Case Report

Brief Report on Use of Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis

Monika A. Izano,[1] Connor Sweetnam,[1] Chenan Zhang,[1] James L. Weese,[3] Douglas Reding,[4] Jonathan Treisman,[4] Anand Patel,[4] Bindu Potugari,[2] Andrew Stafford,[1] Frank M. Wolf,[1] Mary Tran,[1] Thomas D. Brown,[1] Shirish M. Gadgeel[2]

Clinical Practice Points

- In adults diagnosed with advanced NSCLC in the community health system setting, the real-world treatment benefit of pembrolizumab is consistent with that observed in clinical trials.
- In this real world analysis, patients treated with pembrolizumab monotherapy experience longer overall survival compared to those treated with pembrolizumab plus platinum-based chemotherapy.

Clinical Lung Cancer, Vol. 000, No.xxx, 1–4 © 2023 The Authors. Published by Elsevier Inc.

Keywords: Metastatic lung cancer, Non-small cell lung cancer, Immunotherapy, Monoclonal antibodies, First line treatment

Since pembrolizumab's 2016 regulatory approval in the United States (US), immune checkpoint inhibitors, alone or in combination with chemotherapy, have become standard of care for patients with advanced non-small cell lung cancer (aNSCLC) without driver mutations.[1-3] Although there are some exceptions such as seen in a small scale (n = 88), single center retrospective study,[4] previous research has largely confirmed survival benefits for first line pembrolizumab monotherapy (monotherapy) and pembrolizumab used in combination with chemotherapy (combination) compared to chemotherapy alone for mNSCLC patients in the real-world setting through retrospective analysis of administrative claims, electronic medical records, and national cancer registry data (Netherlands, Denmark).[5-9] To our knowledge, comparative data on monotherapy vs. combination are unavailable.

This retrospective analysis of patient-level data examined overall survival (OS) and time to next treatment or death (TTNT) in adults diagnosed at presentation with stage IIIB, IIIC, or IV, or recurrent locally advanced/metastatic non-small cell lung carcinoma (a/mNSCLC) between January 1,2015 – September 30,2020 who received first line pembrolizumab alone or with a platinum-based (cisplatin or carboplatin with paclitaxel, nab-paclitaxel, pemetrexed, gemcitabine, or docetaxel) chemotherapy, with 2+ encounters in a US community health system. Certified tumor registrars abstracted relevant data from electronic health records. All data and associated analyses were compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) to ensure patient privacy, and as a secondary analysis of existing data, institutional review board approval and informed consent were not required for this study. For mortality, patients were followed from first line initiation to the earliest of: date of death, date of last contact or December 31, 2020 (end of study); for TTNT, censoring also occurred at second line therapy. Patients were classified into either the pembrolizumab monotherapy or combination therapy cohorts. The Kaplan-Meier estimator was used to assess the distribution of OS and TTNT in each cohort. In addition, Cox proportional hazards models adjusted for age, sex, race, year and stage of diagnosis, histology, presence of brain and liver metastasis, smoking history, ECOG performance status (PS), comorbidity and tumor proportion score (TPS), and these were used to evaluate the association of first line treatment with OS and TTNT.

Of the 739 study patients (median age 67 years at a/mNSCLC diagnosis; 52% male; 82% White, 12% Black), 79% had non-squamous histology and 82% had *de novo* metastatic disease at diagnosis (Table 1). Brain and liver metastases were documented in 25% and 10% of patients, respectively. The monotherapy

[1]Syapse, San Francisco, CA, USA
[2]Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, USA
[3]Cancer Service Line, Advocate Aurora Health, Milwaukee, WI, USA
[4]Ascension, Milwaukee, WI

Submitted: Nov 8, 2022; Revised: Jan 25, 2023; Accepted: Jan 31, 2023; Epub: xxx

Address for correspondence: Monika Izano, Syapse, Inc., 303 2nd St, North Tower, Suite 550, San Francisco, CA 94107.
E-mail contact: Monika.Izano@syapse.com

https://doi.org/10.1016/j.cllc.2023.01.011

Please cite this article as: Monika A. Izano et al, Brief Report on Use of Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2023.01.011

