Pembrolizumab Plus Chemotherapy Per PD-L1 Stratum In Patients With Metastatic Non–Small Cell Lung Cancer: Real-World Effectiveness Versus Trial Efficacy

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Abstract

This study assessed the real-world survival outcomes of first-line pembrolizumab plus chemotherapy per PD-L1 stratum in nonsquamous (n = 269) and squamous (n = 117) mNSCLC patients and compared these outcomes to those observed in the clinical trial. Nonsquamous patients with PD-L1 <1% treated with pembrolizumab plus chemotherapy had considerably shorter OS in the real-world compared to the trial (10 vs. 17.2 months). No survival differences were observed in other PD-L1 strata.

Background: Clinical trial efficacy and real-world effectiveness of oncological treatments can differ. This study assessed the real-world survival outcomes of first-line pembrolizumab plus chemotherapy per PD-L1 stratum in patients with metastatic non–small cell lung cancer (mNSCLC) and compared them to clinical trial results. **Patients and Methods:** All patients with nonsquamous and squamous mNSCLC who received first-line pembrolizumab plus chemotherapy in 7 Dutch teaching hospitals between January 1, 2019 and December 31, 2021 were included. Hazard ratios (HR) with confidence intervals (95% CI) for overall survival (OS) and progression-free survival (PFS) were estimated to determine the efficacy-effectiveness gap (EE gap) between real-world and clinical trial, stratified by PD-L1 stratum. **Results:** The nonsquamous cohort (n = 486) consisted of 269 patients with PD-L1 < 1%, 158 with PD-L1 1% to 49%, and 59 with PD-L1 ≥ 50%. The squamous cohort (n = 117) consisted of 70 patients with PD-L1 < 1% and 47 with PD-L1 ≥ 1%. For OS, an EE gap was observed in nonsquamous patients with PD-L1 < 1% (HR 1.38 (95% CI 1.06-1.78; median OS 10 vs. 17.2 months) and HRs consistently >1 in all other nonsquamous and squamous PD-L1 strata, although not statistically significant. No EE-gap for PFS was observed in any stratum. **Conclusion:** No significant EE gap was found for pembrolizumab plus chemotherapy, except in the stratum nonsquamous mNSCLC with <1% PD-L1 tumor expression. In these patients, the survival in real-world was considerably shorter compared to the clinical trial results. Further studies are needed to determine which patient, treatment and or context factors contribute to this disparity.

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Introduction

Approximately 1 million patients are worldwide diagnosed with metastatic non–small-cell lung cancer (NSCLC) each year.[1] The introduction of immune checkpoint inhibitors targeting PD-1/PD-L1, such as pembrolizumab, nivolumab, atezolizumab, and cemiplimab, has improved the survival outcomes for metastatic NSCLC patients without oncogenic driver mutations.[2]

The KEYNOTE-189 and KEYNOTE-407 trials evaluated the use of pembrolizumab in combination with chemotherapy as a first-

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line treatment option for metastatic NSCLC patients.[3,4] Both trials demonstrated that pembrolizumab plus chemotherapy improved survival outcomes compared to chemotherapy alone, regardless of PD-L1 expression. In addition, for patients with a high PD-L1 expression (PD-L1 $\geq$ 50%) the KEYNOTE-042 trial reported improved survival outcomes with pembrolizumab as monotherapy.[5] As a result, current guidelines[6] recommend pembrolizumab plus chemotherapy in patients with no (PD-L1 < 1%) or intermediate (PD-L1 1%-49%) PD-L1 expression. For patient with high PD-L1 expression (PD-L1 $\geq$ 50%), pembrolizumab monotherapy is recommended, unless a rapid tumor response is required, in which pembrolizumab plus chemotherapy may be considered.

Treatment effects observed in clinical trials may differ from effects observed in clinical practice, also known as the efficacy-effectiveness gap (EE gap).[7,8] Recently, a systematic evaluation of the EE gap of systemic treatments in metastatic NSCLC (n = 1063) revealed a median OS (mOS) being approximately 30% shorter in clinical practice compared to the corresponding clinical trials.[8] This EE gap was consistently observed for all chemotherapy regimens studied. Now that pembrolizumab is added to chemotherapy, a similar EE gap may exist. Because the choice of treatment regimen is based on PD-L1 status, an appropriate assessment of an EE gap should be conducted per PD-L1 stratum to prevent selection bias.

The objective of the present study is to assess the real-world survival outcomes of pembrolizumab plus chemotherapy per PD-L1 stratum of patients with nonsquamous and squamous metastatic NSCLC and compare these outcomes to the clinical trial results.

