BRIEF REPORT

Brief Report: Long-Term Follow-Up of Adjuvant Pembrolizumab After Locally Ablative Therapy for Oligometastatic NSCLC

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ABSTRACT

Introduction: Patients with oligometastatic NSCLC benefit from locally ablative therapies (LAT); the role of adjuvant systemic therapies, however, remains less clear. In a single-arm, phase II clinical trial, we found that patients with oligometastatic NSCLC treated with a year of pembrolizumab after LAT had superior progression-free survival (PFS) compared with a historical control cohort. Herein, we present long-term follow-up on PFS and overall survival (OS).

Methods: From February 1, 2015, to September 30, 2017, 45 patients with synchronous or metachronous oligometastatic ($\leq$4 metastatic sites) NSCLC treated with LAT to all sites received adjuvant pembrolizumab every 21 days for up to 16 cycles. The primary efficacy end point was PFS from the start of pembrolizumab. Secondary end points included OS and safety. Median duration of follow-up was 66 months, and data cutoff was December 1, 2022.

Results: A total of 45 patients were enrolled and treated with pembrolizumab after LAT (median age, 64 y [range, 46–82]; 21 women [47%]; 31 with a solitary oligometastatic site [69%]). At the data cutoff, 32 patients had progressive disease, 19 patients had died, and 13 patients had no evidence of relapse. Median PFS was 19.7 months (95% confidence interval: 7.6–31.7 mo); median OS was not reached (95% confidence interval: 37.7 mo–not reached). OS at 5 years was 60.0% (SE, 7.4%). Metachronous oligometastatic disease was associated with improved OS and PFS through Cox proportional hazard models.

Conclusions: Pembrolizumab after LAT for oligometastatic NSCLC results in promising PFS and OS with a tolerable safety profile.

Keywords: NSCLC; Oligometastatic; Pembrolizumab; LAT

Introduction

Despite significant advances in therapy, NSCLC remains a leading cause of cancer-related mortality.[1] Oligometastatic disease is defined by the presence of a limited number of systemic metastatic disease sites and is increasingly recognized as a common clinical occurrence in patients with NSCLC.[2] For example, in early stage NSCLC, it has been reported that of the patients who have a relapse, 50% present with oligometastatic

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disease.[3] It has been hypothesized that the biology of oligometastatic disease is distinct from more widespread metastatic spread and may represent a more indolent form of metastatic cancer.[4] Current care often includes combining locally ablative therapies (LAT)—radiotherapy, surgery, ablation—with systemic therapies. Supporting this approach, multiple phase II randomized trials have revealed that LAT after systemic therapies improves progression-free survival (PFS) and overall survival (OS) in patients with oligometastatic NSCLC with confirmatory phase III trials underway.[5–9] Unfortunately, most patients who receive LAT to all sites of disease still develop disease progression. Whether there is a role for further consolidative systemic therapy after LAT remains unclear.

Immune checkpoint blockade (ICB) has revolutionized the treatment of locally advanced and metastatic NSCLC and has improved both PFS and OS across numerous trials. In NSCLC, ICB was first introduced in the second line after failure of platinum-based therapy[10] and subsequently moved into the first line after additional studies revealed improvement in OS compared with chemotherapy alone.[11–13] More recently, ICB after definitive chemoradiation (PACIFIC)[14] and surgery (IMPOWER010)[15] has improved patient outcomes, supporting a role for adjuvant ICB after local therapies.

We previously conducted a single-arm, phase II study assessing the efficacy of pembrolizumab after LAT for oligometastatic, with less than or equal to four metastatic sites, NSCLC. Briefly, after LAT, adjuvant pembrolizumab for up to one year resulted in a median PFS of 18.7 months, which was superior to a historical control cohort.[16] Herein, we report long-term PFS and OS outcomes, in which, we further explore whether certain clinicopathologic features are associated with clinical outcomes.

Materials and Methods

Study Design and Participants

The details of the study design and statistical methods have previously been published.[16] All patients were enrolled at the University of Pennsylvania Abramson Cancer Center. Patients with oligometastatic NSCLC ($\leq$4 metastatic sites) who had completed LAT to all sites of metastatic disease were enrolled. Patients with oligometastatic disease at initial diagnosis (synchronous) or who developed oligometastatic disease at least six months after initial definitive therapy (metachronous disease) were eligible. Other eligibility requirements included Eastern Cooperative Oncology Group performance status 0 to 1, the absence of autoimmune or immunodeficiency diseases, no prior anti–PD-1 or anti–PD-L1 therapies, and adequate organ function. Patients were enrolled regardless of PD-L1 status or the number of prior therapies. The trial was approved by the institutional review board at the University of Pennsylvania and was conducted per Good Clinical Practice guidelines. All patients provided written informed consent.