Table 1 Patient Characteristics

	Overall n, (%)	Pembrolizumab + Chemotherapy n (%)	Pembrolizumab n (%)
Total patients	739	398	341
Non-squamous histology	585 (79)	312 (78)	273 (80)
De novo metastatic	608 (82)	337 (85)	271 (79)
Female	353 (48)	174 (44)	179 (52)
Male	386 (52)	224 (56)	162 (48)
Race			
White	607 (82)	324 (81)	283 (83)
Black	91 (12)	54 (14)	37 (11)
Asian/PI	11 (1)	7 (2)	4 (1)
Smoking history			
Current smoker	194 (26)	110 (28)	84 (25)
Former smoker	305 (41)	170 (43)	135 (40)
Never smoker	39 (5)	27 (7)	12 (4)
Site of metastasis			
Brain	185 (25)	95 (24)	90 (26)
Liver	72 (10)	51 (13)	21 (6)
Bone	233 (32)	140 (35)	93 (27)
ECOG			
ECOG 0-1	117 (16)	65 (16)	52 (15)
ECOG 1->1	349 (47)	196 (50)	153 (45)
Unknown	273 (37)	137 (34)	136 (40)
Biomarker testing and results			
PD(L)-1, tested	616 (83)	316 (79)	300 (88)
Positive	512 (83)	217 (69)	295 (98)
Tumor proportion score			
1% - 49%	*111 (22)*	*88 (41)*	*23 (8)*
50% - 100%	*249 (49)*	*55 (25)*	*194 (66)*
Unknown	*152 (30)*	*74 (34)*	*78 (26)*
EGFR, tested	469 (80)	234 (75)	235 (86)
Positive	26 (6)	19 (8)	7 (3)
ALK, tested	434 (74)	226 (72)	208 (76)
Positive	4 (1)	2 (1)	2 (1)
BRAF, tested	354 (48)	204 (51)	150 (44)
Positive	12 (3)	5 (2)	7 (5)
ROS1, tested	481 (65)	251 (63)	230 (67)
Positive	1 (<1)	0 (0)	1 (0)
Died during follow-up	422 (57)	236 (59)	186 (55)

Abbreviations: ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; n = number; PD (L)-1 = programmed death (ligand).

cohort included 341 patients and the combination therapy cohort included 398 patients. Compared with combination patients, a greater proportion of monotherapy patients were female (52% vs. 44%). During the 10-month median follow-up, 24% of all study patients received second line therapy and 57% died. The majority of patients had their tumors tested for PD(L)-1, epidermal growth factor receptor (EGFR), and/or anaplastic lymphoma kinase (ALK) (83%, 80%, and 74%, respectively); testing for each of these biomarkers was more common in the monotherapy cohort than in the combination therapy cohort (Table 1). Among patients tested for PD(L)-1, nearly all of the monotherapy patients (98%) and over two-thirds (69%) of the combination therapy patients had positive results. ROS1 and BRAF testing and positivity were less common (65% and 1%; 48% and 3%).

Kaplan-Meier survival curves indicated that monotherapy patients had longer median OS than combination patients (18 months; 95% Confidence Interval, [14, 22] for monotherapy vs. 13 months [11, 15] for combination therapy; $P = .02$; Table 2). In both treatment cohorts, median OS was longer for patients with non-squamous histology than squamous histology (monotherapy: 20 [14, 24] vs. 12 [7, 18] months; combination therapy 15 [12, 17] vs. 8 [6, 13] months). Monotherapy patients with both non-squamous and squamous tumors, brain metastases and/or liver metastases, and patients with ECOG PS>1 had a longer median OS

Please cite this article as: Monika A. Izano et al, Brief Report on Use of Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2023.01.011