Methods

Study Design, Setting, and Participants

This study was a multicenter cohort study conducted in the Santeon group, a network of 7 large nonuniversity teaching hospitals spread geographically over the Netherlands and serving approximately 15% of the Dutch population. Eligible patients were identified in the "Santeon Farmadatabase", a database that contains prospectively documented individual patient data on drug prescriptions and diagnoses for all patients treated within one of the participating hospitals.[9] For this study, patients were selected if they were diagnosed with metastatic NSCLC without EGFR or ALK genomic aberrations and had received at least 1 cycle of pembrolizumab plus chemotherapy as first line treatment between January 1, 2019 and December 31, 2021. The index date was defined as the date of the first pembrolizumab administration. Subsequently, the electronic health records from all selected patients were manually reviewed to collect baseline characteristics (30 days before and after diagnosis), treatment characteristics and follow-up outcomes. The last date of follow-up was August 1, 2022. The PD-L1 status, measured through immunohistochemistry, was collected from the electronic health records, and patients without an assessable PD-L1 status were excluded at this stage. To compare findings with the relevant corresponding KEYNOTE clinical trials, the study population was split into 2 cohorts. The nonsquamous cohort included patients with nonsquamous histological subtypes who received pembrolizumab plus pemetrexed-platinum. The squamous cohort included patients with squamous or unknown histological subtypes who received pembrolizumab plus paclitaxel-platinum. The construction of the cohorts is schematically depicted in Figure 1. Patients were stratified based on PD-L1 status within both cohorts, allowing for a comparison with the corresponding strata in the trials.

Outcomes

The primary outcome measures were overall survival (OS) and progression-free survival (PFS). The OS was calculated from the index date till the date of death or censoring. Date of censoring was the last clinic visit before the end of follow-up (August 1, 2022). PFS was calculated from the index date till the date of disease progression, death, or censoring, whichever occurred first. Progression of disease was determined according to local protocols including semistandardized response assessment schemes, where the first radiological response assessment was scheduled 6 to 9 weeks after treatment initiation and whenever feasible (immune) Response Evaluation Criteria in Solid Tumors (RECIST) were applied. In this study, the date of disease progression was defined as the date of the first medical note of the thoracic oncologist stating that the disease had progressed.

Patient and Treatment Characteristics

The following patient and treatment characteristics were collected for every patient; age at diagnosis, sex, body mass index, Eastern Cooperative Oncology Group-Performance status (ECOG PS), histological subtype, presence of brain metastasis, the type of platinum-based chemotherapy (cisplatin or carboplatin), the number of cycles of platinum-based chemotherapy, the treatment duration of pembrolizumab, and whether or not further lines of treatment have been initiated.

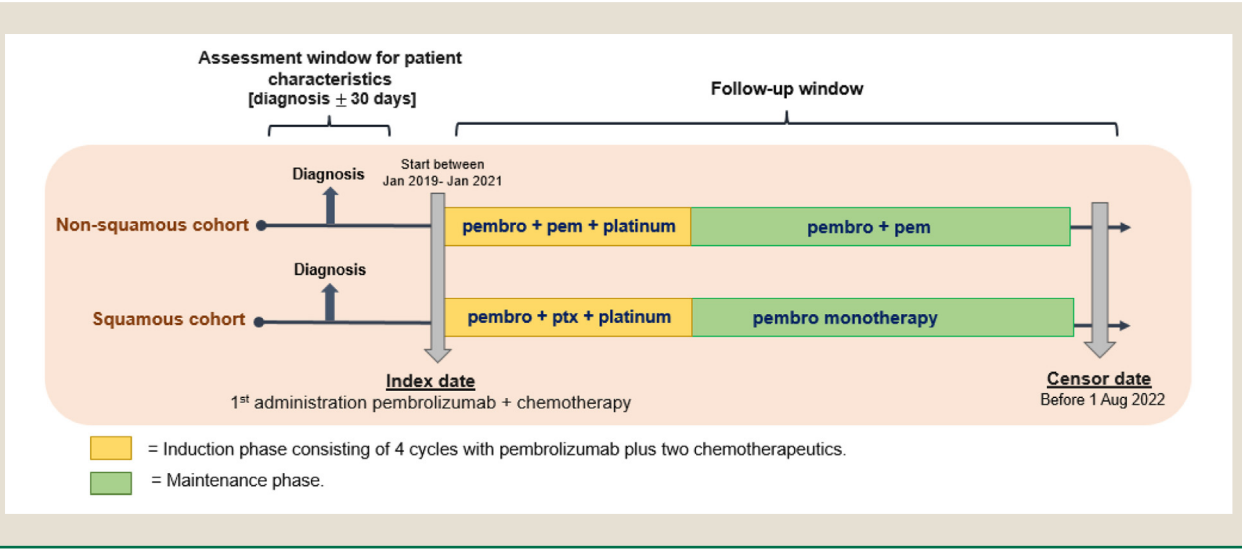
Data Analysis

Statistical software (R version 4.1.2) was used to conduct the data analysis. The patient and treatment characteristics were presented and compared between the real-world PD-L1 strata within the nonsquamous and squamous cohorts, using $\chi 2$, Student *t*-tests, Wilcoxson rank sum test, and fisher exact tests when appropriate. Notably, in absence of PD-L1 stratified patient data from the clinical trials, a comparison with characteristics of trial participants was only possible with the overall trial population.

