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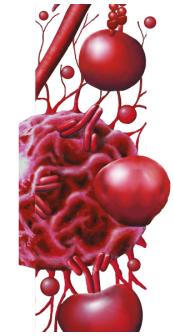

Real-world maintenance therapy and survival outcomes for pembrolizumab plus pemetrexed and platinum for non-small-cell lung cancer in USA

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Aim: To evaluate treatment patterns and overall survival (OS) in real world metastatic non-squamous non-small-cell lung cancer (NSQ-NSCLC) patients that received pembrolizumab plus pemetrexed-platinum (pembro+pem+plat) aligned with KEYNOTE-189. **Materials & methods:** OS was evaluated for the overall cohort and maintenance therapy (MT) subgroups and analyzed using Kaplan-Meier estimates and Cox proportional hazards model. **Results:** Of 2488 patients that received first-line treatment, 45.1% received less than four cycles of pembro+pem+plat, 43.9% received four cycles plus MT with pembro and/or pem, and 11.1% received four cycles without continuing on MT. The median OS was 21.0 months and 9.1 months in patients that continued and did not continue MT. **Conclusion:** Real world patients that received KEYNOTE-189-aligned treatment had similar OS benefits.

Plain language summary:
What is this article about?: KEYNOTE-189 was a research study (i.e., clinical trial) that compared two different combinations of medicine to treat patients with advanced non-squamous (NSQ) non-small-cell lung cancer (NSCLC). This was the first treatment after being diagnosed for all patients, and they received one of two combinations – either pembrolizumab, pemetrexed, plus a platinum-based chemotherapy (pembro+pem+plat) or placebo plus pemetrexed plus a platinum-based chemotherapy. After receiving these combinations four-times, patients were switched to maintenance therapy with pembro and/or pem. In general, patients first treated with pembro+pem+plat survived longer than those treated with placebo plus pemetrexed-platinum. In the current study, researchers wanted to learn if the same results can be expected for patients being treated in the community.
What are the results?: Patients who completed four sessions of pembro+pem+plat and continued on maintenance therapy survived for 21.0 months and those who completed four sessions of pembro+pem+plat but did not continue on maintenance therapy survived for 9.1 months.
What do the results of the study mean?: Patients in the community who were treated with pembro+pem+plat and continued on maintenance therapy survived as long as those in the KEYNOTE-189 study.

Tweetable abstract: A real-world study demonstrates similar survival benefits as those reported in the KEYNOTE-189 study of pembrolizumab, pemetrexed and platinum. The study also highlights the importance of maintenance therapy with the regimen.

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Keywords: electronic health record data • KEYNOTE-189 • maintenance therapy • non-small-cell lung cancer • overall survival • pembrolizumab plus pemetrexed and platinum • real-world evidence

Future Medicine

Pembrolizumab (pembro) in combination with pemetrexed (pem) and platinum chemotherapy (plat; carboplatin or cisplatin) is a front-line standard of care option for patients with metastatic non-squamous (NSQ) non-small-cell lung cancer (NSCLC) without actionable genomic alterations and is recommended by the National Comprehensive Cancer Network (NCCN) guidelines [1]. This recommendation is based on findings from the pivotal phase III KEYNOTE-189 trial [2].

In KEYNOTE-189, first-line treatment with pembro+pem+plat followed by pembro for up to a total of 35 cycles and pem maintenance therapy (MT) demonstrated superior progression-free survival and overall survival (OS) with a tolerable toxicity profile compared with placebo+pem+plat followed by placebo+pem MT in patients with metastatic NSQ NSCLC with no *EGFR* or *ALK* genomic tumor aberrations [2]. In the study's updated analysis (median follow-up of 23.1 months), median OS was 22.0 months in patients who received pembro+pem+plat followed by pembro+pem MT versus 10.7 months in patients who received placebo+pem+plat followed by placebo+pem MT [3]. Similar OS findings were observed at 5 years (median follow-up of 64.6 months; OS 22.0 vs 10.6 months) [4].

Although KEYNOTE-189 and KEYNOTE-21G [5,6] have demonstrated the survival benefit of this regimen, little is known about its benefits in routine clinical practice since first receiving accelerated approval in May 2017 and regular approval in August 2018. Real-world data on treatment patterns, specifically MT utilization among patients receiving pembro+pem+plat in the first-line setting, are limited. This study aimed to describe patient characteristics, treatment patterns, MT utilization, and survival outcomes of patients with advanced NSQ NSCLC receiving first-line treatment with pembro+pem+plat in routine clinical practice in the USA.

Materials & methods

Study design & data source

This retrospective observational descriptive study utilized Flatiron Health's electronic health record (EHR)-derived database for advanced NSCLC. Flatiron is a nationwide longitudinal, demographically and geographically diverse database with data from more than 280 cancer clinics representing over 2.4 million patients in the US. The de-identified patient-level data are both structured and unstructured and curated via technology-enabled abstraction. Patients in the database had stage IIIb, IIIc, IVa or IVb NSCLC at initial diagnosis or presented with earlier stage NSCLC that subsequently advanced, with two or more documented clinical visits on or after 1 January 2011. The database complies with the Health Insurance Portability and Accountability Act and a waiver of informed consent was approved by an institutional review board prior to study conduct.

Study cohort

Adults with advanced NSQ NSCLC who received first-line therapy with pembro+pem+plat between 1 May 2017 and 31 October 2019 were identified in the database and assigned to the overall cohort. These patients were assigned to the MT subgroup if they received MT following pembro+pem+plat in the first-line setting. Eligible patients were followed until the last recorded visit date (loss to follow-up), date of death, or end of the database (30 November 2019), whichever was earliest.

Identification of first-line & MT

First-line therapy was defined as treatment any time after or within 14 days before the diagnosis of advanced disease (index diagnosis) and after the patient's start of structured activity; a cycle of first-line therapy with pembro+pem+plat comprised a unique episode of each drug in the regimen administered within 21 days of each other.

Continuation MT was defined as the use of at least one of the agents given in the first line, beyond 4 to 6 cycles, in the absence of disease progression [1,7]. Switch MT refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4 to 6 cycles of initial therapy [1,7]. In this study continuation MT was examined and refers to continuation of treatment with pembro or pem or pemb+pem upon completion of at least four cycles of first-line treatment with pembro+pem+plat.

Study variables & outcomes

Patient baseline demographics (e.g., age, gender, body mass index [BMI], region of residence, and smoking history) and clinical characteristics (e.g., disease stage at initial diagnosis, Eastern Cooperative Oncology Group [ECOG]

performance status [PS] and biomarker testing status and results for *EGFR, KRAS, ALK, ROS1,* PD-L1 tumor proportion score [TPS]) and treatment-related variables (line of therapy and drugs) were obtained from the database.

OS was the primary outcome and was defined as the time from the start of first-line therapy until death. OS was evaluated for the overall cohort, MT subgroup, and those who did not continue on MT. The date (month and year) of death was obtained from the database.