Table 2 Summary of Median Overall Survival Results

	Pembrolizumab		Pembrolizumab +Chemotherapy	
	n	Median OS, mo (95% CI)	n	Median OS, mo (95% CI)
All patients	341	18 (14, 22)	398	13 (11, 15)
Histology				
Squamous	68	12 (7, 18)	86	8 (6, 13)
Non-squamous	273	20 (14, 24)	312	15(12, 17)
Liver metastases	21	-[a] (3, -)	51	9 (5, 12)
Brain metastases	90	14 (5, 18)	95	11 (7, 17)
Tumor proportion score				
1%-49%	23	14 (4, 24)	88	11 (8, 17)
≥50%	194	15 (8, 21)	55	15 (10, 35)
Unknown	78	18 (14, -)	74	12 (4, 24)
ECOG > 1	54	6 (2, 10)	50	4 (2, 6)

Abbreviations: CI = confidence interval;ECOG = Eastern Cooperative Oncology Group; OS = overall survival
[a] Median OS was not reached.

than their counterparts in the combination therapy cohort. Time to next treatment followed a similar pattern to that observed for OS (Supplemental Table 1).

In Cox proportional hazards models adjusted for age, sex, race, year of treatment initiation, metastatic status, histology, presence of brain and liver metastasis, smoking history, ECOG PS, comorbidity, and tumor proportion score (TPS), monotherapy was associated with reduced mortality (hazard ratio [HR] 0.8 [0.6, 1.0], $P = .02$] and reduced hazard of initiating next treatment (HR 0.8 [0.7, 1.0], $P = .08$) compared with combination therapy (Supplemental Figures 1 & 2). Age of 75 years or older, squamous histology, presence of brain and liver metastasis, and ECOG PS>1 or unknown, were all statistically significantly associated with increased hazard of mortality; female sex and current smoking status were significantly associated with reduced mortality risk (Supplemental-Figure 1). Squamous histology, presence of brain metastasis, ECOG PS >1 and Charlson Comorbidity Index >2 were all statistically significantly associated with increased hazard of initiating next treatment, while female sex was significantly associated with reduced risk of initiating a subsequent treatment (Supplemental Figure 2).

While real-world data is lacking, a recent US Food and Drug Administration (FDA) pooled analysis of 2018 patients from randomized control trials, compared the progression-free and overall survival of patients receiving first-line treatment with anti-PD(L)-1 therapy in combination with chemotherapy vs. immunotherapy alone for aNSCLC with PD(L)-1 score 1% to 49%.[10] The study reported longer progression free and overall survival in the combination therapy group, both in crude analyses (Kaplan-Meier median OS 21.4 vs. 14.5 months; median PFS 7.7 vs. 4.2 months), as well as in Cox proportional hazards models adjusted for age, ECOG PS, and smoking (OS HR 0.6 [0.52, 0.90]; PFS HR 0.60 [0.48, 0.76]). The study found similar outcomes in both treatment arms for patients 75 and older. Differences in population characteristics such as the distribution of TPS, age and histology as well as differences in immunotherapeutic agents received (not reported) may have led to differences with this report. While we adjusted for key known confounders of the relationship between treatment and clinical outcomes, residual confounding may be present.

Our study confirms extended OS among patients with a/mNSCLC who received first line pembrolizumab in the real-world, although the observed benefits were more modest than those reported in clinical trials, particularly for patients with squamous histology. In addition, our study also demonstrates, for the first time, longer OS among patients with first line pembrolizumab monotherapy compared with patients who received first line pembrolizumab in combination with platinum-based chemotherapy. While these findings must be replicated in larger populations, this study provides an important case study of how well-curated, clinically detailed real-world data can be used to evaluate treatment efficacy outside of the clinical trial setting.

Disclosure

Shirish Gadgeel has served on advisory boards for Merck, Blueprint, Gilead, Novartis, BMS, Genentech/Roche, Astra-Zeneca, Mirati, Daichii, Takeda, and Pfizer. Monika Izano, Chenan Zhang, Connor Sweetnam, Frank Wolf, Mary Tran, and Thomas Brown are all employees and stockholders of Syapse. Andrew Stafford was employed by Syapse at the time the study was conducted. James Weese, Douglas Reding, Jonathan Treisman, Anand Patel, and Bindu Potugari have no conflicts to disclose.