The Kaplan-Meier method was used to visualize the PFS and OS survival curves and estimate median OS (mOS) and median PFS (mPFS) of real-world patients for the following strata: nonsquamous <1% PD-L1, nonsquamous 1% to 49% PD-L1, nonsquamous $\geq$50% PD-L1, squamous <1% PD-L1, and squamous >1% PD-L1.

The EE gap for the survival curves for the aforementioned strata of the real-world population were compared with the data from the corresponding trial strata using COX proportional regression modelling to estimate Hazard Ratios (HR) and 95% confidence intervals (95% CI). The algorithm developed by Guyot et al.[10] was used to reconstruct data from the available OS and PFS curves from the PD-L1 strata of the KEYNOTE-189[11] and -407[12] trials. The survival curves of all models were visually assessed to test whether the proportional hazard assumption was met, and in cases where the assumption was violated, HRs were not reported. Lastly, a sensitivity analysis was performed, including only patients with an ECOG PS

Figure 1 Study design.
Abbreviations: ptx = paclitaxel; pem = pemetrexed; pembro = pembrolizumab; platinum = cisplatin, or carboplatin.



of 0 and 1, to evaluate whether differences in ECOG PS impacted the OS and PFS EE gaps.

Ethical Statement

All methods were carried out in accordance with relevant guidelines and regulations. The ethics committee—the Santeon Institutional Review Board—approved the study (SDB 2019-008) and waived the need for informed consent because of the retrospective nature of the study and most patients were deceased at time of conducting the study. The study was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

In total, 633 patients started with pembrolizumab plus chemotherapy in the study period. Of these patients, 30 (23 nonsquamous and 7 squamous) had no PD-L1 assessment available, resulting in an overall study population of 603 patients, including 486 patients with nonsquamous and 117 patients with squamous histology.

Patient and Treatment Characteristics

Table 1 presents the patient characteristics and Table 2 presents the treatment characteristics of both cohorts and their PD-L1 strata.

Nonsquamous Cohort. In the nonsquamous population, 269 (55.4%) patients had <1% PD-L1 expression, 158 (32.5%) patients had 1% to 49% PD-L1 expression, and 59 patients (12.1%) had ≥50% PD-L1 expression. In the KEYNOTE-189 trial 410 patients received pembrolizumab plus chemotherapy of whom 127 (31%) patients had <1% PD-L1 expression, 128 (31.2%) patients had 1% to 49% PD-L1 expression and 132 (32.2%) patients had ≥50% PD-L1 expression. The characteristics of the patients were similar for all PD-L1 strata in clinical practice, except for the presence of brain metastases and the duration of pembrolizumab therapy.

In comparison to the KEYNOTE-189, the proportion of patients with an ECOG PS ≥ 2 and an unknown ECOG PS were higher in all PD-L1 strata (Table 1). The proportion of patients receiving ≥4 cycles of platinum-based chemotherapy and subsequent treatment were lower in all PD-L1 strata (Table 2).

Squamous Cohort. In the squamous cohort, 70 (59.8%) and 47 (40.2%) patients had a PD-L1 expression of <1% and ≥1% respectively, compared to 95 (34.2%) and 176 (63.4%) patients in pembrolizumab arm of the KEYNOTE-407 trial (n = 278). In the real-world, brain metastasis were more frequent in patients with ≥1% PD-L1 expression than in patients with <1% PD-L1 expression.

In comparison to the KEYNOTE-407, the median age and the proportion of patients with ECOG PS ≥ 2 and an unknown ECOG PS were higher in both PD-L1 strata. The proportions of patients receiving ≥4 cycles of platinum-based chemotherapy and subsequent treatment were lower in both PD-L1 strata. (Table 2).