Treatment

Before the enrollment, patients completed LAT of any type, including surgery, radiation therapy, and interventional radiology ablation. Chemotherapy, either in combination with radiation or as an adjunct to other forms of LAT, was allowed. Four to 12 weeks after LAT, patients started intravenous pembrolizumab 200 mg every 21 days for eight cycles. Patients without evidence of disease progression after eight cycles of pembrolizumab were eligible for an additional eight cycles at the discretion of the treating physician. PD-L1 staining was performed on available archival tissue using the 22C3 assay (Dako).

Outcomes and Statistical Analyses

Detailed description of statistical analyses has previously been reported.[16] The primary outcome, PFS, was defined from the time of pembrolizumab treatment to disease progression, death, or last patient contact. Secondary end points included OS, determined by date of death or censored at last contact, and safety.

Median duration of follow-up was 66 months, and data cutoff was December 1, 2022. Median PFS and OS were estimated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard models were used to estimate the hazard ratios and generate p values for subgroup analysis. Statistical analyses were performed using GraphPad software or SPSS software (IBM).

Results

As noted in our initial publication,[16] 51 eligible patients were enrolled in the study from February 1, 2015, to September 30, 2017. A total of 45 patients received adjuvant pembrolizumab. Their baseline characteristics have been reported.[16] Patients received a median of 11 cycles of pembrolizumab, and 18 patients (40%) received 16 cycles of pembrolizumab (Supplementary Fig. 1).

At the data cutoff for this updated analysis (December 1, 2022), the median duration of follow-up was 65.8 months; 32 patients had progressive disease (PD), 19 patients had died, and 13 patients had no evidence of relapse (Supplementary Table 1). Median PFS after the start of pembrolizumab was 19.7 months (95% confidence interval [CI]: 10.8–28.5 mo) (Fig. 1*A*). Median OS was not reached (NR) (95% CI: 37.7 mo–NR) (Fig. 1*B*). Survival at 5 years was 60.0% (SE, 7.4%)

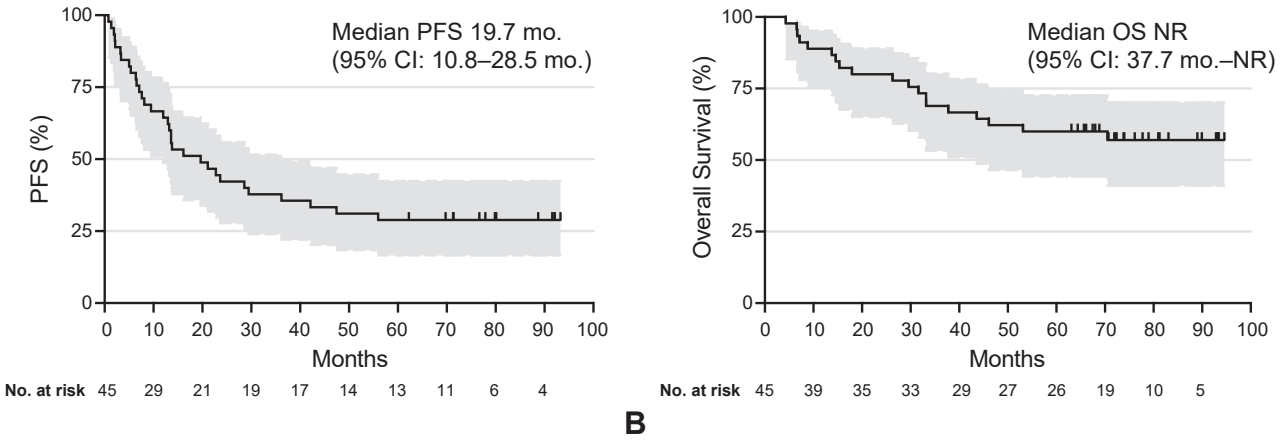

Figure 1. PFS and OS. (*A*) PFS and (*B*) OS from the start of pembrolizumab therapy. Shaded areas represent the 95% CI. Data cutoff was December 1, 2022. CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression-free survival.

(Fig. 1*B*). Of the patients with PD, 94% received further therapy with seven patients receiving further ICI (Supplementary Table 1). Salvage therapies and the disease status of all patients are summarized in Supplementary Table 1. Median OS after progression was 39.7 months (95% CI: 13.1 mo–NR) (Fig. 2).

