%$, the majority of whom had stage IV NSCLC [13,14,28,29].

Statistical analyses

A formal calculation of sample size and power was not performed because of the descriptive nature of the study. Baseline patient characteristics were summarized with mean (SD) or median (interquartile range [IQR]) to describe continuous variables, as appropriate, and count and percentage to describe categorical and count variables. In addition, the number and proportion of patients were calculated for the response categories of CR, PR, SD, PD and other (pseudoprogression, indeterminate, not documented).

Time-to-event analysis using the Kaplan–Meier method was used to estimate OS and rwPFS from the time of pembrolizumab initiation. The rwPFS analysis included pseudoprogression as a rwP event. In addition, a sensitivity analysis was conducted excluding pseudoprogression events.

Statistical analyses were performed using the R language for statistical computing, version 3.5.0 (R Core Team, 2018).

Figure 1. Patient selection for the EHR cohort from the Flatiron Health Database.

aNSCLC: Advanced non-small-cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; TPS: Tumor proportion score.

Results

Patients

Patient selection for the EHR cohort identified 1409 patients who initiated pembrolizumab monotherapy as first-line therapy for aNSCLC with no documented *EGFR*, *ALK* or *ROS1* aberration; and 861 patients (61%) had stage IV NSCLC with PD-L1 TPS $\geq 50\%$. Of these 861 patients, the 423 (49%) with recorded ECOG PS 0–1 are the subject of this report, in line with KEYNOTE trial eligibility criteria (Figure 1). For the spotlight cohort, 1875 patients with lung cancer who received pembrolizumab within the prespecified time period were randomly selected for enhanced manual chart review; of these, 402 (21%) had stage IV NSCLC and confirmed first-line pembrolizumab monotherapy, including 188/402 patients (47%) with confirmed PD-L1 TPS $\geq 50\%$ and ECOG PS 0–1 (Figure 2). We did not evaluate the extent of overlap between patients in the two cohorts.

The median age in both study cohorts was 72 years, and almost three-quarters of patients in both cohorts were ≥ 65 years old (Table 1). The EHR cohort included a greater percentage of men (54 vs 48% in spotlight cohort) and a greater percentage with ECOG PS of 1 (65 vs 57%). Other baseline characteristics of the two study cohorts

Figure 2. Patient selection for the spotlight cohort from the Flatiron Health Database.

ECOG PS: Eastern Cooperative Oncology Group performance status; EHR: Electronic health record; ICD: International Classification of Diseases; TPS: Tumor proportion score.

were mostly similar, although not compared statistically. Five patients (1%) in the EHR cohort received treatment at academic centers; all other patients in both cohorts received treatment at community oncology clinics.

Clinical outcomes

The length of observed follow-up from pembrolizumab initiation to data cutoff was a median of 18.4 months (range: 6.2–28.7 months) in the EHR cohort and 15.5 months (range: 10.0–22.1) in the spotlight cohort.

The median OS in the EHR and spotlight cohorts was 18.9 months (95% CI: 14.9–25.5) and 19.1 months (95% CI: 12.6–NR), respectively (Table 2). At 12 months, the survival rates were 59 and 60%, respectively (Table 2). The Kaplan–Meier results are depicted over time in Figure 3.

Table 1. Baseline demographic and clinical characteristics of patients with stage IV non-small-cell lung cancer, PD-L1 tumor proportion score $\geq 50\%$.