Statistical analyses

Descriptive statistics were used to summarize the baseline demographics, clinical characteristics, and treatment patterns of patients in the overall cohort and MT subgroup. Continuous variables were summarized using means and standard deviations or medians and ranges; comparisons between MT subgroups (i.e., pembro or pembro+pem) were made using the t-test for normally distributed variables or Wilcoxon rank sum test for non-normally distributed variables. Categorical variables were summarized using frequencies and percentages and comparisons between MT subgroups made using the chi-square test or Fisher's exact test when the expected frequency was ≤5.

Multivariable logistic regression was used to evaluate the association between patient baseline characteristics and MT utilization. Kaplan-Meier methods were used to estimate unadjusted median OS and 95% confidence interval (CI) for the overall cohort and MT subgroup. A multivariable Cox proportional hazards regression model was used to examine factors associated with longer OS for the overall cohort and included the following variables: age, gender, race, year of advanced NSCLC diagnosis, weight, BMI, disease stage at initial diagnosis, smoking status, ECOG PS, biomarker status, and receipt of MT.

Patients who were lost to follow-up or who reached the end of the study period without evidence of death were censored at their last activity date (i.e., any drug administration or visit date) for OS analysis. Given the descriptive, noncomparative design of this study, no formal sample size and power calculations were conducted, and no specific hypotheses were tested. All statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., NC, USA).

Results

Patient cohort

A total of 58,423 patients with a diagnosis of advanced NSCLC were identified from the database, of whom 2488 met the selection criteria for NSQ histology and first-line treatment with pembro+pem+plat between 1 May 2017 and 31 October 2019; these patients were assigned to the overall cohort (Figure 1). Of the overall cohort, 1121 (45.1%) received less than four cycles of pembro+pem+plat, 1091 (43.9%) received four cycles plus MT with pembro and/or pem (MT subgroup), and 276 (11.1%) received four cycles without continuing on MT. Of those that completed four cycles (n = 1,367), 79.8% and 20.2% received or did not receive MT, respectively.

Eighteen percent of patients continued on pembro (n = 449), 16.4% on pembro+pem only (n = 408), 0.2% on pem only (n = 4), or 9.2% switched between these regimens (n = 230). Switch patterns for these MT regimens were observed: started with pembro and added pem (n = 185, 7.4%); started with pembro+pem and dropped pembro to continue on pem (n = 32, 1.3%); started with pembro, added pem, and then dropped pembro to continue on pem (n = 11, 0.44%); and started with pembro and switched to pem (n = 2, 0.08%).

Patient baseline characteristics

Patient baseline demographics and clinical characteristics at the start of first-line therapy are presented in Table 1. Patients in the overall cohort were primarily White (68.1%) with a mean age of 67.4 ± 9.6 years, and there were more males than females (54.5 vs 45.5%). Most patients had a history of smoking (89.3%) and presented with stage IV disease at initial diagnosis (83.5%); and almost two-thirds of patients (61.3%) had ECOG PS of 0 or 1. The median follow-up was 6.1 months (range 0.03 to 30.2 months). The proportions of patients in the PD-L1 TPS subgroups of <1%, 1–49%, ≥50%, or unknown were 33.5, 21.9, 18.9 and 25.8%, respectively. The baseline characteristics for the MT subgroup (n = 1,091) were similar. However, the median follow-up for the subgroup of patients receiving MT was 10.4 months (range 2.8 to 30.2 months).

Significant baseline differences were observed in PD-L1 TPS, advanced diagnosis year, and median follow-up time between patients on pembro+pem MT versus pembro MT. A higher percentage of patients on pembro+pem MT had PD-L1 TPS ≤1% compared with patients on pembro MT (36.8 vs 27.8%; p = 0.0131); a higher percentage of patients with unknown PD-L1 TPS continued on pembro MT versus pembro+pem MT (28.1 vs 22.1%). A higher percentage of patients diagnosed with advanced NSCLC in 2017 continued on pembro MT versus pembro+pem

Table 1. Baseline demographics and clinical characteristics at the start of first-line treatment.

Characteristic	n (%), except where noted	Overall	<4 cycles	≥4 cycles but no MT	All maintenance	Mixed maintenance	Maintenance therapy comparison		p-value[†,‡]
							Only Pembro	Pembro+Pem	
Age at initial diagnosis, year	N	**n = 2488**	**n = 1,121**	**n = 276**	**n = 1,091**	**n = 230**	**n = 449**	**n = 408**	0.1452
	Mean (SD)	67.38 (9.57)	67.95 (9.53)	66.57 (10.21)	67.01 (9.43)	67.96 (9.49)	67.19 (9.17)	66.25 (9.63)	.
	Median	68.09	68.97	66.75	67.7	68.53	68.32	66.68	.
	Min, Max	22.91, 85.33	22.91, 85.33	38.19, 84.87	27.08, 84.87	37.87, 84.60	29.41, 84.79	27.08, 84.87	.
	Q1	60.61	61.06	59.9	60.47	60.47	60.98	60.19	.
	Q3	74.7	75.1	74.73	74.14	74.89	73.92	73.81	.
Age group at start of LOT1	<30	3 (0.12)	1 (0.09)	0 (0.00)	2 (0.18)	0 (0.00)	1 (0.22)	1 (0.25)	0.3814
	30 – 50	105 (4.22)	38 (3.39)	19 (6.88)	48 (4.40)	7 (3.04)	17 (3.79)	24 (5.88)	.
	50 – 65	870 (34.97)	379 (33.81)	101 (36.59)	390 (35.75)	80 (34.78)	155 (34.52)	154 (37.75)	.
	65–75	926 (37.22)	416 (37.11)	89 (32.25)	421 (38.59)	87 (37.83)	186 (41.43)	147 (36.03)	.
	75+	584 (23.47)	287 (25.60)	67 (24.28)	230 (21.08)	56 (24.35)	90 (20.04)	82 (20.10)	.
Gender	Female	1132 (45.50)	489 (43.62)	133 (48.19)	510 (46.75)	103 (44.78)	203 (45.21)	201 (49.26)	0.2352
	Male	1356 (54.50)	632 (56.38)	143 (51.81)	581 (53.25)	127 (55.22)	246 (54.79)	207 (50.74)	.
Race	Black	221 (8.88)	86 (7.67)	24 (8.70)	111 (10.17)	24 (10.43)	42 (9.35)	45 (11.03)	0.4594
	Other	223 (8.96)	91 (8.12)	25 (9.06)	107 (9.81)	20 (8.70)	48 (10.69)	39 (9.56)	.
	Asian	42 (1.69)	20 (1.78)	8 (2.90)	14 (1.28)	4 (1.74)	5 (1.11)	5 (1.23)	.
	White	1694 (68.09)	782 (69.76)	172 (62.32)	740 (67.83)	162 (70.43)	310 (69.04)	265 (64.95)	.
	Missing	308 (12.38)	142 (12.67)	47 (17.03)	119 (10.91)	20 (8.70)	44 (9.80)	54 (13.24)	.
Practice type	Academic	112 (4.50)	63 (5.62)	6 (2.17)	43 (3.94)	8 (3.48)	20 (4.45)	15 (3.68)	0.5655
	Community	2376 (95.50)	1058 (94.38)	270 (97.83)	1048 (96.06)	222 (96.52)	429 (95.55)	393 (96.32)	.
Advanced diagnosis year	2011	3 (0.12)	2 (0.18)	0 (0.00)	1 (0.09)	0 (0.00)	1 (0.22)	0 (0.00)	<0.0001
	2012	1 (0.04)	1 (0.09)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	.
	2013	3 (0.12)	1 (0.09)	0 (0.00)	2 (0.18)	2 (0.87)	0 (0.00)	0 (0.00)	.
	2014	5 (0.20)	2 (0.18)	1 (0.36)	2 (0.18)	1 (0.43)	0 (0.00)	1 (0.25)	.
	2015	2 (0.08)	2 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	.
	2016	15 (0.60)	7 (0.62)	1 (0.36)	7 (0.64)	3 (1.30)	4 (0.89)	0 (0.00)	.
	2017	522 (20.98)	213 (19.00)	55 (19.93)	254 (23.28)	65 (28.26)	122 (27.17)	67 (16.42)	.
	2018	1109 (44.57)	459 (40.95)	113 (40.94)	537 (49.22)	129 (56.09)	217 (48.33)	187 (45.83)	.
	2019	828 (33.28)	434 (38.72)	106 (38.41)	288 (26.40)	30 (13.04)	105 (23.39)	153 (37.50)	.