In our initial report, no clinicopathologic features were significantly associated with PFS although metachronous oligometastatic disease and positive PD-L1 status trended with improved PFS.[16] Herein, we performed updated univariate analyses to assess whether metachronous disease, nodal status, the presence of central nervous system (CNS) disease, the number of oligometastatic metastatic sites, or PD-L1 status was significantly associated with clinical outcomes as these features have been linked to clinical outcomes in oligometastatic disease.[17] We found a significant association between PFS and OS in patients with metachronous versus synchronous oligometastatic (OS hazard ratio [HR], 2.52 [95% CI: 1.03–6.18]; PFS HR, 3.09 [95% CI: 1.45–6.52]) (Table 1). We did not find an association between survival outcomes and PD-L1 status; however, PD-L1 data were only available for 24 patients. The presence of CNS metastasis, nodal status, or the number of oligometastatic lesions was not significantly associated with PFS or OS (Table 1). Multivariate analyses including metachronous versus synchronous oligometastatic disease, nodal status, the presence of CNS metastasis, and the number of oligometastatic lesions identified a significant association between metachronous oligometastatic NSCLC and PFS (HR, 3.09 [95% CI: 1.45–6.52]) and OS (HR, 2.82 [95% CI: 1.09–7.36]) (Supplementary Table 2). In addition, there was a nonsignificant trend for fewer metastatic lesions correlating with improved outcomes (Supplementary Table 2). Finally, no adverse events were observed aside from those previously reported.[16]

Discussion

Our previous findings, to our knowledge, were the first to describe the potential role of ICB after LAT for oligometastatic NSCLC. These updated PFS and OS results again point to the potential benefit of consolidative ICB for oligometastatic NSCLC definitively treated with LAT. Although difficult to compare outcomes across trials, both the PFS and OS of our patient cohort are longer compared with prior long-term follow-up of patients who received LAT alone for oligometastatic disease.[6] Moreover, OS after progression was similar to previous reports[6] suggesting that pembrolizumab after LAT did not merely delay time to progression. Adjuvant ICB improves patient outcomes after definitive chemoradiation (PACIFIC)[14] and surgery (IMPOWER010)[15]; our findings further support consolidative ICB when given to patients with NSCLC in a minimal disease state.

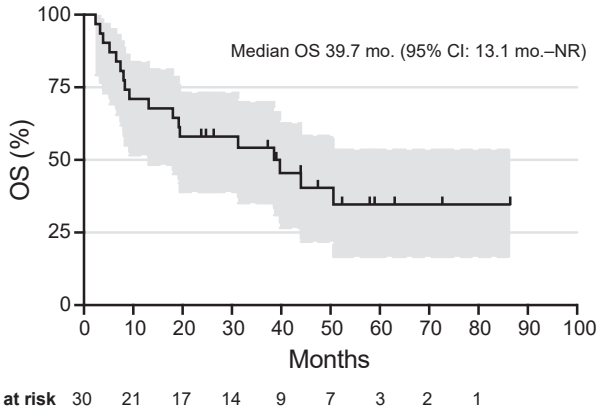

Figure 2. OS following disease progression. OS of patients following disease progression. Shaded areas represent the 95% CI. n =30. CI, confidence interval; NR, not reached; OS, overall survival.

Table 1. Univariate Analysis of Progression-Free Survival and Overall Survival

Clinicopathologic Parameter	No. of Patients	Progression-Free Survival		Overall Survival	
		HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Metastases					
Metachronous	31	1 [Reference]	0.002	1 [Reference]	0.04
Synchronous	14	3.19 (1.51-6.64)		2.52 (1.03-6.18)	
CNS metastases					
No	29	1 [Reference]	0.15	1 [Reference]	0.3
Yes	16	1.70 (0.80-3.46)		1.60 (0.64-3.86)	
No. of metastatic lesions					
1	31	1 [Reference]	0.12	1 [Reference]	0.04
>1	14	1.79 (0.84-3.66)		2.48 (1.00-6.02)	
Nodal status					
N0, N1	29	1 [Reference]	0.58	1 [Reference]	0.63
N2, N3	16	1.23 (0.58-2.48)		1.25 (0.47-3.12)	
PD-L1 status					
Positive (≥1%)	11	1 [Reference]		1 [Reference]	
Negative (<1%)	13	1.58 (0.62-4.31)	0.35	0.96 (0.18-5.18)	0.96
Unknown	21	1.71 (0.71-4.53)	0.25	3.93 (1.26-17.21)	0.03

CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PD-L1, programmed death-ligand 1.

An important question in the management of oligometastatic disease is identifying specific patients who would benefit from further therapies as oligometastatic NSCLC includes a mix of diverse phenotypes with different underlying biology.[2] In addition, a recent meta-analysis of oligometastatic NSCLC found that LAT benefited patients across different oligometastatic subtypes, albeit to varying degrees.[18] Consistent with prior reports,[17] we found that patients with synchronous metastatic disease had inferior outcomes compared with those with metachronous disease. Furthermore, patients with fewer metastatic lesions had nonsignificant trends for improved clinical outcomes. Whether consolidative ICB affects patient outcomes differently across the subtypes of oligometastatic NSCLC is not known, and the addition of stratification based on subtype should be considered in future trials.

These results are subject to numerous limitations. First, and most notably, this single-arm study is unable to formally reveal an improvement in PFS or OS using pembrolizumab after LAT compared with LAT alone. Although our study compares favorably to published reports, a potential explanation for the clinical outcomes observed could be due to the intrinsically favorable prognosis of the patient population specific to this study. To truly reveal the benefit of adjuvant pembrolizumab, a randomized, phase III clinical trial comparing LAT combined with pembrolizumab versus LAT alone would be necessary. Second, oligometastatic NSCLC is a heterogeneous disease with the most recent European consensus definition describing nine subtypes,[2] making comparisons across trials difficult. Finally, our trial opened in 2015 before first-line immunotherapy was the standard of care for patients with locally advanced and metastatic NSCLC, and we investigated a unique patient population that was naive to anti–PD-(L)1 therapies. In current practice, many patients with oligometastatic disease would have received anti–PD-(L)1 therapies earlier in their disease course; thus, the exact role of pembrolizumab in these patients as part of retreatment post-LAT is unclear given contemporary patient treatment practices.

In summary, pembrolizumab after LAT resulted in impressive PFS and OS compared with reports in the literature, with an acceptable toxicity profile. This approach warrants further investigation with a randomized clinical trial.

CRediT Authorship Contribution Statement

David Cantor: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing—original draft, Writing—review and editing, Visualization.

Christiana Davis: Data curation, Investigation, Project administration.

Christine Ciunci: Conceptualization, Methodology, Investigation, Writing—review and editing.

Charu Aggarwal: Conceptualization, Methodology, Investigation, Writing—review and editing.

Tracey Evans: Investigation.

Cohen: Investigation, Writing—review and editing.

Joshua Bauml: Conceptualization, Methodology, Investigation, Writing—review and editing, Funding acquisition.

Corey Langer: Conceptualization, Methodology, Formal Analysis, Investigation, Writing—original draft, Writing—review and editing, Supervision, Funding acquisition.

Disclosure

Dr. Cantor reports receiving honoraria from HMP. Dr. Aggarwal reports receiving institutional research funding from AstraZeneca, Genentech, Incyte, Macrogenics, Medimmune, and Merck Sharp and Dohme, and receiving consultation fees from Genentech, Lilly, Celgene Merck, AstraZeneca, Blueprint Genetics, Shionogi, Daiichi Sankyo, Regeneron, Sanofi, Eisai, BeiGene, Turning Point, Pfizer, Janssen, and Boehringer Ingelheim. Dr. Evans reports receiving honoraria from Merck. Dr. Cohen reports receiving institutional research funding from F-Star Biotechnology, Innate Biopharma, and Cantargia. Dr. Bauml is currently employed by Janssen Research and Development but all work for this study was done as an employee at the University of Pennsylvania, and reports owning stock in Johnson & Johnson. Dr. Langer reports receiving institutional research funding from AstraZeneca, Eli Lilly, Fujifilm, Janssen Pharmaceuticals, Inovio, Merck, Oncocyte, Takeda, and Trizell; receiving consulting fees from AstraZeneca, Boehringer Ingelheim, Genentech, Roche, Gilead, GlaxoSmithKline, Merck, Mirati, Novocure, Pfizer, Regeneron, Sanofi-Aventis, and Takeda; and having participation on a safety monitoring board or advisory board for Amgen, OncocyteDX, the Radiation Therapy Oncology Group Foundation, and the Veterans Administration. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100667.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:17–48.
2. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21:e18–e28.
3. Torok JA, Gu L, Tandberg DJ, et al. Patterns of distant metastases after surgical management of non-small-cell lung cancer. *Clin Lung Cancer*. 2017;18:e57–e70.
4. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13:8–10.
5. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016;17:1672–1682.
6. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019;37:1558–1565.
7. Tsai CJ, Yang JT, Guttmann DM, et al. Consolidative use of radiotherapy to block (CURB) oligoprogression – interim analysis of the first randomized study of stereotactic body radiotherapy in patients with oligoprogressive metastatic cancers of the lung and breast. *Int J Radiat Oncol Biol Phys*. 2021;111:1325–1326.
8. Wang XS, Bai YF, Verma V, et al. Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic EGFR-mutated non-small cell lung cancer. *J Natl Cancer Inst*. 2023;115:742–748.
9. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4:e173501.
10. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540–1550.
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
12. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
13. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
14. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40:1301–1311.
15. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398:1344–1357.

16. Bauml JM, Mick R, Ciunci C, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung cancer: a phase 2 trial. *JAMA Oncol*. 2019;5:1283–1290.
17. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer*. 2014;15:346–355.
18. Rim CH, Cho WK, Park S, Yoon WS, Yang DS. Role of local ablative treatment in oligometastatic non-small cell lung cancer: a meta-analysis. *Int J Surg*. 2023;109:1006–1014.