Variable	EHR cohort (n = 423)	Spotlight cohort (n = 188)
Male sex	228 (53.9)	90 (47.9)
Age, median (range), years	72 (45–84)	72 (46–84)
– <65 years	119 (28.1)	50 (26.6)
– 65–74 years	132 (31.2)	62 (33.0)
– ≥ 75 years	172 (40.7)	76 (40.4)
Race data available [†]	382 (90.3)	165 (87.8)
– White	299 (78.3)	127 (77.0)
– Black	33 (8.6)	16 (9.7)
– Asian	10 (2.6)	3 (1.8)
– Other race	40 (10.5)	19 (11.5)
US CB region, data available [†]	417 (98.6)	186 (98.9)
– Midwest	103 (24.7)	50 (26.9)
– Northeast	85 (20.4)	45 (24.2)
– South	176 (42.2)	71 (38.2)
– West	53 (12.7)	20 (10.8)
Current/former smoker	390 (92.2)	171 (91.0)
– No smoking history	33 (7.8)	17 (9.0)
CCI score, mean (SD)	3.2 (3.1)	3.4 (3.2)
– Median (range)	2 (0–11)	2 (0–9)
NSCLC histology		
– Nonsquamous	302 (71.4)	129 (68.6)
– NSCLC histology NOS	22 (5.2)	13 (6.9)
– Squamous	99 (23.4)	46 (24.5)
Stage IV at diagnosis	423 (100)	159 (84.6)
EGFR mutation status		
– Negative	355 (83.9)	162 (86.2)
– Indeterminate, unknown, pending, untested	68 (16.1)	26 (13.8)
ALK rearrangement status		
– Negative	349 (82.5)	156 (83.0)
– Indeterminate, unknown, pending, untested	74 (17.5)	32 (17.0)
ROS1 rearrangement status		
– Negative	299 (70.7)	129 (68.6)
– Indeterminate, unknown, pending, untested	124 (29.3)	59 (31.4)
PD-L1 percentage staining		
– 50–59%	66 (15.6)	32 (17.0)
– 60–69%	47 (11.1)	26 (13.8)
– 70–79%	57 (13.5)	26 (13.8)
– 80–89%	67 (15.8)	30 (16.0)
– 90–99%	129 (30.5)	51 (27.1)
– 100%	57 (13.5)	23 (12.2)
Immunohistochemistry clone, data available [†]	375 (88.7)	167 (88.8)
– 22C3 [‡]	352 (93.9)	155 (92.8)
– SP263	15 (4.0)	7 (4.2)
– Other	8 (2.1)	5 (3.0)

Data are n (%) unless otherwise indicated. Percentages may not add up to 100% because of rounding.

[†]Percentages for race, US CB and immunohistochemistry clone represent the percentages of patients with available data.

[‡]Of the 22C3 immunohistochemistry assays, 341/352 (96.9%) and 150/155 (96.8%) in EHR and spotlight cohorts, respectively, used the 22C3 pharmDx (Agilent Technologies, CA, USA; pembrolizumab companion diagnostic).

[§]Information about prior treatment of brain metastases was not available.

[¶]Corticosteroid administration or order (oral or systemic) within 2 days of pembrolizumab initiation.

CCI: Charlson comorbidity index; ECOG: Eastern Cooperative Oncology Group; NSCLC histology NOS: Non-small-cell lung cancer histology not otherwise specified; US CB: United States Census Bureau; SD: Standard deviation.

Table 1. Baseline demographic and clinical characteristics of patients with stage IV non-small-cell lung cancer, PD-L1 tumor proportion score $\geq 50\%$ (cont.).

Variable	EHR cohort (n = 423)	Spotlight cohort (n = 188)
ECOG performance status		
– 0	148 (35.0)	80 (42.6)
– 1	275 (65.0)	108 (57.4)
Record of brain metastases [§]		
– Yes	48 (11.3)	23 (12.2)
Corticosteroid order/administration [¶]		
– ≤ 2 days before pembrolizumab initiation	41 (9.7)	18 (9.6)

Data are n (%) unless otherwise indicated. Percentages may not add up to 100% because of rounding.
[†] Percentages for race, US CB and immunohistochemistry clone represent the percentages of patients with available data.
[‡] Of the 22C3 immunohistochemistry assays, 341/352 (96.9%) and 150/155 (96.8%) in EHR and spotlight cohorts, respectively, used the 22C3 pharmDx (Agilent Technologies, CA, USA; pembrolizumab companion diagnostic).
[§] Information about prior treatment of brain metastases was not available.
[¶] Corticosteroid administration or order (oral or systemic) within 2 days of pembrolizumab initiation.
 CCI: Charlson comorbidity index; ECOG: Eastern Cooperative Oncology Group; NSCLC histology NOS: Non-small-cell lung cancer histology not otherwise specified; US CB: United States Census Bureau; SD: Standard deviation.

Table 2. Outcomes with first-line pembrolizumab monotherapy.