[†]P-value for only pembrolizumab vs pembrolizumab + pemetrexed; Maintenance therapy with pemetrexed only was not analyzed due to very small sample size.
[‡]First-line treatment.
Data are n (%) unless otherwise noted. Percentages may not add up to 100 because of rounding.
BMI: Body mass index; LOT: Line of treatment; MT: Maintenance therapy; NSQ: Non-squamous; NS: Not specified; Pem: Pemetrexed; Pembro: Pembrolizumab; Q: Quartile; SD: Standard deviation.

Table 1. Baseline demographics and clinical characteristics at the start of first-line treatment (cont.).

Characteristic	n (%), except where noted	Overall	<4 cycles	≥4 cycles but no MT	All maintenance	Mixed maintenance	Maintenance therapy comparison		p-value[†,‡]
							Only Pembro	Pembro+Pem	
Body weight, kg	N	2480	1117	276	1087	230	449	404	0.0747
	Mean (SD)	75.34 (18.59)	75.09 (19.53)	74.65 (17.59)	75.77 (17.85)	78.80 (18.62)	76.03 (17.73)	73.88 (17.30)	.
	Median	73.48	73.35	73.75	73.66	75.98	73.66	71.49	.
	Min, Max	34.20, 176.90	34.20, 176.90	37.65,125.19	37.92, 144.70	40.10, 144.70	37.92, 136.98	38.61, 135.62	.
	Q1	62.14	61	62.14	63.5	65.05	63.96	61.79	.
	Q3	86.55	86.45	86.32	86.68	91.17	86.64	85.55	.
BMI	Underweight	174 (6.99)	87 (7.76)	23 (8.33)	64 (5.87)	7 (3.04)	26 (5.79)	31 (7.60)	0.0804
	Normal	943 (37.90)	431 (38.45)	94 (34.06)	418 (38.31)	83 (36.09)	174 (38.75)	158 (38.73)	.
	Overweight	815 (32.76)	351 (31.31)	101 (36.59)	363 (33.27)	78 (33.91)	144 (32.07)	140 (34.31)	.
	Obese	548 (22.03)	248 (22.12)	58 (21.01)	242 (22.18)	62 (26.96)	105 (23.39)	75 (18.38)	.
	Missing or unknown	8 (0.32)	4 (0.36)	0 (0.00)	4 (0.37)	0 (0.00)	0 (0.00)	4 (0.98)	.
Stage at initial diagnosis	Stage I	150 (6.03)	58 (5.17)	15 (5.43)	77 (7.06)	22 (9.57)	28 (6.24)	27 (6.62)	0.567
	Stage II	59 (2.37)	25 (2.23)	7 (2.54)	27 (2.47)	7 (3.04)	13 (2.90)	7 (1.72)	.
	Stage III	155 (6.23)	67 (5.98)	25 (9.06)	63 (5.77)	15 (6.52)	22 (4.90)	26 (6.37)	.
	Stage IV	2077 (83.48)	948 (84.57)	222 (80.43)	907 (83.13)	183 (79.57)	377 (83.96)	343 (84.07)	.
	Missing	47 (1.89)	23 (2.05)	7 (2.54)	17 (1.56)	3 (1.30)	9 (2.00)	5 (1.23)	.
Histology	NSQ cell carcinoma	2488 (100.00)	1121 (100.00)	276 (100.00)	1091 (100.00)	230 (100.00)	449 (100.00)	408 (100.00)	.
Smoking status	Yes	2221 (89.27)	1001 (89.30)	241 (87.32)	979 (89.73)	199 (86.52)	413 (91.98)	363 (88.97)	0.1722
	No	261 (10.49)	117 (10.44)	33 (11.96)	111 (10.17)	31 (13.48)	35 (7.80)	45 (11.03)	.
	Unknown/not determined	6 (0.24)	3 (0.27)	2 (0.72)	1 (0.09)	0 (0.00)	1 (0.22)	0 (0.00)	.
Performance status	0	635 (25.52)	219 (19.54)	90 (32.61)	326 (29.88)	64 (27.83)	143 (31.85)	118 (28.92)	0.8075
	1	891 (35.81)	410 (36.57)	86 (31.16)	395 (36.21)	89 (38.70)	161 (35.86)	143 (35.05)	.
	2	296 (11.90)	181 (16.15)	25 (9.06)	90 (8.25)	17 (7.39)	36 (8.02)	37 (9.07)	.
	3+	40 (1.61)	28 (2.50)	1 (0.36)	11 (1.01)	0 (0.00)	5 (1.11)	6 (1.47)	.
	Missing	626 (25.16)	283 (25.25)	74 (26.81)	269 (24.66)	60 (26.09)	104 (23.16)	104 (25.49)	.
EGFR mutation	Yes	86 (3.46)	41 (3.66)	12 (4.35)	33 (3.02)	9 (3.91)	11 (2.45)	12 (2.94)	0.0576
	No	1893 (76.09)	824 (73.51)	214 (77.54)	855 (78.37)	187 (81.30)	344 (76.61)	322 (78.92)	.
	Unknown/NS	143 (5.75)	65 (5.80)	17 (6.16)	61 (5.59)	13 (5.65)	19 (4.23)	28 (6.86)	.
	Untested	366 (14.71)	191 (17.04)	33 (11.96)	142 (13.02)	21 (9.13)	75 (16.70)	46 (11.27)	.

[†]P-value for only pembrolizumab vs pembrolizumab + pemetrexed; Maintenance therapy with pemetrexed only was not analyzed due to very small sample size.
[‡]First-line treatment.
Data are n (%) unless otherwise noted. Percentages may not add up to 100 because of rounding.
BMI: Body mass index; LOT: Line of treatment; MT: Maintenance therapy; NSQ: Non-squamous; NS: Not specified; Pem: Pemetrexed; Pembro: Pembrolizumab; Q: Quartile; SD: Standard deviation.

Table 1. Baseline demographics and clinical characteristics at the start of first-line treatment (cont.).