Survival Outcomes

Nonsquamous Cohort. For all PD-L1 strata, the mOS in the real-world was shorter than in the KEYNOTE-189 trial (Figure 2). The difference in mOS was most pronounced in patients with a PD-L1 expression of less than 1% with a significantly shorter mOS in the real-world than in the trial (10 vs. 17.2 months; HR = 1.38 [95% CI, 1.06-1.78]). The mOS was slightly, but not significantly, shorter in the real-world for patients with a PD-L1 expression of 1-49% (19.9 vs. 21.8 months; HR 1.10 [95% CI, 0.80-1.51]) and for patients with a PD-L1 expression of ≥50% (26.2 vs. 27.7 months,

Table 1 Patient characteristics Stratified Per PD-L1 status and Overall Characteristics from The KEYNOTE Trials for Nonsquamous and Squamous Metastatic NSCLC Patients

Characteristics	Nonsquamous					Squamous			
	Real-World (n = 486)				KEYNOTE-189	Real-World (n = 117)			KEYNOTE-407
	PD-L1 < 1%	PD-L1 1%-49%	PD-L1 ≥ 50%	*P*-value[c]	Pembrolizumab arm	PD-L1 <1%	PD-L1 ≥ 1%	*P*-Value[c]	Pembrolizumab arm
	(n = 269)	(n = 158)	(n = 59)		(n = 410)[a]	(n = 70)	(n = 47)		(n = 278)[b]
Age (median, [range])	66 [35-85]	65 [40-81]	61 [38-80]	0.49	65 [34-84]	71 [56-86]	68 [53-82]	0.10	65 [29-87]
Sex (male, n (%))	139 (51.6)	66 (41.8)	27 (45.8)	0.13	254 (62)	51 (72.8)	32 (68.1)	0.72	220 (79.1)
BMI (mean, (sd))	24.5 (4.4)	25.4 (4.8)	25.5 (4.7)	0.41	–	26.2 (6)	24.9 (3.9)	0.18	–
ECOG-PS (n (%))				0.95				0.73	
0	91 (33.8)	58 (36.7)	21 (36.7)		186 (45.4)	18 (25.7)	16 (34.0)		73 (26.3)
1	93 (34.6)	55 (34.8)	18 (30.5)		221 (53.9)	30 (42.9)	17 (36.2)		205 (73.7)
≥2	27 (10)	12 (7.6)	7 (11.8)		1 (0.2)	8 (11.4)	4 (8.5)		0
unknown	58 (18.6)	33 (20.9)	13 (22)		2 (0.5)	17 (24.3)	10 (21.3)		0
Histology (n, (%))				0.91				0.06	
Adeno	244 (90.7)	145 (91.8)	53 (89.8)		394 (96.1)	–	–		–
Squamous	–	–	–		–	57 (81.4)	45 (95.7)		272 (97.8)
NOS or other	25 (9.3)	13 (8.2)	6 (10.2)		16 (3.9)	13 (18.6)	2 (4.3)		6 (2.2)
Brain metastases (n, (%))	50 (18.6)	23 (38.9)	16 (27.1)	<0.01	73 (17.8)	4 (5.7)	5 (10.6)	<0.01	20 (7.2)

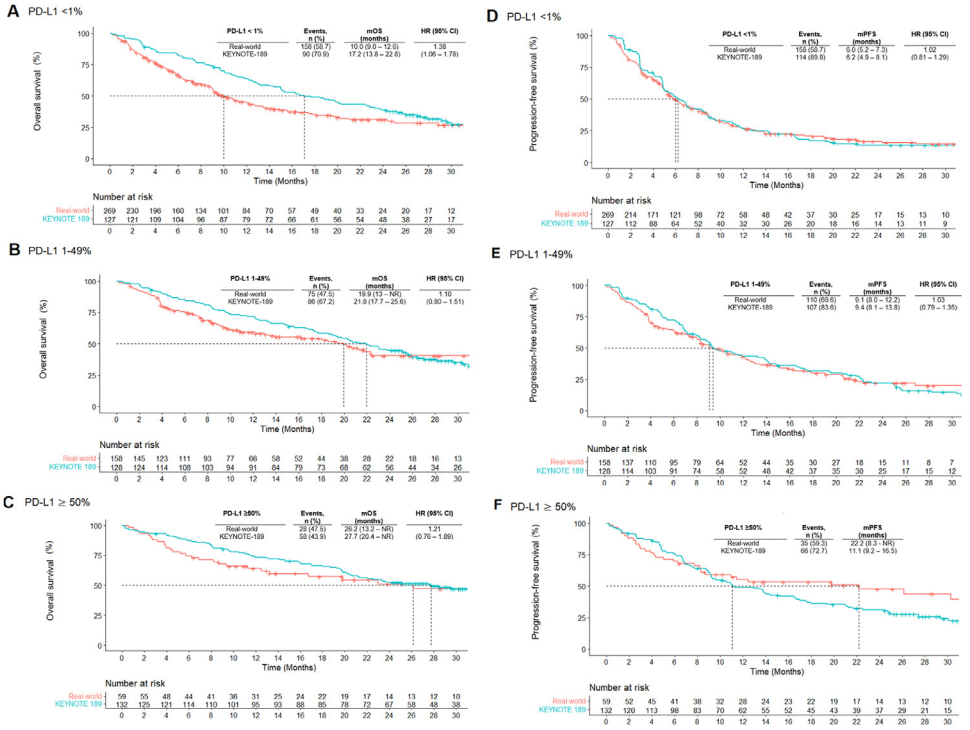
Abbreviations: BMI = body mass index; ECOG-PS = eastern cooperative group performance status; NA = not applicable; nos = not otherwise specified.
[a] Intention to treat population including all patients who were randomly allocated to pembrolizumab plus chemotherapy
[b] As treated population, which included all patients who underwent randomization and received ≥1 dose of pembrolizumab plus chemotherapy
[c] *P*-value represents a comparison of real-world patient characteristics between the PD-L1 stratum within the nonsquamous or squamous cohort