Variable	Real-world cohorts [†]		Clinical trial data [‡]	
	EHR cohort (n = 423)	Spotlight cohort (n = 188)	KN024 (n = 154)	KN042, TPS $\geq 50\%$ [§] (n = 299)
Observed follow-up, median (range), mo [¶]	18.4 (6.2–28.7)	15.5 (10.0–22.1)	25.0 (20.4–33.7)	28.6 (18.3–43.9)
Patient follow-up, median (range), mo [¶]	11.3 (0.1–28.7)	11.8 (0.1–22.1)	22.0 (0.1–32.9)	18.9 (0.1–43.4)
rwTRR/TRR, n [#]	–	91	69	118
– % (95% CI)	–	48.4 (41.1–55.8)	44.8 (36.8–53.0)	39.5 (33.9–45.3)
– Time to response, median (range), mo	–	3.4 (0.5–16.7)	2.1 (1.4–14.6)	–
rwPFS/PFS [#]				
– Events, n (%)	–	123 (65.4)	111 (72.1)	245 (81.9)
– rwPFS/PFS, median (95% CI), mo	–	6.8 (5.3–8.1)	7.6 (6.0–10.0)	6.1 (5.7–8.2)
– 6-month rwPFS, % (95% CI)	–	53.6 (46.0–60.6)	–	–
– 12-month rwPFS/PFS, % (95% CI)	–	35.2 (28.1–42.3)	40.4 (32.5–48.1)	34.4 (29.0–39.8)
OS				
– Events, n (%)	193 (45.6)	80 (42.6)	73 (47.4)	180 (60.2)
– OS, median (95% CI), mo	18.9 (14.9–25.5)	19.1 (12.6–NR)	30.0 (18.3–NR)	20.0 (15.9–24.2)
– 6-month survival, % (95% CI)	74.0 (69.5–77.9)	74.3 (67.3–80.0)	–	–
– 12-month survival, % (95% CI)	59.1 (54.0–63.9)	60.4 (52.7–67.2)	70.3 (62.3–76.9)	63.5 (57.8–68.7)

[†] EHR cohort data cutoff, 31 March 2019; spotlight cohort data cutoff, 30 September 2018.

[‡] KN024 cutoff, 10 July 2017; KN042 cutoff, 4 September 2018 [13,14,28,29]. Investigator-assessed tumor response and PFS in the KEYNOTE trials are reported.

[§] Results from KN042 are reported for patients with PD-L1 TPS $\geq 50\%$ with locally advanced or metastatic NSCLC, the majority of whom had metastatic NSCLC (n = 275; 92%).

[¶] Observed follow-up was defined as the duration of follow-up from pembrolizumab initiation (in EHR data) or randomization (in KN clinical trials) to database cutoff. Patient follow-up was defined as time from pembrolizumab initiation (in EHR data) or randomization (in the clinical trials) to the date of death or data cutoff, whichever occurred first.

[#] rwTRR refers to the real-world tumor response rate, defined as complete response + partial response, and rwPFS to real-world progression-free survival (see the Methods section), while TRR and PFS refer to investigator-assessed tumor response rate (objective response) and progression-free survival, respectively, in KN024 and KN042 (prespecified exploratory end points [UNPUBLISHED DATA]) [13,14,28,29]. The objective response in KN024/KN042 is defined as investigator-assessed complete or partial response per RECIST. KN: KEYNOTE trial; mo: Month; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; RECIST: Response evaluation criteria in solid tumors; rwPFS: Real-world PFS; rwTRR: Real-world tumor response rate; TPS: Tumor proportion score.

In the EHR cohort, 114 patients (27%) received second-line therapy, most commonly platinum-based chemotherapy combination or anti-PD-(L)1-based therapy, and 23 (5%) continued to third-line therapy, most commonly with single agent chemotherapy (Table 3). Five and two patients received fourth-line and fifth-line therapy, respectively. In the spotlight cohort, 53 (28%) continued to second-line systemic therapy, most commonly a platinum-based chemotherapy combination or anti-PD-(L)1-based therapy; and 13 patients (7%) continued to third-line therapy (Table 3). Three and one patients received fourth-line and fifth-line therapy, respectively.

Figure 3. Kaplan–Meier estimates of overall survival and real-world progression-free survival from the time of pembrolizumab initiation. (A) OS in the EHR cohort, (B) OS in the spotlight cohort and (C) rwPFS in the spotlight cohort.
 mo: Month; NR: Not reached; OS: Overall survival; rwPFS: Real-world progression-free survival.

Spotlight cohort: rwP & rwTR

In the spotlight cohort, the median rwPFS was 6.8 months (95% CI: 5.3–8.1 months), with 123 patients (65%) experiencing an episode of rwP or death from any cause (Table 2 & Figure 3C). In the sensitivity analysis excluding rwP events assessed as pseudoprogression, the median rwPFS was 7.3 months (95% CI: 6.1–8.8 months), with 117 patients (62%) experiencing an episode of rwP or death.

Ninety-one patients (48%) had a best rwTR assessed as CR ($n = 12$; 6%) or PR ($n = 79$; 42%), as summarized in Table 4. A total of 116 patients (62%) experienced disease control (CR + PR + SD).

A total of 111 patients (59%) discontinued pembrolizumab in the spotlight cohort, including approximately half because of disease progression (52/111; 47%) and a quarter because of adverse effects of therapy (29/111; 26%; Table 5).