Characteristic	n (%), except where noted	Overall	<4 cycles	≥4 cycles but no MT	All maintenance	Mixed maintenance	Maintenance therapy comparison		p-value†,‡
							Only Pembro	Pembro+Pem	
ALK mutation	Yes	13 (0.52)	5 (0.45)	1 (0.36)	7 (0.64)	1 (0.43)	2 (0.45)	4 (0.98)	0.2515
	No	1939 (77.93)	847 (75.56)	215 (77.90)	877 (80.38)	193 (83.91)	351 (78.17)	330 (80.88)	.
	Unknown/NS	144 (5.79)	65 (5.80)	21 (7.61)	58 (5.32)	11 (4.78)	22 (4.90)	24 (5.88)	.
	Untested	392 (15.76)	204 (18.20)	39 (14.13)	149 (13.66)	25 (10.87)	74 (16.48)	50 (12.25)	.
KRAS mutation	Yes	557 (22.39)	257 (22.93)	61 (22.10)	239 (21.91)	46 (20.00)	91 (20.27)	102 (25.00)	0.3049
	No	796 (31.99)	349 (31.13)	78 (28.26)	369 (33.82)	84 (36.52)	148 (32.96)	136 (33.33)	.
	Unknown/NS	60 (2.41)	27 (2.41)	9 (3.26)	24 (2.20)	3 (1.30)	10 (2.23)	10 (2.45)	.
	Untested	1075 (43.21)	488 (43.53)	128 (46.38)	459 (42.07)	97 (42.17)	200 (44.54)	160 (39.22)	.
ROS1 mutation	Yes	6 (0.24)	4 (0.36)	0 (0.00)	2 (0.18)	0 (0.00)	1 (0.22)	1 (0.25)	0.0843
	No	1773 (71.26)	783 (69.85)	198 (71.74)	792 (72.59)	171 (74.35)	312 (69.49)	306 (75.00)	.
	Unknown/NS	155 (6.23)	66 (5.89)	25 (9.06)	64 (5.87)	11 (4.78)	24 (5.35)	28 (6.86)	.
	Untested	554 (22.27)	268 (23.91)	53 (19.20)	233 (21.36)	48 (20.87)	112 (24.94)	73 (17.89)	.
BRAF mutation	Yes	77 (3.09)	35 (3.12)	12 (4.35)	30 (2.75)	4 (1.74)	14 (3.12)	12 (2.94)	0.0384
	No	1463 (58.80)	651 (58.07)	149 (53.99)	663 (60.77)	141 (61.30)	255 (56.79)	265 (64.95)	.
	Unknown/NS	78 (3.14)	33 (2.94)	6 (2.17)	39 (3.57)	6 (2.61)	15 (3.34)	18 (4.41)	.
	Untested	870 (34.97)	402 (35.86)	109 (39.49)	359 (32.91)	79 (34.35)	165 (36.75)	113 (27.70)	.
PD-L1 percent staining	< = 1%	833 (33.48)	382 (34.08)	95 (34.42)	356 (32.63)	79 (34.35)	125 (27.84)	150 (36.76)	0.0131
	1–49%	544 (21.86)	233 (20.79)	69 (25.00)	242 (22.18)	54 (23.48)	95 (21.16)	93 (22.79)	.
	> = 50%	469 (18.85)	199 (17.75)	48 (17.39)	222 (20.35)	44 (19.13)	103 (22.94)	75 (18.38)	.
	Unknown	642 (25.80)	307 (27.39)	64 (23.19)	271 (24.84)	53 (23.04)	126 (28.06)	90 (22.06)	.
Time PD-L1 test to the start of LOT1, day	N	1846	814	212	820	177	323	318	0.7798
	Mean (SD)	71.92 (198.76)	64.39 (142.69)	64.03 134.58)	81.42 (252.89)	74.00 (185.20)	86.48 (308.01)	80.53 (223.09)	.
	Median	34	33	33	34	32	35	34	.
	Min, Max	1.00, 4701.00	1.00, 2020.00	4.00, 1237.00	1.00, 4701.00	3.00, 1578.00	3.00, 4701.00	1.00, 2871.00	.
	Q1	21	21	20	22	22	22	22	.
	Q3	51	51	49	51	49	54	50	.
Follow-up time, month	N	2488	1121	276	1091	230	449	408	<0.0001
	Mean (SD)	8.03 (6.94)	4.33 (5.12)	7.45 (6.10)	11.98 (6.62)	14.91 (6.51)	12.28 (6.87)	9.98 (5.69)	.
	Median	6.09	2.3	4.98	10.39	14.24	10.33	8.54	.
	Min, Max	0.03, 30.23	0.03, 28.19	2.07, 30.23	2.76, 30.20	4.18, 30.20	2.76, 29.77	2.76, 28.55	.
	Q1	2.55	1.18	3.11	6.84	9.8	6.94	5.61	.
	Q3	11.78	5.43	9.39	16.18	19.11	17.01	12.7	.

†P-value for only pembrolizumab vs pembrolizumab + pemetrexed; Maintenance therapy with pemetrexed only was not analyzed due to very small sample size.
‡First-line treatment.
Data are n (%) unless otherwise noted. Percentages may not add up to 100 because of rounding.
BMI: Body mass index; LOT: Line of treatment; MT: Maintenance therapy; NSQ: Non-squamous; NS: Not specified; Pem: Pemetrexed; Pembro: Pembrolizumab; Q: Quartile; SD: Standard deviation.

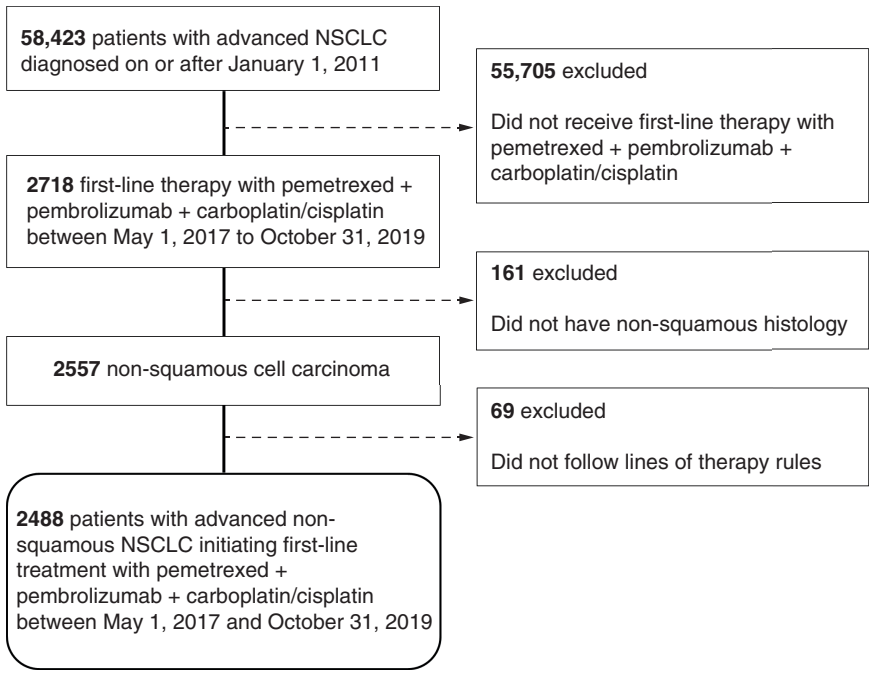

Figure 1. Patient selection. Patient selection from the Flatiron Health advanced NSCLC database. A total of 55,975 of 58,423 patients excluded and 2488 patients included in the overall study cohort.
NSCLC: Non-small-cell lung cancer.