Table 2 Treatment Characteristics Stratified Per PD-L1 Status and Overall Characteristics from The KEYNOTE Trials for Nonsquamous and Squamous Metastatic NSCLC Patients

Treatment Characteristics	Nonsquamous					Squamous			
	Real-World (n = 486)				KEYNOTE-189	Real-World (n = 117)			KEYNOTE-407
	PD-L1 < 1% (n = 269)	PD-L1 1%-49% (n = 158)	PD-L1 < 50% (n = 59)	*P* value[c]	Pembrolizumab arm (n = 405[a] /410[b])	PD-L1 < 1% (n =70)	PD- L1 > 1% (n = 47)	*P* value[c]	Pembrolizumab arm (n = 278) [a]
Type of platinum-based drug (n, (%))				0.39				0.77	
Carboplatin	219 (81.4)	120 (75.9)	46 (78)		294 (71.7)[a]	60 (85.7)	42 (89.4)		167 (60.1)
Cisplatin	50 (18.6)	38 (24.1)	13 (22)		111 (27.4)[a]	10 (14.2)	5 (10.6)		113 (40.6)
Number of platinum cycles in the induction phase (n, (%))				0.37				0.35	
< 4	99 (36.7)	55 (34.8)	16 (27.1)		71 (17.5)[a]	28 (40)	14 (29.8)		59 (21.2)
≥ 4	170 (63.2)	103 (65.2)	43 (72.9)		334 (82.5)[a]	42 (60)	33 (70.2)		219 (78.8)
Treatment duration pembrolizumab (mean, (sd))	6.3 (7.1)	7.9 (7.6)	9.9 (10.2)	0.02	9.8 (7.8)[a]	6.6 (7)	8.6 (8.1)	0.02	6.3 (4.1)
Subsequent therapy				0.45					
Any subsequent therapy (n, (%))	45 (16.7)	25 (15.8)	6 (10.2)		183 (44.6)[b]	15 (21.4)	11 (23.4)	0.98	89 (32)
Number of subsequent therapies (n,% of any subsequent therapy)				0.08				<0.01	
1	38 (84.4)	19 (76)	5 (83.3)		107 (58.4)[b]	11 (73.3)	7 (63.6)		NA
2	3 (6.7)	6 (14)	0		44 (24)[b]	3 (20)	4 (36.4)		NA
≥3	4 (8.9)	0	1 (16.7)		32 (17.5)[b]	1 (6.7)	0		NA

Abbreviation: NA = not applicable.
[a] Intention to treat population including all patients who were randomly allocated to pembrolizumab plus chemotherapy (nonsquamous, n = 405; squamous, n = 278))
[b] As treated population which included all patients who underwent randomization and received ≥1 dose of pembrolizumab plus chemotherapy (n = 410)
[c] *P*-value represents a comparison between real-world patient characteristics between the PD-L1 strata within the nonsquamous or squamous cohort

Figure 2 Kaplan-Meier survival curves for nonsquamous patients stratified for PD-L1 strata: comparison of real-world versus KEYNOTE-189 on overall survival (A) PD-L1 < 1% stratum (B) PD-L1-49% stratum (C) PD-L1 > 50% stratum and progression-free survival (D) PD-L1 < 1% stratum (E) PD-L1-49% stratum (F) PD-L1 > 50% stratum.



HR = 1.21 [95%CI, 0.76-1.89]). The 1-year survival was lower across all PD-L1 strata when compared to the trial, namely 44.8% versus 63.4% for PD-L1 <1%, 59.1% versus 71.1% for PD-L1 1% to 49% and 63.9% versus 73.3% for PD-L1 ≥ 50%. Regarding PFS, for the PD-L1 <1% and 1% to 49% strata no significant difference was observed between the real-world and the trial. In the PD-L1 ≥50% stratum, the mPFS was longer in the real-world than in the trial (22.2 vs. 11.1 months). However, this should be interpreted with caution since the proportional hazard assumption was violated (Figure 2F). A sensitivity analysis including only patients with ECOG 0 and 1 yielded similar OS and PFS EE-gaps (Supplemental Table S1).