Discussion

In this retrospective observational study, we found that real-world outcomes of first-line pembrolizumab monotherapy for patients with metastatic NSCLC, with PD-L1 TPS $\geq 50\%$ and no documented *EGFR/ALK/ROS1* aberration, were consistent with those of clinically similar patients enrolled in KN024 and KN042 pivotal trials. Most of these patients with metastatic NSCLC received pembrolizumab at US community oncology practices (vs academic clinics), where anti-PD-(L)1 therapies have been rapidly adopted [15]. Survival rates in the two real-world cohorts at

Table 3. Subsequent lines of systemic anticancer therapy.

Variable	EHR (n = 423)	Spotlight (n = 188)
Second-line systemic therapy, n (%)	114 (27.0)	53 (28.2)
– Platinum-based chemotherapy combination [†]	42 (9.9)	21 (11.2)
– Anti-PD-(L)1-based combination therapy	21 (5.0)	9 (4.8)
– Anti-PD-(L)1 monotherapy	17 (4.0)	5 (2.7)
– Single agent chemotherapy	10 (2.4)	10 (5.3)
– Anti-VEGF-based combination therapy	20 (4.7)	7 (3.7)
– Nonplatinum-based chemotherapy combination	2 (0.5)	1 (0.5)
– Tyrosine kinase inhibitor	2 (0.5)	0
Third-line systemic therapy, n (%)	23 (5.4)	13 (6.9)
– Platinum-based chemotherapy combination [†]	5 (1.2)	3 (1.6)
– Anti-PD-(L)1-based combination therapy	1 (0.2)	1 (0.5)
– Anti-PD-(L)1 monotherapy	4 (0.9)	4 (2.1)
– Single agent chemotherapy	8 (1.9)	3 (1.6)
– Anti-VEGF-based combination therapy	2 (0.5)	0
– Non-platinum-based chemotherapy combination	1 (0.2)	0
– Tyrosine kinase inhibitor	2 (0.5)	2 (1.1)
Fourth-line systemic therapy, n (%)	5 (1.2)	3 (1.6)
– Platinum-based chemotherapy combination [†]	1 (0.2)	1 (0.5)
– Anti-PD-(L)1 monotherapy	2 (0.5)	1 (0.5)
– Single agent chemotherapy	1 (0.2)	0
– Tyrosine kinase inhibitor	1 (0.2)	1 (0.5)
Fifth-line systemic therapy, n (%)	2 (0.5)	1 (0.5)
– Platinum-based chemotherapy combination	2 (0.5)	1 (0.5)

[†]Platinum-based chemotherapy combinations without anti-VEGF agent.

Table 4. Best real-world tumor response to first-line pembrolizumab monotherapy: spotlight cohort.

	Spotlight (n = 188)
CR	12 (6.4)
PR	79 (42.0)
SD	25 (13.3)
PD	29 (15.4)
No evaluable assessment	43 (22.9)
– Indeterminate	11 (5.9)
– Pseudoprogression	11 (5.9)
– Not documented	23 (12.2)

Data are n (%).

For the patients with multiple rwTR assessments, the best response was used to classify the patient (CR > PR > SD > PD). Patients without an evaluable assessment (no CR, PR, SD or PD) could be counted more than one time in the subcategories of 'no evaluable assessment'.

CR: Complete response; PD: Progressive disease; PR: Partial response; rwTR: Real-world tumor response; SD: Stable disease.

12 months (59.1 and 60.4%) were similar to that in the KN042 subpopulation with locally advanced or metastatic NSCLC with PD-L1 TPS $\geq 50\%$ (63.5%) [29]. While median OS of approximately 19 months in EHR and spotlight cohorts was shorter than in KN024 (30 months) [13], it was similar to that for the KN042 subpopulation (20 months) [29].

The use of enhanced manual chart review enabled us to investigate outcomes of first-line pembrolizumab monotherapy in greater detail for the 188 patients in the spotlight cohort, for whom the rwPFS (median: 6.8 months) was similar to PFS as assessed by investigators in KN024 and the KN042 subpopulation with PD-L1 TPS $\geq 50\%$, with PFS medians of 7.6 and 6.1 months, respectively (Data on File [28,29]). The proportion of patients with rwTR (48%) was similar to proportions with investigator-assessed tumor response in the pivotal trials as well (45 and 40%, respectively). The real-world end points in the current study most closely resemble the investigator-assessed end

Table 5. Summary of reasons for pembrolizumab discontinuation: spotlight cohort.	
	Spotlight (n = 188)
Discontinued, n (%)	111 (59.0)
Reasons for discontinuation, n (%)	N = 111 [†]
– Progression	52 (46.8)
– Adverse effect of therapy	29 (26.1)
– Disease-related symptoms not due to therapy	17 (15.3)
– Patient request	4 (3.6)
– Other [‡]	14 (12.6)
– Unknown	1 (0.9)

[†]Patients could have more than one reason for discontinuation.
[‡]For patients with ongoing treatment until the time of death, the reason recorded was ‘Other’ to comply with data deidentification requirements.

points in clinical trials, which thus provide the most appropriate context for the real-world findings. Nonetheless, we acknowledge that our findings are likely less precise than prospectively gathered information on PFS and tumor response by investigators in clinical trials. Moreover, patient follow-up in our study was considerably shorter than follow-up to date in KN024 and KN042 [13,14,29].