MT (27.2 vs 16.4%; $p < 0.0001$), while a higher percentage of patients diagnosed with advanced disease in 2019 continued on pembro+pem MT versus pembro MT (37.5 vs 23.4%). Patients that received pembro MT had longer follow-up compared with pembro+pem MT (10.3 months [2.8–29.8] vs 8.5 months [2.8–28.6]; $p < 0.0001$).

Treatment duration

Patients were treated with pembro+pem+plat in the induction phase for a median duration of 2.1 months (interquartile range [IQR] pembro 1.2–2.8; pem 0.9–2.5; and plat 0.8–2.3, respectively). The median number of cycles for each drug in the regimen was four (IQR each 2–4).

Patients received pembro MT for a median duration of 3.5 months (IQR 1.4–7.9) and pembro+pem MT for a median of 2.8 months for each drug in the regimen (IQR each 0.9–5.1). The median number of cycles for pembro MT was six (IQR 3–12) and was four for each drug in the pembro+pem MT (IQR 2–8).

Factors associated with receiving MT

Data from the multivariable logistic regression model to evaluate factors associated with receiving MT are provided in the online supplement (Supplementary Table 1).

ECOG PS was significantly associated with receiving MT; patients with worse PS were less likely to receive MT compared with those with better PS. Compared with patients with PS scores of 0, those with PS 1 were 23% less likely to receive MT (odds ratio [OR]: 0.77; 95% CI: 0.62, 0.95), those with PS 2 were 56% less likely to receive MT (OR: 0.44; 95% CI: 0.33, 0.59), and those with PS ≥3 were 64% less likely to receive MT (OR: 0.36; 95% CI: 0.17, 0.75).

Race also was associated with receiving MT. Asian Americans were 55% less likely (OR: 0.45; 95% CI: 0.21, 0.94) and Whites were 27% less likely (OR: 0.73; 55, 0.98) to receive MT than Blacks.

Patients diagnosed with NSQ NSCLC in 2019 were 42% less likely to receive MT than those who were diagnosed prior to 2018. This finding may reflect the short follow-up time for patients diagnosed in 2019 who may still be in the induction phase of treatment.

OS

Unadjusted median OS

The unadjusted median OS in the overall cohort was 11.8 months (95% CI: 10.82, 12.76; Figure 2) and 21.0 months (N = 1091; 95% CI 19.31, 25.16) in the MT subgroup. Patients who did not continue on MT upon completion of four cycles of pembro+pem+plat had a median OS of 9.1 months (N = 276; 95% CI: 7.04, 12.70). Those who received less than four cycles of pembro+pem+plat had a median OS of 3.6 months (N = 1121; 95% CI 3.29, 4.01).

Multivariable cox proportional hazards model

A multivariable Cox regression model evaluated OS among patients who received first-line treatment with pembro+pem+plat; results showed that MT utilization, age, gender, advanced diagnosis year, ECOG PS, stage IV disease, *ROS1* mutation and PD-L1 TPS were significant predictors of OS (Table 2). The risk of death was lower for those who continued on MT (82%) and those who did not (59%) upon completion of four cycles of pembro+pem+plat, compared with those who received less than four cycles of pembro+pem+plat (hazard ratio [HR]: 0.18; 95% CI: 0.16, 0.20 and 0.41; 95% CI: 0.34, 0.51, respectively). The risk of death was 70% lower for those without a *ROS1* mutation compared with those with a mutation (HR: 0.30; 95% CI: 0.12, 0.74), 36% lower for those with PD-L1 TPS ≥50% compared with those with PD-L1 TPS <1% (HR: 0.64; 95% CI: 0.54, 0.77), and 16% lower for those ages 50 to 65 years compared with those 75 years or older (HR: 0.84; 95% CI: 0.72, 0.98).

The risk of death was 88% higher for patients with an initial diagnosis of stage IV disease compared with stage I (HR: 1.88; 95% CI: 1.39, 2.53), more than 20% higher for those diagnosed with advanced NSCLC in 2018 and 2019 compared with those diagnosed between 2011 and 2017 (HR: 1.21; 95% CI: 1.05, 1.40 and HR: 1.26; 95% CI: 1.04, 1.52, respectively) and 40% higher for men compared with women (HR: 1.40; 95% CI: 1.21, 1.62).

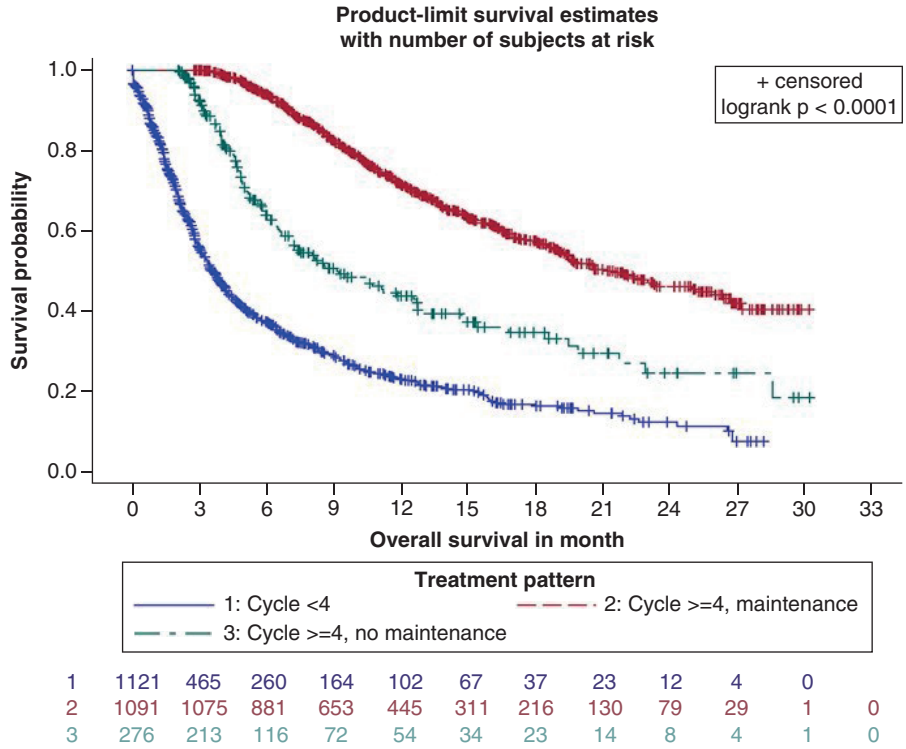

Figure 2. Overall survival. Kaplan–Meier curves depict real-world overall survival for 2488 patients with metastatic non-squamous non-small-cell lung cancer who initiated first-line pembrolizumab in combination with pemetrexed and platinum chemotherapy. Unadjusted overall survival are presented for patients who: continued on maintenance therapy upon completion of four cycles of pembro+pem+plat, did not continue on maintenance therapy upon completion of four cycles of pembro+pem+plat and received less than four cycles of pembro+pem+plat.