Squamous Cohort. The mOS observed in patients with <1% PD-L1 was shorter in the real-world than in the KEYNOTE-407 trial (10.0 vs. 15.0 months; HR = 1.37 [95% CI 0.92-2.04]), see Figure 3. For patients with ≥ 1% PD-L1, the mOS observed in the real-world was longer than the mOS observed in the trial (25.6 vs. 18.9 months). However, the observed mOS should be interpreted with caution since the proportional hazard assumption was violated (Figure 3B). The 1-year survival for PD-L1 <1% was lower in the real-world than in the trial (49.9% vs. 64.2%), while it was similar for PD-L1 ≥1% (61.3% vs. 64.8%). There were no differences in PFS with the KEYNOTE-407 trial in both PD-L1 strata.

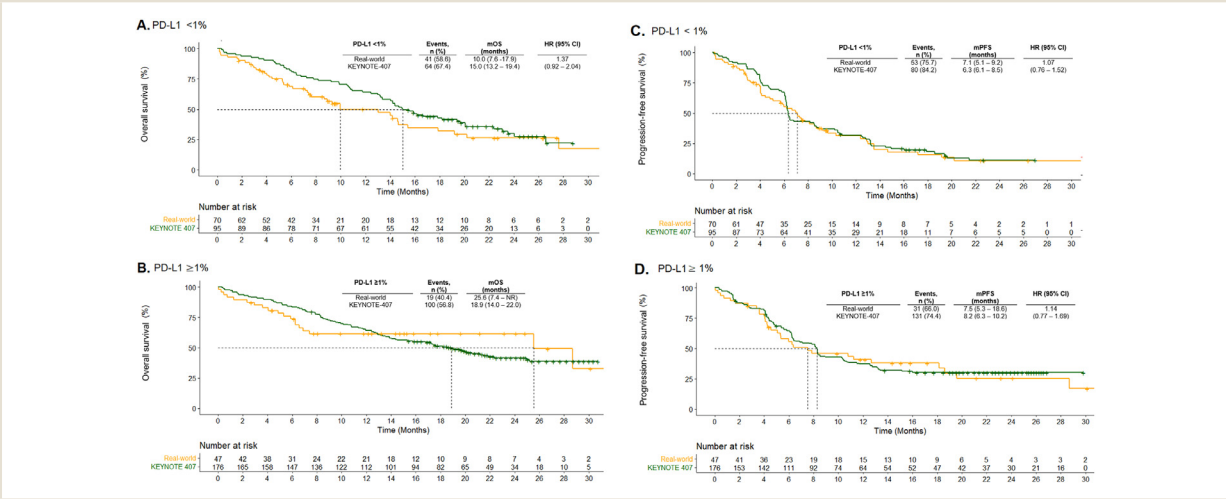
Discussion

This study found that in real-world clinical practice, patients with nonsquamous metastatic NSCLC and <1% PD-L1 expression who were treated with first line pembrolizumab plus chemotherapy experienced significantly shorter OS compared to the corresponding clinical trial. Additionally, HRs above 1 were observed for OS in the other nonsquamous and squamous PD-L1 strata, although these results did not reach statistical significance. For PFS no EE gap was detected in any of the PD-L1 strata.

Our observation, which demonstrates a tendency towards shorter OS in clinical practice than in the clinical trials, builds upon existing literature on chemotherapy-treatment outcome disparities in NSCLC[8] and aligns with previous real-world studies evaluating the effectiveness of pembrolizumab plus chemotherapy in nonsquamous metastatic NSCLC patients. For example, the observed 1-year survival rates approximate the findings from Liu et al.,[13] and Velcheti et al.[14] except for patients with <1% PD-L1 where we observed worse survival rates (44.8% vs. 54.5%[13] and 54%[14]).

Explanations for the observed divergence in OS could be differences in the patient and treatment characteristics between the real-world and trial cohorts. In the KEYNOTE-189 and -407 trial, only patients with an ECOG PS of 0 and 1 were enrolled, whereas our study also has patients with an ECOG PS ≥ 2, a significant predictor of poorer survival outcomes,[15] as well as patients with

Figure 3 Kaplan-Meier survival curves for squamous patients stratified for PD-L1 strata: comparison of real-world versus KEYNOTE-407 on overall survival (A) PD-L1 < 1% stratum (B) PD-L1 ≥ 1% stratum and on progression-free survival (C) PD-L1 < 1% stratum (D) PD-L1 ≥ 1% stratum.



unknown ECOG PS. However, after excluding these patients, the EE gap (presented as HR estimate) remained above 1 in all PD-L1 strata indicating less effect even in ECOG PS 0 to 1 patients (Supplemental Table S1). Although it cannot be excluded that in routine care ECOG PS is scored favorably sometimes,[16] this suggests that also factors other than the ECOG PS play a role. For example, in the real-world population, less patients received subsequent lines of treatment, and a lower proportion of patients completed 4 or more cycles of platinum-based chemotherapy during the induction phase. This could indicate differences in patient's perference or physician's awareness of additional treatment options (eg, investigational products). However, other unmeasured factors are likely to be involved as well. Recently, Lasiter et al.[17] showed that even with a common protocol approach in 5 datasets, heterogeneity in real-world OS outcomes from pembrolizumab plus chemotherapy persists.