The determination of OS for both EHR and spotlight cohorts employed the recently validated Flatiron Health mortality 2.0 end point to identify date of death [24,25]. The rwTR and rwP end points were derived from a combination of structured data and unstructured data such as physicians’ notes and radiology reports and were developed for different clinical context and analytical applications; therefore, the progression events in these two variables could differ. Namely, the rwTR end point considered only radiologic evidence, while rwP captured other types of evidence (e.g., pathology, physical examination) and included progression events that were based only on clinician assessment (i.e., without supporting radiologic evidence). The determination of rwP events in patients with lung cancer from the Flatiron Health database has recently been assessed as feasible and replicable, providing an intermediate end point for use in retrospective database studies, although not directly comparable with trial-based progression events assessed by blinded review using RECIST (response evaluation criteria in solid tumors) [26,27]. Furthermore, in sensitivity analyses, Griffith *et al.* [27] examined the impact of censoring on correlations between OS and the real-world end points, including rwPFS, and they reported slight variability in the correlation of these end points with OS but consistency in magnitude and direction with the primary analysis.

Disease progression was the most common reason for pembrolizumab discontinuation in the spotlight cohort. In an earlier study, we investigated the real-world time on treatment (rwToT) for a similar cohort of patients identified in the Flatiron Health database as receiving first-line pembrolizumab monotherapy for mNSCLC with PD-L1 TPS ≥50% and no documented *EGFR/ALK/ROS1* aberrations [30]. The rwToT definition draws on structured EHR data and is the same as that of time to treatment discontinuation used in a recent analysis of NSCLC clinical trials and proposed for use as a pragmatic end point in light of its association with PFS across NSCLC therapeutic classes [31]. Interestingly, we found broad similarity in median rwToT for 386 patients with ECOG PS of 0–1 in the prior study (6.9 months; 95% CI: 5.6–8.3) and the median rwPFS recorded for the spotlight cohort (6.8 months; 95% CI: 5.3–8.1) [30]. While Flatiron Health data privacy rules prohibit an assessment of patient overlap between the EHR and spotlight cohorts, we note that 359/423 (85%) patients in the EHR cohort of the present study were also included in the EHR cohort with ECOG 0–1 of the prior study, thus most of that prior cohort (359/386, or 93%). Therefore, because of similar eligibility criteria for EHR and spotlight cohorts in the present study, there was likely substantial overlap between patients with ECOG PS of 0–1 in the prior study and the spotlight cohort in the present study.

We selected our EHR and spotlight patient populations to be clinically similar with regard to tumor characteristics and ECOG PS to those in KN024 and KN042 (subpopulation with PD-L1 TPS ≥50%). However, there were notable demographic differences from the clinical trials, as the real-world cohorts tended to be older and included a greater percentage of women [13,14]. These characteristics align with those reported in the early years after pembrolizumab approval, with real-world populations including proportionately more women and older patients than in the pivotal trials [3,15]. Sex and age disparities relative to real-world populations are not unique to pembrolizumab clinical trials, as similar disparities have been reported for prior lung cancer trials sponsored by the National Cancer Institute [2] as well as oncology registration trials in general [32]. Indeed, two-thirds of lung cancer diagnoses in

the USA are made in patients older than 65 years [33,34]. Thus, there are concerns that these older patients may be more likely to experience adverse events associated with anti-PD-(L)1 therapy. In our study, enhanced manual chart review identified 29 (15%) of patients in the spotlight cohort who discontinued pembrolizumab because of treatment-related adverse effects. In recent small observational studies, there was no indication that patients ≥ 75 years old experienced greater incidence of adverse events related to anti-PD-(L)1 therapy [16,19]. Moreover, preliminary data suggest that older patients can derive similar benefits from pembrolizumab and nivolumab therapy as younger patients [16,17,19,20,22,35].