Table 2. COX regressions: factors associated with overall survival from the start of first-line treatment.

Characteristic	n	Group	OS from first line of therapy; N = 2488; HR (95% CI)	p-value†
Maintenance therapy	1121	Cycles <4	Reference	<0.0001
	1091	Cycles ≥4, maintenance	0.18 (0.16, 0.20)	–
	276	Cycles ≥4, no maintenance	0.41 (0.34, 0.51)	–
Age group at start of first line of therapy	584	≥75	Reference	0.0068
	926	65 to <75	0.95 (0.82, 1.11)	–
	870	50 to <65	0.84 (0.72, 0.98)	–
	108	<50	1.36 (1.00, 1.86)	–
Gender	1132	Female	Reference	<0.0001
	1356	Male	1.40 (1.21, 1.63)	–
Race	221	Black	Reference	0.1728
	42	Asian	0.58 (0.33, 1.01)	–
	1694	White	0.93 (0.76, 1.15)	–
	308	Other	0.82 (0.61, 1.09)	–
	223	Missing	0.83 (0.64, 1.07)	–
Advanced diagnosis year	551	2011–2017	Reference	0.0182
	1109	2018	1.21 (1.05, 1.40)	–
	828	2019	1.26 (1.04, 1.52)	–
Body weight, kilogram	2480	–	1.00 (0.99, 1.00)	0.1581
BMI	174	Underweight	Reference	0.8210
	943	Normal	0.90 (0.70, 1.15)	–
	815	Overweight	0.93 (0.69, 1.26)	–
	548	Obese	0.91 (0.60, 1.36)	–
Stage at initial diagnosis	150	Stage I	Reference	<0.0001
	59	Stage II	1.54 (0.93, 2.52)	–
	155	Stage III	1.17 (0.80, 1.70)	–
	2077	Stage IV	1.88 (1.39, 2.53)	–
	47	Missing	1.38 (0.79, 2.41)	–
Smoking status	2221	Yes	Reference	0.0121
	261	No	0.82 (0.66, 1.02)	–
	6	Unknown/not documented	3.33 (1.21, 9.16)	–
Performance status	635	0	Reference	<0.0001
	891	1	1.67 (1.42, 1.96)	–
	296	2	2.12 (1.73, 2.60)	–
	40	≥3	2.68 (1.76, 4.09)	–
	626	Missing	1.39 (1.17, 1.66)	–
EGFR mutation	86	Yes	Reference	0.2382
	1893	No	1.37 (0.96, 1.96)	–
	143	Unknown or not specified	1.18 (0.73, 1.88)	–
	366	Untested	1.44 (0.89, 2.34)	–
ALK mutation	13	Yes	Reference	0.0362
	1939	No	10.87 (1.52,77.61)	–
	144	Unknown or not specified	11.27 (1.54,82.25)	–
	392	Untested	8.11 (1.11,59.48)	–
KRAS mutation	557	Yes	Reference	0.2619
	796	No	0.85 (0.71, 1.00)	–
	60	Unknown or not specified	0.82 (0.51, 1.33)	–
	1075	Untested	0.91 (0.76, 1.10)	-

†p-value was calculated by Cox proportional hazards regression model and hazards ratio was shown as the ratio of risk of death in specified groups relative to the reference group.
BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival.

Table 2. COX regressions: factors associated with overall survival from the start of first-line treatment (cont.).

Characteristic	n	Group	OS from first line of therapy; N = 2488; HR (95% CI)	p-value†
ROS1 mutation	6	Yes	Reference	0.0001
	1773	No	0.30 (0.12, 0.74)	–
	155	Unknown or not specified	0.27 (0.10, 0.70)	–
	554	Untested	0.43 (0.17, 1.09)	–
BRAF mutation	77	Yes	Reference	0.5193
	1463	No	1.29 (0.87, 1.92)	–
	78	Unknown or not specified	1.52 (0.86, 2.69)	–
	870	Untested	1.34 (0.87, 2.06)	–
PD-L1 percent staining	833	≤1%	Reference	<0.0001
	544	1%–49%	0.95 (0.81, 1.12)	–
	469	≥50%	0.64 (0.54, 0.77)	–
	642	Unknown	1.10 (0.94, 1.30)	–

†p-value was calculated by Cox proportional hazards regression model and hazards ratio was shown as the ratio of risk of death in specified groups relative to the reference group.
BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival.

Worse ECOG PS scores were also associated with a higher risk of death—67% higher for patients with ECOG PS 1 versus PS 0 (HR: 1.67; 95% CI: 1.42, 1.96); those with ECOG PS 2 or 3/4 were more than twice as likely to die compared with those with PS 0 (HR: 2.12; 95% CI: 1.73, 2.60 and HR: 2.68; 95% CI: 1.76, 4.09, respectively).

Discussion

This retrospective analysis focused on patients who continued on MT following pembro+pem+plat. Patient characteristics for the overall cohort and the MT subgroup were comparable – most patients were White, male, older than 65, had a history of smoking, presented with stage IV disease at initial diagnosis, and had an ECOG PS of 0 or 1. Similar patient characteristics were reported in other real-world studies of patients with metastatic NSCLC treated with PD-L1 inhibitors in terms of being a smoker, White, older than 65, and male [8–11]. More patients in our study presented with stage IV disease (84 vs 64%) [9] and fewer had ECOG PS of 0 or 1 (61 vs 100%) [10], which may be attributed to variations in study designs. The patient population in our study was not restricted by ECOG PS whereas the patient population in the study by Velcheti and colleagues was restricted to those with an ECOG PS of 0 or 1.

Differences in patient baseline characteristics were also noted between this study and the KEYNOTE-189 trial [2,3]. Higher proportions of patients in this study were 75 years or older (23 vs 9%) and female (46 vs 41%) compared with KEYNOTE-189, while there were lower proportions with an ECOG PS of 0 or 1 (61 vs 99%) and PD-L1 TPS ≥1% (41 vs 63%). These findings are not unexpected as patients who are elderly or have a poor PS are often excluded due to stringent eligibility criteria of clinical trials, as in KEYNOTE-189 where the trial population was restricted to those with an ECOG PS of 0 or 1. Inconsistencies in PD-L1 status between KEYNOTE-189 and our study may be due to differences in the proportion of patients with unknown PD-L1 status (6% vs 26%, respectively), whom if classified accurately may increase the number of patients with PD-L1 ≥1% in our study.

The proportion of patients with unknown PD-L1 status receiving pembro+pem+plat treatment in our study is consistent with those reported by Leapman and colleagues (2020) [12] which showed that 33% of patients with advanced NSCLC with untested PD-L1 expression received first-line treatment with an immune checkpoint inhibitor in the community setting. The timeframes for these two real-world studies were subsequent to or along the continuum of regulatory approval of pembro+pem+plat for metastatic NSQ NSCLC indication. Given the survival benefit seen in KEYNOTE-189 for patients regardless of their PD-L1 status, clinicians could treat patients with pembro+pem+plat prior to determining their PD-L1 level.