Notably, in contrast to OS, no EE gap for PFS was observed in the present study. This, however, does not necessarily mean that there is no gap because the PFS in the real-world could be overestimated. In our previous study investigating the EE gap of durvalumab,[18] we observed longer PFS in clinical settings than in the trial. This discrepancy may be attributed to variances in the assessment of disease progression. In clinical trial settings, treatment response is assessed using strict imaging schemes, and independent radiologists interpret these images while adhering strictly to (i)RECIST criteria. On the other hand, in real-world settings, treatment response is assessed with varying frequency of imaging and involves interpretation by different radiologists and thoracic oncologists, who may not consistently adhere to (i)RECIST criteria.[19]

A clinically relevant finding of this study is that the OS EE gap was most pronounced in nonsquamous patients with <1% PD-L1 expression. Various factors could explain this observation. First, the shorter OS in patients with <1% PD-L1 could be attributable to post progression treatment effects. Notably, only 16.7% of PD-L1< 1% patients received subsequent treatment in our study whereas 44.6% of the total trial population received a subsequent treatment (Table 2). Although a lower frequency of subsequent treatments is also observed in the PD-L1 1%-49% and ≥50% strata in our study, the impact on survival might be larger in PD-L1 <1% patients. This is supported by the 4-year update of KEYNOTE-189, that showed that second-line treatments were more effective than first-line treatment in PD-L1 < 1% patients as measured by PFS, but not for the other PD-L1 strata.[20] Another possible explanation could be that in clinical practice, early discontinuation of immunotherapy, along with chemotherapy, took place more frequently in patients with <1% PD-L1 (82% vs. 64% (PD-L1 1%-49%) and 75% (PD-L1≥ 50%), $P = .04$, see Supplemental Table S2). This could suggest a lower conviction to maintain immunotherapy in patients with PD-L1 < 1%. At the same time, the recent results of the EMPOWER-3 trial might have contributed decisions to discontinue pembrolizumab, since the trial demonstrated no OS benefit (HR = 1.01, 95% CI 0.63-1.60) for patients with PD-L1 < 1% treated with cemiplimab plus chemotherapy versus chemotherapy alone.[21] Another possible explanation for the more pronounced EE gap in the PD-L1 < 1% stratum could be that fewer patients in clinical practice completed the 4 cycles of induction chemotherapy. Cytotoxic chemotherapy is considered to enhance modulation of the immune response through PD-L1 inhibition[22,23] and it is conceivable that the noncompletion of 4 cycles has a larger impact in patients with a priori no PD-L1 expression compared to patients with PD-L1 expression at baseline. Lastly, considering the lack of efficacy observed in other immuno-chemotherapy trials, it is possible that the effects seen in patients with <1% PD-L1 treated with pembrolizumab combination in the KEYNOTE-189 trial might be overestimated due to favorable patient characteristics occurring by chance. Unfortunately, neither aggregated baseline and treatment characteristics nor individual patient level data per PD-L1 stratum from the KEYNOTE-189 are available in the public domain. Access

to individual patient level data from trial participants would allow a more comprehensive multivariable regression analysis into potential factors responsible for the observed EE gap.[24]

In all PD-L1 strata, the real-world mOS for patients treated with pembrolizumab plus chemotherapy was longer compared to the real-world mOS reported by Cramer-van der Welle et.al.[7] for chemotherapy alone in the preimmunotherapy era, with the smallest survival benefit observed in patients with <1% PD-L1 expression. In this stratum, the absolute mOS difference observed in the real-world was smaller (10 vs. 8.9 and 6.5 months for cisplatin-pemetrexed and carboplatin-pemetrexed) than in the KEYNOTE-189 trial (17.2 vs. 10.2 months). This supports that the real-world effectiveness of pembrolizumab plus chemotherapy is impaired in patients with no PD-L1 tumor expression. Another licensed regimen with nivolumab plus ipilimumab and chemotherapy might be an alternative for these patients[25] because this combination targets both the PD-L1 and CTLA-4 receptors. Unfortunately, real-world comparative effectiveness data of these 2 regimens in PD-L1 <1% patients are not available yet, but needed to judge about the optimal first-line systemic treatment in these specific patients.