Author Contributions

Shirish Gadgeel, Thomas Brown, Monika Izano, and Chenan Zhang developed the conceptualization, methodology, and validation of the study. Connor Sweetnam and Andrew Stafford performed the formal analysis. Thomas Brown and Monika Izano supervised this research. All authors contributed to the writing of the original draft and the review and editing of subsequent drafts; additionally, all authors approved the final version of this manuscript.

Prior Presentations

Selected results from this study were presented at the IASLC 2021 World Conference on Lung Cancer.

Please cite this article as: Monika A. Izano et al, Brief Report on Use of Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2023.01.011

Data Availability

The datasets generated and analyzed for the current study are proprietary and therefore, not publicly available.

Acknowledgment

The authors would like to thank Sally Wade (Wade Outcomes Research and Consulting, Salt Lake City, Utah) for medical writing support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2023.01.011.

References

1. FDA Approves Expanded Label for Merck's Keytruda (pembrolizumab) in Patients with Metastatic Nonsquamous NSCLC with No EGFR or ALK Genomic Tumor Aberrations. Drugs.com. Available at: https://www.drugs.com/newdrugs/fda-approves-expanded-label-merck-s-keytruda-pembrolizumab-patients-metastatic-nonsquamous-nsclc-no-4805.html.Accessed June 6, 2022
2. FDA Approves Keytruda (pembrolizumab) in Combination with Carboplatin and Either Paclitaxel or Nab-Paclitaxel for the First-Line Treatment of Patients with Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC). Drugs.com. Available at: https://www.drugs.com/newdrugs/fda-approves-keytruda-pembrolizumab-combination-carboplatin-either-paclitaxel-nab-paclitaxel-first-4853.html. Accessed June 6, 2022.
3. FDA Approves First Immunotherapy Treatment for Lung Cancer - National Cancer Institute. Available at: https://www.cancer.gov/news-events/cancer-currents-blog/2015/fda-opdivo. Accessed June 7, 2021
4. Jiménez Galán R, Prado-Mel E, Pérez-Moreno MA, Caballano-Infantes E, Flores Moreno S. Influence of performance status on the effectiveness of pembrolizumab monotherapy in first-line for advanced non-small-cell lung cancer: Results in a real-world population. *Biology*. 2021;10(9):890.
5. Cramer-van der Welle CM, Verschueren MV, Tonn M, et al. Real-world outcomes versus clinical trial results of immunotherapy in stage IV non-small cell lung cancer (NSCLC) in the Netherlands. *Sci Rep*. 2021;11(1):6306. doi:10.1038/s41598-021-85696-3.
6. Ivanović M, Knez L, Herzog A, Kovačević M, Cufer T. Immunotherapy for Metastatic Non-Small Cell Lung Cancer: Real-World Data from an Academic Central and Eastern European Center. *Oncologist*. 2021;26(12):e2143–e2150. doi:10.1002/onco.13909.
7. Mouritzen MT, Carus A, Ladekarl M, et al. Nationwide Survival Benefit after implementation of first-line immunotherapy for patients with advanced NSCLC—real world efficacy. *Cancers (Basel)*. 2021;13(19):4846. doi:10.3390/cancers13194846.
8. Velcheti V, Hu X, Piperdi B, Burke T. Real-world outcomes of first-line pembrolizumab plus pemetrexed-carboplatin for metastatic nonsquamous NSCLC at US oncology practices. *Sci Rep*. 2021;11(1):9222. doi:10.1038/s41598-021-88453-8.
9. Velcheti V, Hu X, Yang L, Pietanza MC, Burke T. Long-term real-world outcomes of first-line pembrolizumab monotherapy for metastatic non-small cell lung Cancer With ≥50% expression of programmed cell death-ligand 1. *Front Oncol*. 2022;12. doi:10.3389/fonc.2022.834761.
10. Akinboro O, Vallejo JJ, Mishra-Kalyani PS, et al. Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis. *JCO*. 2021;39(15_suppl):9001. doi:10.1200/JCO.2021.39.15_suppl.9001.

Please cite this article as: Monika A. Izano et al, Brief Report on Use of Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis, Clinical Lung Cancer, https://doi.org/10.1016/j.cllc.2023.01.011