Consistent with KEYNOTE-189 [2,3], the overall cohort in this study received a median of four cycles of pembro+pem+plat therapy in the induction phase. However, 44% of patients in the overall cohort continued on MT compared with nearly 80% in the trial. This may reflect censoring based on data cut off for our real-world study, where some patients were still in the induction phase of the treatment and did not have the opportunity to continue on to MT. This may also be due to disease progression, toxicity, or death occurring within the first four cycles of the treatment. When looking at the subgroup of patients in our study that completed four cycles, a similar proportion of patients continued on MT (80%).

Notably, almost one-quarter of patients in this study were 75 years or older and slightly more than one-tenth had an ECOG PS ≥2 which may be indicative of tolerability of pembro+pem+plat in these patients. Though tolerability was not examined in this study, there are data that suggests that MT with pembro+pem was tolerable in patients treated with pembro+pem+plat. Adverse event (AE) rates for those receiving pembro+pem+plat and subsequent MT in KEYNOTE-189 were 99.8% for any grade AE and 65.8% to 67.2% for grades 3 to 5 [2,3]; the authors noted that the toxicity associated with this regimen was manageable. A post-hoc analysis of KEYNOTE-189 data showed that all hematologic and most non-hematologic AEs grade 3 or higher occurred within four cycles of treatment and most resolved within two weeks [13]. The analysis also showed that for those receiving triplet therapy, a third of discontinuation of either pembro or pem due to AEs occurred within the first four cycles. Furthermore, findings from a retrospective, observational study of patients with advanced NSQ NSCLC receiving triplet therapy and subsequent MT with pembro+pem suggested that AE rates during MT for anemia, neutropenia, and kidney injury in the real world were comparable to those reported in KEYNOTE-189 [2,3,14]. Together, these data provide evidence that MT with pembro+pem was tolerable in trials and real-world settings.

In terms of factors associated with receiving MT, this study showed that ECOG PS at diagnosis, race, and advanced diagnosis year influenced whether patients continued on MT after four cycles of pembro+pem+plat. Patients with PS scores of ≥2 were half as likely to continue on MT compared with those with PS scores of 0. Patients who had missing PS scores at diagnosis were as likely to continue on MT as those with PS scores of 1, suggesting that clinicians may recommend MT based on other factors when PS data are not available.

Findings from this study confirmed previous research regarding prognostic factors for survival. The risk of death was lower for those receiving MT [11], while the risk of death was higher for men, for those with metastatic disease at initial diagnosis, and those with poor ECOG PS at baseline [11,15,16]. The risk of death was a third lower for those with PD-L1 TPS ≥50% compared with those with PD-L1 <1% and one-sixth lower for 50- to 65-year-olds compared with those 75 years or older. The relationship between PD-L1 and survival is similarly observed by Velcheti and colleagues and confirmed by Liu and colleagues, where OS for those with PD-L1 expression levels ≥50% and <1% were 20.6 months and 13.2 months, respectively [10,17].

Immuno-oncology monotherapy has been shown to be extremely effective in patients with high PD-L1 expression levels in clinical trials and real-word studies with median OS ranging from 18.9 to 30.0 months [18–20]. While we did not address decision-making, it was notable that more patients who received MT with pembro+pem had low PD-L1 expression levels and more patients who received pembro MT had high PD-L1 expression levels, suggesting that clinicians may recommend combination therapy when PD-L1 is low. Clinicians may also initiate pembro+pem+plat in the absence of tests results and switch to pembro monotherapy once tests results become available for those with high PD-L1.

The median OS was similar for the patients in our study – a heterogenous population in a real-world setting –and the relatively homogenous population in KEYNOTE-189. Our study reported a median OS of 21.0 months (95% CI: 18.6, 25.2) for patients who continued on MT with pembro and/or pem after completing four cycles of pembro+pem+plat compared with 22.0 months (95% CI: 19.5, 25.2) in KEYNOTE-189. Although the median OS in these studies is similar, it should be noted that the study designs and analysis populations are different and the results should be interpreted in light of differences in the two studies. As noted previously, fewer patients in our study had PD-L1 TPS ≥50% (19 vs 33%), the PD-L1 expression level showing the greatest OS benefit in the KEYNOTE-189 trial [2], which be attributed to a larger proportion of patients in our study having unknown PD-L1 status compared with KEYNOTE-189; and fewer patients had ECOG PS of 0 or 1. Patients who progressed on pembro+pem+plat were not included in the OS estimation in this study, but were included in the KEYNOTE-189 estimate.

Survival benefit was seen in two other real-world studies that evaluated the KEYNOTE 189 treatment regimen using the Flatiron database (16.5 months [95% CI: 13.2–20.6]; and 17.2 months [95% CI: 13.6–19.9]) [10,17]. Median OS in the overall cohort in our study was shorter (11.8 months [95% CI: 10.8–12.5]), which may be attributed to differences in selection criteria for the analysis cohorts. Unlike our study, the cohorts were restricted to those with ECOG PS of 0 or 1, without *EGFR* and *ALK* genomic aberrations, and with a minimum 12- and 19-month follow-up. In our study, slightly more than a third of patients had ECOG PS greater than 2 or missing, which could have contributed to poorer OS outcomes. Similarly 3.5% and 0.5% of patients in our cohort harbored *EGFR* and *ALK* alterations and 20% and 22% were either not tested or had unknown status, respectively. Research has shown that *EGFR* and *ALK* alterations are associated with low efficacy of immunochemotherapy [21,22], suggesting that these patients or patients with unknown *EGFR* or *ALK* status treated with pembro+pem+plat in

our study may have received limited OS benefit. Also, the minimum follow-up in our study was one month, which could have negatively biased our study as it did not allow for longer assessment of potential treatment benefit. Note that Velcheti *et al.* and Liu *et al.* did not report OS data for MT separately which prevented any comparison to median OS observed in the subgroup of patients who received MT in our study.

The current study was limited by certain factors. First, the majority of oncology practices in the Flatiron network are community practices in the US. Therefore, these findings may not be generalizable to academic settings or practices outside of the US. Second, data availability is limited to what is documented in the EHR database for participating clinics and healthcare providers; and data may be missing for patients who moved to and from participating and non-participating clinics. Third, data for variables such as ECOG PS or PD-L1 TPS were missing or unknown for one-quarter of the sample, which may have introduced selection bias. Last, tumor response, progression-free survival, and AE reports were not included in the EHR database used for analyses and thus, precluded assessment of these outcomes in our study.

This study gives context to how regulatory approvals and treatment guidelines for advanced NSCLC are being applied in clinical practice. Most patients with advanced NSCLC that completed induction with pembro+pem+plat in this real-world study continued on MT with pembro and/or pem; these patients who went on MT demonstrated OS benefit similar to that observed in the KEYNOTE-189 trial. These findings demonstrate the importance of treating patients in routine clinical practice similar to how drugs are studied in clinical trials to attain survival benefit seen in trials.