A strength of our study is the inclusion of two large, well-characterized patient populations administered first-line pembrolizumab monotherapy for mNSCLC. Eligibility criteria required a minimum of 6 months' potential follow-up after pembrolizumab initiation, and individual patients were followed for a median of almost 1 year in both EHR and spotlight cohorts. We drew on a well-managed, geographically representative EHR-derived database that has been developed for clinical research and frequently used to study patients with NSCLC [15,20–23]. The majority of patients in our study were treated at community oncology practices, the most common treatment setting for cancer in the USA. Study results may not be generalizable to patients treated at academic medical centers, where management practices may differ. In addition, we found that many patients were rechallenged with anti-PD-(L)1 monotherapy or combination therapy in second line and later, an approach that is not in line with guideline recommendations [36]. Therefore, similar to findings in other observational studies, our findings suggest that real-world prescribing does not always follow guidelines.

While enhanced manual chart review enabled us to characterize rwTR and rwPFS for the spotlight cohort, 43 patients (23%) had no evaluable assessment for rwTR. Other data points that were not available in this EHR-derived study include details of adverse events (type and severity) and the frequency of computed tomography imaging. Other limitations of this study include those common to all retrospective database studies, including the potential for errors in data recording, EHR data gathering and EHR interpretation, the latter particularly applicable to enhanced manual chart review. Moreover, there is the potential for selection bias, as we included only patients with recorded PD-L1 TPS and ECOG PS, excluding patients with missing data for those two variables.

Further research is needed to evaluate the outcomes in clinical settings of pembrolizumab therapy, both as monotherapy and in combination with platinum-based chemotherapy, for different and larger patient populations, including those with poor performance status (ECOG PS ≥ 2), who may experience inferior survival (vs ECOG PS 0–1) [17,35]. In addition, further work is needed to evaluate the relationship between rwP events and OS, as well as with the rwTR end point.

Conclusion

In real-world oncology practice, patients prescribed first-line pembrolizumab monotherapy for PD-L1-expressing (TPS $\geq 50\%$) metastatic NSCLC tend to be older and include fewer men than in clinical trials, even after limiting to key trial eligibility criteria, such as good performance status. The outcomes observed, including OS, rwPFS and rwTR, were consistent with pivotal trial findings, supporting the effectiveness of first-line pembrolizumab monotherapy in real-world settings. Continued research is needed to investigate short- and long-term outcomes of anti-PD-(L)1 therapies for the heterogeneous patient populations with NSCLC requiring care in clinical practice.

Author contributions

V Velcheti, S Chandwani, B Piperdi and T Burke were responsible for the conception and design of the study. X Chen performed the data analysis. V Velcheti, S Chandwani, X Chen, MC Pietanza, B Piperdi and T Burke were responsible for the interpretation of findings, critical review and revision of the manuscript. All the authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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and/or consultant role for Merck, Bristol-Myers Squibb, Genentech, AstraZeneca, Celgene, Novartis, Amgen, Fulgent Genetics, Reddy Labs, Alkermes, Nektar Therapeutics, Novocure, and Foundation Medicine. S Chandwani, X Chen, MC Pietanza, B Piperdi and T Burke are full-time employees of MSD and own stock of Merck & Co., Inc., Kenilworth, NJ, USA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The deidentified dataset supporting the conclusions of this article was provided by Flatiron Health. Ethical approval was obtained before study initiation from the Copernicus Group Institutional Review Board, including a waiver of informed consent for working with deidentified data. The data remained deidentified throughout the analyses to protect patient confidentiality.

