Editorial Commentary

Combined PARP and PD-L1 inhibition: a promising treatment option for relapsed small-cell lung cancer

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Comment on: Krebs MG, Delord JP, Jeffry Evans TR, *et al.* Olaparib and durvalumab in patients with relapsed small cell lung cancer (MEDIOLA): An open-label, multicenter, phase 1/2, basket study. Lung Cancer 2023;180:107216.

Keywords: Small-cell lung cancer (SCLC); durvalumab; olaparib

Submitted Feb 19, 2024. Accepted for publication May 15, 2024. Published online Jun 25, 2024.
doi: 10.21037/jtd-24-269
View this article at: https://dx.doi.org/10.21037/jtd-24-269

Small-cell lung cancers (SCLCs) are aggressive, high-grade neuroendocrine carcinomas characterized by a rapid doubling time and widespread metastasis, accounting for 10–20% of all lung cancers (1,2). The combination of chemotherapy with anti-programmed death-ligand 1 (PD-L1) immunotherapy has been established globally as the first-line treatment for patients with extensive-stage SCLC, based on sustained survival benefits and well-tolerated safety profiles in two randomized phase 3 trials (CASPIAN and IMpower133). PD-L1 antibodies, durvalumab and atezolizumab, were approved for use in combination with platinum-etoposide-based chemotherapy as first-line treatment for patients with extensive-stage SCLC (3,4). However, their associated long-term survival rates remain low; the CASPIAN trial reported a 3-year survival rate of 18% (5,6).

Novel therapies are required to further improve the prognosis of SCLC. Poly (ADP-ribose) polymerase 1 (PARP1), a DNA repair protein, is more expressed in SCLC than in other histologic subtypes of lung cancer (7), and is gaining attention as a new therapeutic target molecule. The STOMP phase 2 trial demonstrated that the maintenance of monotherapy with the PARP inhibitor olaparib, compared with placebo, improved progression-free survival in patients with SCLC who had completed first-line treatment with platinum-based chemotherapy (8). Additionally, preclinical studies have demonstrated that the combination of DNA damage response (DDR) inhibition with immune checkpoint blockade is more effective than either alone (9,10). DDR proteins, such as PARP and checkpoint kinase 1, markedly increase the protein and surface expression of PD-L1 (9). DDR inhibition significantly enhances the antitumor effect of the PD-L1 blockade, augments cytotoxic T-cell infiltration through the activation of the STING/TBK1/IRF3 innate immune pathway, and increases the concentrations of chemokines, such as CXCL10 and CCL5 (10).

In the article titled "Olaparib and durvalumab in patients with relapsed small cell lung cancer (MEDIOLA): An open-label, multicenter, phase 1/2, basket study" recently published in *Lung Cancer* (11), Krebs *et al.* assessed the combination of olaparib and durvalumab as a potential treatment option for patients with SCLC who had relapsed after platinum-based chemotherapy. Patients received oral olaparib 300 mg twice daily for 4 weeks, followed by durvalumab (1,500 mg intravenously every 4 weeks) until disease progression. The primary endpoints were safety, tolerability, and the 12-week disease control rate (DCR). The secondary endpoints included 28-week DCR, objective response rate, duration of response, progression-free

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survival, overall survival, change in tumor size, and PD-L1 expression. From May 3, 2016, to December 16, 2016, 40 patients were enrolled and assessed for safety, with 38 were analyzed for efficacy. Eleven [28.9%; 90% confidence interval (CI): 17.2–43.3%] and two (5.3%) patients had disease control at 12 and 28 weeks, respectively. The objective response rate was 10.5% (95% CI: 2.9–24.8%). The median progression-free and overall survival were 2.4 (95% CI: 0.9–3.0) and 7.6 (95% CI: 5.6–8.8) months, respectively. Fourteen patients (36.8%) showed a reduction in the target tumor size from baseline, and eight patients (21.1%) showed a reduction greater than 10.0%. The most common adverse events (AEs) were anemia (n=30; 75.0%), nausea (n=19; 47.5%), and fatigue (n=16; 40.0%). AEs with grades of ≥3 occurred in 32 patients (80.0%), with two patients (5.0%) experiencing grade 4 AEs. One AE, pneumonia was considered related to durvalumab treatment, and lymphopenia was related to both study treatments. Three patients (7.5%) had a grade 5 AE, one of which (pancytopenia) was considered treatment-related to olaparib. Preliminary biomarker analysis evaluating PD-L1 concentrations, tumor mutational burden, and other genetic mutations revealed no significant correlations with clinical outcomes.