The success of immunotherapy in treatment of advanced NSCLC has brought new hope to further the treatment of cancer patients. Clinical trials are underway that evaluate immunotherapy in treatment of early-stage disease. Atezolizumab and nivolumab were recently approved in the US in patients with stage II to IIIA NSCLC for those with PD-L1 $\geq$1% or regardless of PD-L1 expression, respectively; and pembro is currently being studied in patients with stage II to IIIA NSCLC with an available PD-L1 immunohistochemistry expression assessment (ImPower010, CheckMate-816, and KEYNOTE-91, respectively) [23–25].

Immunotherapy is also being studied in biomarker-driven NSCLC patient populations. CheckMate-722 [26], Orient-31 [27], and KEYNOTE-789 [28] are trials for patient populations with *EGFR* mutations. Novel combinations of immunotherapy with antibody drug conjugate [29] and targeted therapies such as KRAS G12C are also underway [30]. In addition new routes of drug administration (e.g., subcutaneous) are being studied and approved [31]. Literature on retreatment with immunotherapy also is available as a feasible treatment option [32,33].

Conclusion

The rate of MT utilization in advanced NSCLC patients primarily treated in community oncology centers in the USA was less than 50%. Patients that continued on MT with pembro and/or pem had longer OS compared with those who did not continue on MT upon completion of induction therapy in this study. Furthermore, the survival benefit observed in this real-world patient population that continued on MT was similar to that reported in the pivotal trial (KEYNOTE-189). These findings highlighted the role of MT in prolonging survival; and underscored the benefit of treatment with drugs consistent with how they are studied in clinical trials. Further efforts are needed to increase MT utilization in advanced NSCLC patients to realize the survival benefit observed in the pivotal trial.

Summary points

- Pembrolizumab (pembro) in combination with pemetrexed (pem) and platinum chemotherapy (plat; carboplatin or cisplatin) is a front-line standard of care option for patients with metastatic non-squamous (NSQ) non-small-cell lung cancer (NSCLC) without actionable genomic alterations and is recommended by the National Comprehensive Cancer Network (NCCN) guidelines.
- This study aimed to describe patient characteristics, treatment patterns, maintenance therapy (MT) utilization, and survival outcomes of patients with advanced NSQ NSCLC receiving first-line treatment with pembro+pem+plat in routine clinical practice in the USA.
- This retrospective observational descriptive study utilized Flatiron Health's electronic health record-derived database for advanced NSCLC.
- The overall cohort included adults with advanced NSQ NSCLC who received first-line therapy with pembro+pem+plat between 1 May 2017 and 31 October 2019.
- Patients were assigned to the MT subgroup if they received MT following pembro+pem+plat in the first-line setting.

- 58,423 patients with a diagnosis of advanced NSCLC were identified from the database, of whom 2488 met the selection criteria for NSQ histology and first-line treatment with pembro+pem+plat between 1 May 2017 and 31 October 2019.
- Of the overall cohort, 1121 (45.1%) received less than four cycles of pembro+pem+plat, 1091 (43.9%) received 4 cycles plus MT with pembro and/or pem (MT subgroup), and 276 (11.1%) received four cycles without continuing on MT.
- Of those that completed 4 cycles (n = 1367), 79.8% and 20.2% received or did not receive MT, respectively.
- Patients in the overall cohort were primarily White (68.1%) with a mean age of 67.4 ± 9.6 years, and there were more males than females (54.5% vs 45.5%). Most patients had a history of smoking (89.3%) and presented with stage IV disease at initial diagnosis (83.5%); 61.3% had Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The proportions of patients in the PD-L1 TPS subgroups of <1%, 1%–49%, ≥50%, or unknown were 33.5%, 21.9%, 18.9%, and 25.8%, respectively. The baseline characteristics for the MT subgroup (n = 1091) were similar.
- Patients were treated with pembro+pem+plat in the induction phase for a median duration of 2.1 months (interquartile range [IQR] pembro 1.2–2.8; pem 0.9–2.5; and plat 0.8–2.3, respectively). The median number of cycles for each drug in the regimen was four (IQR each 2–4).
- Patients received pembro MT for a median duration of 3.5 months (IQR 1.4–7.9) and pembro+pem MT for a median of 2.8 months for each drug in the regimen (IQR each 0.9–5.1). The median number of cycles for pembro MT was six (IQR 3–12) and was four for each drug in the pembro+pem MT (IQR 2–8).
- ECOG PS was significantly associated with receiving MT; patients with worse PS were less likely to receive MT compared with those with better PS.
- Race also was associated with receiving MT.
- Patients diagnosed with NSQ NSCLC in 2019 were 42% less likely to receive MT than those who were diagnosed prior to 2018.
- The unadjusted median OS in the overall cohort was 11.8 months (95% confidence interval [CI] 10.82, 12.76; Figure 1) and 21.0 months (n = 1091; 95% CI: 19.31, 25.16) in the MT subgroup.
- Patients who did not continue on MT upon completion of four cycles of pembro+pem+plat had a median OS of 9.1 months (n = 276; 95% CI 7.04, 12.70).
- Those who received less than four cycles of pembro+pem+plat had a median OS of 3.6 months (n = 1121; 95% CI: 3.29, 4.01).
- The risk of death was lower for those who continued on MT (82%) and those who did not (59%) upon completion of four cycles of pembro+pem+plat, compared with those who received less than four cycles of pembro+pem+plat (hazard ratio [HR], 0.18; 95% CI: 0.16, 0.20 and 0.41; 95% CI: 0.34, 0.51, respectively).
- Patient characteristics for the overall cohort and the MT subgroup were comparable – most patients were White, male, had a history of smoking, presented with stage IV disease at initial diagnosis, and had an ECOG PS of 0 or 1.
- Consistent with KEYNOTE-189, the overall cohort in this study received a median of four cycles of pembro+pem+plat therapy in the induction phase. However, 44% of patients in the overall cohort continued on MT compared with 76% to 79% in the trial.
- The median OS was similar for the patients in our study – a heterogenous population in a real-world setting – and the relatively homogenous population in KEYNOTE-189. Our study reported a median OS of 21.0 months (95% CI: 18.6, 25.2) for patients who continued on MT with pembro and/or pem after completing four cycles of pembro+pem+plat compared with 22.0 months (95% CI: 19.5, 25.2) in KEYNOTE-189.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2022-0166

Author contributions

All authors and Eli Lilly and Company were involved in data interpretation, and reviewed and approved the manuscript. The authors maintained control over the final content. A list of the contributions is provided below:

- Conception of the work: H Aggarwal, CE Muehlenbein.
- Design of the work: H Aggarwal, K Bayo, CE Muehlenbein.
- Acquisition of data for the work: Y Han.
- Analysis of data for the work: H Aggarwal, K Bayo, Y Han, YE Zu.
- Interpretation of data for the work: H Aggarwal, K Bayo, Y Han, CE Muehlenbein, YE Zu, JS Kim.
- Drafting of the work: H Aggarwal, K Bayo, YE Zu.
- Critical revision of the work for important intellectual content: H Aggarwal, K Bayo, Y Han, CE Muehlenbein, YE Zu, JS Kim.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. This retrospective observational descriptive study utilized Flatiron Health's electronic health record (EHR)-derived database for advanced NSCLC. The database complies with the Health Insurance Portability and Accountability Act and a waiver of informed consent was approved by an institutional review board prior to study conduct.

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