The study has several strengths, including its multicenter design, large total sample size and long follow-up time. However, this study also has some limitations. First, both trials lacked data about patient's characteristics per PD-L1 stratum, preventing an evaluation of patient characteristics as explanation for the EE gap. Additionally, the sample sizes of the squamous PD-L1 ≥ 1% and nonsquamous PD-L1≥ 50% strata are relatively small. While the survival curves showed divergence, there results should be interpreted with caution. Furthermore, the absence of information on the frequency of radiological imaging to determine disease progression limited the investigation of a less strictly timed imaging scheme as a possible explanation for the absence of an EE gap in PFS. Finally, the real-world cohorts had a higher proportion of PD-L1 <1% patients compared to the trials (nonsquamous cohort: 59.8% vs. 31.2% and squamous cohort: 55.4% vs. 31%). This was partly due to the exclusion of patients treated with pembrolizumab monotherapy for PD-L1 expression ≥50%. Nonetheless, the ratio of PD-L1< 1%/PD-L1 1%-49% indicates a relatively high proportion of PD-L1 <1% patients. This could indicate differences in how PD-L1 status is assessed in the Netherlands. On the other hand, when patients would have been misclassified as no PD-L1 expression, exclusion of misclassified patients would only increase the magnitude of the EE gap in this stratum even further.

Conclusion

No significant EE gap was found for pembrolizumab plus chemotherapy, except in the stratum nonsquamous metastatic NSCLC with <1% PD-L1 tumor expression. In these patients, the survival in real-world was considerably shorter compared to the clinical trial results. Further studies are needed to determine which patient, treatment and or context factors contribute to this disparity.

Clinical Practice Points

- Based on the KEYNOTE-189 and KEYNOTE-407 trials, pembrolizumab plus chemotherapy is currently established as one of the standard of care options for patients with nononcogenic metastatic non–small cell lung cancer. Nevertheless, treatment effects observed in clinical trials may differ from effects observed in real-world clinical settings.
- This study assessed the real-world survival outcomes of pembrolizumab plus chemotherapy per PD-L1 stratum of patients with nonsquamous and squamous metastatic NSCLC and compared these outcomes to the clinical trial results.
- In the real-world, patients with nonsquamous metastatic NSCLC and <1% PD-L1 expression who were treated with first-line pembrolizumab plus chemotherapy had considerably shorter overall survival (OS) compared to the corresponding clinical trial (median OS 10 vs 17.2 months).
- In all other nonsquamous and squamous PD-L1 strata, the real-world OS outcomes were worse than those in the clinical trial, although statistical significance was not reached. In addition, no differences in progression-free survival outcomes were observed in any PD-L1 stratum.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Marjon V. Verschueren: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Bas JM. Peters:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Lourens T. Bloem:** Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Veerle R. Kruik:** Data curation, Validation, Visualization, Writing – review & editing. **Elien B. Uitvlugt:** Data curation, Investigation, Writing – review & editing. **Annette R. Bijsmans:** Data curation, Validation, Visualization, Writing – review & editing. **Antoine CG. Egberts:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Ewoudt MW. van de Garde:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Supplementary materials

Table S1 Sensitivity analysis for the EE gap for OS and PFS (expressed as HR) for each PD-L1 stratum, only including patients with an ECOG PS 0 and ECOG PS 1

Stratum	Number of pembrolizumab patients		HR for OS (95%CI) (real-world vs trial)	HR for PFS (95%CI) (real-world vs trial)
	Real-world (n)	Clinical trial (n)		
Non-squamous cohort				
PD-L1 < 1%	184	127	1.24 (0.60 – 1.08)	1.06 (0.77 – 1.28)
PD-L1 1-49%	113	128	1.17 (0.60 – 1.20)	1.13 (0.66 – 1.18)
PD-L1 ≥ 50%	39	132	1.13 (0.52 - 1.51)	Non proportional hazard
Squamous cohort				
PD-L1 < 1%	45	95	1.32 (0.49 – 1.19)	1.14 (0.60 – 1.30)
PD-L1 ≥ 1%	26	176	Non-proportional hazard	0.91 (0.68 – 1.76)

Table S2 Patients who prematurely discontinue platinum based chemotherapy (<4 cycles) and also prematurely discontinue pembrolizumab (<4 cycles), stratified per PD-L1 stratum

	PD-L1 <1% (n = 269)	PD-L1 1-49% (n = 158)	PD-L1 ≥ 50% (n =59)	p value
Premature discontinuation (<4 cycles) of chemotherapy (n, (%))	99 (36.7)	55 (34.8)	16 (27.1)	0.37
Premature discontinuation (< 4 cycles) of pembrolizumab in patients who prematurely discontinue chemotherapy (n, (%*))	81 (81.8)	35 (63.6)	12 (75.0)	0.04

* percentage was calculated from the number of patient who prematurely discontinue chemotherapy