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Summary points

- Immune checkpoint inhibitors of PD-1 have been rapidly adopted in clinical practice for therapy of metastatic non-small-cell lung cancer; however, the outcomes of anti-PD-1 therapy are poorly understood for heterogeneous patient populations with metastatic NSCLC in real-world settings outside of clinical trials.
- This retrospective observational study investigated the outcomes of first-line pembrolizumab monotherapy for metastatic NSCLC with PD-L1 tumor proportion score (TPS) $\geq 50\%$ at community oncology practices in the USA using technology-enabled abstraction from deidentified electronic health records (EHR cohort) along with enhanced manual chart review (spotlight cohort).
- Eligible patients were adults (≥ 18 years old) with diagnosis after 1 January 2011, of pathologically confirmed metastatic NSCLC with PD-L1 TPS $\geq 50\%$ and no documented *EGFR/ALK/ROS1* aberration, ECOG performance status 0–1 and ≥ 6 months' follow-up after pembrolizumab initiation on or after 24 October 2016 (EHR cohort) or from 1 December 2016 through 30 November 2017 (spotlight cohort).
- Overall survival was calculated by the Kaplan–Meier method (both cohorts); and we also estimated (for spotlight cohort only) real-world progression-free survival by the Kaplan–Meier and real-world tumor response.
- Median follow-up was 18.4 months (range: 6.2–28.7 months) in the EHR cohort ($n = 423$; median age: 72 years, 54% men) and 15.5 months (range: 10.0–22.1 months) in the spotlight cohort ($n = 188$; median age: 72, 48% men) from pembrolizumab initiation to data cutoff (31 March 2019 and 30 September 2018, respectively).
- Median overall survival was 18.9 months (95% CI: 14.9–25.5) and 19.1 months (95% CI: 12.6–not reached) in EHR and spotlight cohorts, respectively, with 12-month survival rates of 59 and 60%.
- In the spotlight cohort, median real-world progression-free survival was 6.8 months (95% CI: 5.3–8.1), and 91 patients (48%; 95% CI: 41–56%) experienced real-world tumor response of complete or partial response.
- For 111 patients (59%) who discontinued pembrolizumab in the spotlight cohort, the most common reasons for discontinuation were disease progression (52 [47%]) and therapy-related adverse effects (29 [26%]).
- At US oncology practices, patients with good performance status prescribed first-line pembrolizumab monotherapy for metastatic NSCLC with PD-L1 TPS $\geq 50\%$ include proportionately more women and are older than those in clinical trials but experience similar outcomes of therapy.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Sherman RE, Anderson SA, Dal Pan GJ *et al.* Real-world evidence – what is it and what can it tell us? *N. Engl. J. Med.* 375(23), 2293–2297 (2016).
2. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA* 291(22), 2720–2726 (2004).
3. Khozin S, Abernethy AP, Nussbaum NC *et al.* Characteristics of real-world metastatic non-small cell lung cancer patients treated with nivolumab and pembrolizumab during the year following approval. *Oncologist* 23(3), 328–336 (2018).
4. Sacher AG, Le LW, Leighl NB, Coate LE. Elderly patients with advanced NSCLC in Phase III clinical trials: are the elderly excluded from practice-changing trials in advanced NSCLC? *J. Thorac. Oncol.* 8(3), 366–368 (2013).
5. Hendriks LEL, Henon C, Auclin E *et al.* Outcome of patients with non-small cell lung cancer and brain metastases treated with checkpoint inhibitors. *J. Thorac. Oncol.* 14(7), 1244–1254 (2019).