Developing novel treatment options for relapsed SCLC is challenging due to the poor efficacy of numerous tested combinations (12,13). Given the advancing understanding of SCLC biology and biomarkers, such as SCLC subtyping (14), novel approaches are imperative. The phase 1/2 MEDIOLA basket study aimed to evaluate whether increased DNA damage resulting from PARP inhibition would enhance antitumor activity, further augmented by the addition of an immune checkpoint inhibitor, without compromising safety outcomes in patients with relapsed platinum-sensitive SCLC. This study demonstrates methodological rigor with supported research designs and findings. Preclinical studies validating the combination of DDR inhibition and immune checkpoint blockade (9,10), along with promising clinical activity of olaparib with durvalumab in various cancers (15,16), supported the study design. The safety profile of the olaparib and durvalumab combination mirrors that of each agent alone, with no new safety concerns. Moreover, the safety and tolerability findings for the combination of olaparib and durvalumab (primary safety endpoint) were consistent with those reported in a phase 1 study including pretreated patients with breast, cervical, ovarian, or uterine cancers (15).

However, considering the efficacy findings in this study, some concerns about the feasibility of olaparib in combination with durvalumab as a novel treatment for patients with relapsed SCLC remain. While the median overall survival in this study (7.6 months; 95% CI: 5.6–8.8) was promising for its similarity to those associated with other treatments for a pretreated SCLC population (17,18), the observed DCR of 28.9% (90% CI: 17.2–43.3%) at 12 weeks (primary efficacy endpoint in this study) did not meet the prespecified target DCR of 60.0% and was inferior to other previously reported treatments (18-20) for patients with relapsed-SCLC. Additionally, a significant proportion of patients (44.4%) showed disease progression before the end of the 4 weeks of olaparib monotherapy, suggesting insufficient disease control with olaparib alone. Moreover, anti PD-L1 immunotherapy is now administered in the first-line setting with maintenance therapy for patients with extensive-stage SCLC (3,4), and these patients would have been excluded from this study. Thus, olaparib plus an immune checkpoint inhibitor (durvalumab or atezolizumab) should be tested as maintenance therapy for patients with SCLC who have completed first-line treatment with platinum-based chemotherapy and immunotherapy without progression. A previous study has reported that only a small population of patients with SCLC benefit from PARP inhibition (12). Therefore, translational biomarker analysis is warranted to determine the populations that will benefit from a combination of PARP inhibition and immune checkpoint blockade. In the preliminary biomarker analysis in this study, the authors explored several potential biomarkers in the SCLC cohort, including PD-L1, tumor mutational burden, and genetic mutations; however, no significant correlations with clinical outcomes were observed. The authors suggested that this could be due to the limited sample size and high tumor heterogeneity. Further biomarker-driven studies involving larger cohorts are required to determine the significant correlations with clinical prognosis. Additionally, liquid biopsy, which has been clinically used in recent years, is a possible alternative approach for overcoming the limited sample size and high tumor heterogeneity. Moreover, as for other therapeutic targets, Delta-like ligand 3 (DLL3) is a Notch ligand aberrantly expressed on the surface of SCLC cells and minimally expressed in normal tissues. Tarlatamab, a bispecific T cell engager molecule designed to bind DLL3 on target cancer cells and CD3 on T cells, has been reported to show promising antitumor activity with durable objective responses and promising survival outcomes and tolerability in patients with relapsed SCLC (21).

In summary, Krebs *et al.* presented several findings from the phase 1/2 MEDIOLA study regarding the safety, tolerability, and antitumor activity of durvalumab in combination with olaparib in patients with SCLC who relapsed after platinum-based chemotherapy (11). While the combination's tolerability matches previous safety profiles, its moderate antitumor activity dose not meet primary endpoints. Optimizing treatment strategies and patient selection may lead to more effective novel therapies for relapsed SCLC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article has undergone external peer review.

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-269/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-269/coif). N.Y. has previously received payment for lectures from MSD and Chugai Pharma. S.W. has received grants from Boehringer Ingelheim and Nippon Kayaku, and received honoraria for speaker bureaus from Lilly, Novartis Pharma, Chugai Pharma, Bristol-Myers, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Nippon Kayaku, Kyowa Kirin, Merck, Takeda Pharmaceutical, Celltrion and AstraZeneca. T.K. has received grants from Nobelpharma, Boehringer Ingelheim, Taiho Pharmaceutical, KYORIN Pharmaceutical, Shionogi, Chugai Pharma, Asahi Kasei, Daiichi Sankyo, Nippon Kayaku, TEIJIN PHARMA, consulting fees from AN2 Therapeutics, and received honoraria for speakers bureaus from Viatris, Astellas Pharma, Insmed, Boehringer Ingelheim, Terumo, Eli Lilly, AstraZeneca, Daiichi Sankyo, KYORIN Pharmaceutical, Novartis, Merck, Bristol-Myers, NIPRO, Eisai, Ono Pharmaceutical, Chugai Pharma, GSK, Sumitomo Pharma, Kyowa Kirin, MSD, Sanofi, Shionogi, Meiji Seika Pharm and Taiho Pharmaceutical, and participate Advisory Board for Janssen Pharmaceutical, and received drugs from Nobelpharma. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Yanagimura N, Watanabe S, Kikuchi T. Combined PARP and PD-L1 inhibition: a promising treatment option for relapsed small-cell lung cancer. J Thorac Dis 2024;16(6):4075-4078. doi: 10.21037/jtd-24-269