6. Prince RM, Atenafu EG, Krzyzanowska MK. Hospitalizations during systemic therapy for metastatic lung cancer: a systematic review of real world vs clinical trial outcomes. *JAMA Oncol.* 1(9), 1333–1339 (2015).
7. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *J. Natl Cancer Inst.* 109(11), dx187 (2017).
- **Review of the sources of real-world data, the advantages and challenges of analyzing real-world data, and recommendations for working with real-world data.**
8. Miller RS, Wong JL. Using oncology real-world evidence for quality improvement and discovery: the case for ASCO's CancerLinQ. *Future Oncol.* 14(1), 5–8 (2018).
9. Berger ML, Curtis MD, Smith G, Harnett J, Abernethy AP. Opportunities and challenges in leveraging electronic health record data in oncology. *Future Oncol.* 12(10), 1261–1274 (2016).
10. Friends of Cancer Research. Real-World Evidence: Pilot Project 2.0: establishing the utility of real-world endpoints. <https://www.focr.org/rwe>
- **Current, ongoing initiative by the Friends of Cancer Research, and involving multiple key stakeholders, to establish the utility of real-world end points for studies of approved cancer therapies.**
11. Abdel Karim N, Kelly K. Role of targeted therapy and immune checkpoint blockers in advanced non-small cell lung cancer: a review. *Oncologist* 24(9), 1270–1284 (2019).
12. Reck M, Rodriguez-Abreu D, Robinson AG *et al.* Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* 375(19), 1823–1833 (2016).
13. Reck M, Rodriguez-Abreu D, Robinson AG *et al.* Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J. Clin. Oncol.* 37(7), 537–546 (2019).
- **Recent update of findings through July 2017 of the KEYNOTE-024 clinical trial, studying pembrolizumab therapy for patients with stage IV non-small-cell lung cancer (NSCLC) with PD-L1 tumor proportion score (TPS) $\geq 50\%$ and no sensitizing *EGFR* mutation or *ALK* translocation, and from which patient-level data are reported in this article.**
14. Mok TSK, Wu YL, Kudaba I *et al.* Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, Phase III trial. *Lancet* 393(10183), 1819–1830 (2019).
- **Recently published results of the KEYNOTE-042 trial, from which patient-level data for those with advanced NSCLC with PD-L1 TPS $\geq 50\%$ and no sensitizing *EGFR* mutation or *ALK* translocation are reported in this article.**
15. O'Connor JM, Fessele KL, Steiner J *et al.* Speed of adoption of immune checkpoint inhibitors of programmed cell death 1 protein and comparison of patient ages in clinical practice vs pivotal clinical trials. *JAMA Oncol.* 4(8), e180798 (2018).
16. Ksienski D, Wai ES, Croteau N *et al.* Pembrolizumab for advanced nonsmall cell lung cancer: efficacy and safety in everyday clinical practice. *Lung Cancer* 133, 110–116 (2019).
17. Ahn BC, Pyo KH, Xin CF *et al.* Comprehensive analysis of the characteristics and treatment outcomes of patients with non-small cell lung cancer treated with anti-PD-1 therapy in real-world practice. *J. Cancer Res. Clin. Oncol.* 145(6), 1613–1623 (2019).
18. Lin SY, Yang CY, Liao BC *et al.* Tumor PD-L1 expression and clinical outcomes in advanced-stage non-small cell lung cancer patients treated with nivolumab or pembrolizumab: real-world data in Taiwan. *J. Cancer* 9(10), 1813–1820 (2018).
19. Sattar J, Kartolo A, Hopman WM, Lakoff JM, Baetz T. The efficacy and toxicity of immune checkpoint inhibitors in a real-world older patient population. *J. Geriatr. Oncol.* 10(3), 411–414 (2019).
20. Khozin S, Carson KR, Zhi J *et al.* Real-world outcomes of patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors in the year following U.S. regulatory approval. *Oncologist* 24(5), 648–656 (2019).
21. Schwartzberg L, Korytowsky B, Penrod JR *et al.* Real-world clinical impact of immune checkpoint inhibitors in patients with advanced/metastatic non-small cell lung cancer after platinum chemotherapy. *Clin. Lung Cancer* 20(4), 287–296 e284 (2019).
22. Khozin S, Miksad RA, Adami J *et al.* Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. *Cancer* 125(22), 4019–4032 (2019).
- **Recent study describing treatment patterns, patient characteristics, PD-L1 testing rates and outcomes for 5257 patients prescribed a PD-L1 inhibitor for advanced NSCLC in the USA through June 2017, with minimum of 6 months' follow-up.**
23. Flatiron Health Database. <https://flatiron.com/real-world-evidence/>
24. Curtis MD, Griffith SD, Tucker M *et al.* Development and validation of a high-quality composite real-world mortality endpoint. *Health Serv. Res.* 53(6), 4460–4476 (2018).
25. Carrigan G, Whipple S, Taylor MD *et al.* An evaluation of the impact of missing deaths on overall survival analyses of advanced non-small cell lung cancer patients conducted in an electronic health records database. *Pharmacoepidemiol. Drug Saf.* 28(5), 572–581 (2019).
26. Griffith SD, Tucker M, Bowser B *et al.* Generating real-world tumor burden endpoints from electronic health record data: comparison of RECIST, radiology-anchored, and clinician-anchored approaches for abstracting real-world progression in non-small cell lung cancer. *Adv. Ther.* 36(8), 2122–2136 (2019).

27. Griffith SD, Miksad RA, Calkins G *et al.* Characterizing the feasibility and performance of real-world tumor progression end points and their association with overall survival in a large advanced non-small-cell lung cancer data set. *JCO Clin. Cancer Inform.* 3, 1–13 (2019).
- **Study evaluating real-world progression-free survival, one of the real-world end points used in the current study, and its association with overall survival.**
28. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. KEYNOTE-024 Trial Data on File (data cutoff July 10, 2017), ClinicalTrials.gov identifier: NCT02142738.
29. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. KEYNOTE-042 Trial Data on File (data cutoff September 4, 2018), ClinicalTrials.gov identifier: NCT02220894.
30. Velcheti V, Chandwani S, Chen X, Pietanza MC, Burke T. First-line pembrolizumab monotherapy for metastatic PD-L1-positive NSCLC: real-world analysis of time on treatment. *Immunotherapy* 11(10), 889–901 (2019).
31. Blumenthal GM, Gong Y, Kehl K *et al.* Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer. *Ann. Oncol.* 30(5), 830–838 (2019).
32. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. *J. Clin. Oncol.* 30(17), 2036–2038 (2012).
33. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J. Clin.* 69(1), 7–34 (2019).
34. Barta JA, Zinner RG, Unger M. Lung cancer in the older patient. *Clin. Geriatr. Med.* 33(4), 563–577 (2017).
35. Dudnik E, Moskovitz M, Daher S *et al.* Effectiveness and safety of nivolumab in advanced non-small cell lung cancer: the real-life data. *Lung Cancer* 126, 217–223 (2018).
36. NCCN. NCCN Clinical Practice Guidelines in Oncology: non-small cell lung cancer, version 7.2019. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp