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ORIGINAL ARTICLE

Durvalumab in Combination with Olaparib in Patients with Relapsed SCLC: Results from a Phase II Study

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ABSTRACT

Purpose: Despite high tumor mutationburden, immune checkpoint blockade has limited efficacy in SCLC. We hypothesized that poly (ADP-ribose) polymerase inhibition could render SCLC more susceptible to immune checkpoint blockade.

Methods: A single-arm, phase II trial (NCT02484404) enrolled patients with relapsed SCLC who received durvalumab, 1500 mg every 4 weeks, and olaparib, 300 mg twice a day. The primary outcome was objective response rate. Correlative studies included mandatory collection of pretreatment and during-treatment biopsy specimens, which were assessed to define SCLC immunephenotypes: desert (CD8-positive T-cell prevalence low), excluded (CD8-positive T cells in stroma immediately adjacent/within tumor), and inflamed (CD8-positive T cells in direct contact with tumor).

Results: A total of 20 patients were enrolled. Their median age was 64 years, and most patients (60%) had platinum-resistant/refractory disease. Of 19 evaluable patients, two were observed to have partial or complete responses

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(10.5%), including a patient with EGFR-transformed SCLC. Clinical benefit was observed in four patients (21.1% [95% confidence interval: 6.1%–45.6%]) with confirmed responses or prolonged stable disease (≥8 months). The most common treatment-related adverse events were anemia (80%), lymphopenia (60%), and leukopenia (50%). Nine of 14 tumors (64%) exhibited an excluded phenotype; 21% and 14% of tumors exhibited the inflamed and desert phenotypes, respectively. Tumor responses were observed in all instances in which pretreatment tumors showed an inflamed phenotype. Of the five tumors without an inflamed phenotype at baseline, no during-treatment increase in T-cell infiltration or programmed death ligand 1 expression on tumor-infiltrating immune cells was observed.

Conclusions: The study combination did not meet the preset bar for efficacy. Pretreatment and during-treatment biopsy specimens suggested that tumor immune phenotypes may be relevant for SCLC responses to immune checkpoint blockade combinations. The predictive value of preexisting CD8-positive T-cell infiltrates observed in this study needs to be confirmed in larger cohorts.

Keywords: Small cell lung cancer; PARP inhibitors; immune checkpoint blockade; tumor immune phenotype; DNA repair

Introduction

SCLC is the most aggressive and lethal form of lung cancer. It represents 15% of all lung cancers, with an annual incidence of more than 34,000 cases in the United States. SCLC is characterized by rapid doubling time, high growth fraction, and early and widespread metastatic involvement.[1] Although response rates to first-line platinum-based chemotherapy are exceptionally high, tumor usually recurs in months. Additional chemotherapy is usually ineffective at relapse, and fewer than 5% of patients with extensive-stage SCLC survive 2 years.

Despite recent advances in immune checkpoint blockade, only a minority of patients with SCLC benefit from these therapies. Nivolumab, an anti–programmed death 1 (PD-1) antibody yielded objective response rates (ORRs) of 10% and median overall survival (OS) of 4.4 months in previously treated patients with SCLC.[2] Although efficacy is better in programmed death-ligand 1 (PD-L1)-positive SCLC and with combined immune checkpoint blockade, these approaches are applicable in only a limited number of patients and are associated with substantial toxicities.[2–4]

One approach to augment the clinical activity of immune checkpoint inhibitors is to modulate the DNA damage response (DDR).[5] Poly (ADP-ribose) polymerase (PARP) 1 is highly expressed in SCLC, and PARP inhibitors have shown antitumor activity in both preclinical models of and patients with SCLC.[6–9] Preclinical observations suggest that combination of immune checkpoint blockade with PARP inhibition may be an effective therapeutic strategy.[10–12] PARP inhibition potentiated the antitumor effect of PD-L1 blockade and augmented cytotoxic T-cell infiltration in multiple immunocompetent SCLC models.[13] Accumulating evidence also suggests that DNA double-strand break and cytosolic DNA can induce PD-L1 expression through mechanisms including a stimulator of interferon gene–mediated innate immune response.[10,14–16]

Durvalumab (MEDI4736) is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, thereby enhancing the function of tumor-directed T cells.[17] Durvalumab is approved for metastatic urothelial carcinoma and unresectable stage III NSCLC after chemoradiation. The PARP inhibitor olaparib blocks the DNA repair function of these enzymes and traps inactivated PARP onto single-strand DNA breaks, preventing repair and generating a DNA replication block and leading to DNA double-strand break.[18] Olaparib is approved for epithelial ovarian cancers and germline (BRCA1, DNA repair associated gene [*BRCA*])-mutated metastatic breast and ovarian cancers. We previously established the safety and tolerability of a combination of durvalumab and olaparib in a phase I trial.[19] No dose-limiting toxicities were observed and the most common adverse events (AEs) were hematologic, which were manageable with supportive care.

We hypothesized that PARP inhibition could render SCLC more susceptible to immune checkpoint blockade and expanded the phase II trial of durvalumab and olaparib to enroll a cohort of patients with SCLC. The primary objective was to determine antitumor activity in patients with relapsed SCLC. Mandatory fresh biopsy specimens were obtained at baseline and during treatment to assess the dynamic changes in T-cell infiltration and PD-L1 expression before and during treatment. Here we report the efficacy, safety, and biomarker results from patients with SCLC treated with durvalumab plus olaparib.

Patients and Methods

Eligible patients had histologically confirmed SCLC and one or more platinum-based chemotherapy treatments. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 2 or lower and adequate organ/bone marrow function. Previous therapy with an immune checkpoint inhibitor was not an exclusion. Patients with both platinum-sensitive (progression ≥90 days from last platinum dose) and

platinum-resistant/refractory (progression <90 days) disease were eligible. Key exclusion criteria were previous treatment with PARP inhibitors, symptomatic brain metastases, autoimmune disease requiring steroids, pneumonitis and/or interstitial lung disease, or inflammatory bowel disease. The trial was conducted under a National Cancer Institute Center for Cancer Research–sponsored investigational new drug application with institutional review board approval. Written informed consent was obtained from all patients (ClinicalTrials.gov identifier NCT02484404).

Study Design and Treatment

This was an open-label, single-arm phase II study of a combination of durvalumab and olaparib in patients with relapsed SCLC (Fig. 1*A*). Treatment cycles were 28 days long. Durvalumab (1500 mg) was administered intravenously every 28 days. Olaparib tablets (300 mg twice daily) were administered continuously.

Efficacy and Safety Evaluations

A history and physical examination were conducted at baseline and before each cycle. Complete blood counts with differential and serum chemistries were performed at baseline, 2 weeks later, and before each cycle. Radiographic evaluation was performed at baseline and every two cycles, and tumor response was assessed on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1. Toxicities were graded by using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). Given reports of neurological immune-related AEs in patients with SCLC who were receiving immune checkpoint inhibitors,[2] patients underwent baseline and follow-up neurological examinations by an expert in neuromuscular disorders, as needed.

Tumor Biopsies and Correlative Studies

.Patients underwent mandatory pretreatment and optional during-treatment biopsy (2–4 weeks after treatment, with the specimen taken from the same location) (see Fig. 1*A*). Five-micron sections of formalin-fixed, paraffin-embedded tissue were assessed for PD-L1 expression and T-cell infiltration by immunohistochemistry with use of the following antibodies and detection methods: PD-L1 (1:3 dilution, clone SP142 [Springer Biosciences], Leica Bond [Leica Biosystems]), CD3 (predilute, clone 2GV6, Ventana and Ventana BenchMark Ultra [Ventana Medical Sytems]), and CD8 (1:25, clone CD8/144B [Dako], Ventana BenchMark Ultra [Ventana Medical Systems]) following the manufacturer's protocol.

The location of tumor-infiltrating T cells was noted as follows: intratumoral (within the mass of tumor cells, with direct proximity between cancer and immune cells), stromal (in the surrounding connective tissues and blood vessels), or peritumoral (around the tumor at the advancing margin of the tumor, in the stroma or the tissues adjacent to the tumor). On the basis of the presence of CD3-positive and CD8-positive T cells and the pattern of infiltration with respect to tumor cells, tumors were categorized into immunophenotypes as described previously[20]: "desert" when the prevalence of CD8-positive T cells was low, "excluded" if CD8-positive T cells were exclusively seen in stroma immediately adjacent to or within the tumor, or "inflamed" if CD8-positive T cells were seen in direct contact with tumor cells either in the form of spillover of stromal infiltrates into tumor cell aggregates or in the form of diffuse infiltration of CD8-positive T cells in aggregates or sheets of tumor cells.

Plasma cytokines were assessed before treatment, at cycle 1 day 15, and at cycle 3 day 1. Circulating free-DNA was assessed in selected patients. Methodological details are provided in the Supplementary Data.

Statistical Methods

The primary end point was ORR. Progression-free survival (PFS), defined as time from start of treatment to time of progression or death, and safety were secondary end points. Identification of biomarkers of response was an exploratory end point. The trial was conducted with use of an optimal two-stage phase II trial design to rule out an unacceptably low ORR rate of 15% in favor of an improved response rate of 35% with an alpha value of 0.10 and beta value of 0.10. Futility was defined as zero to three responses in the first 19 patients; accrual would continue to 33 patients if there were four or more responses in the first stage. PFS, OS, and duration of response were calculated by using the Kaplan-Meier method.

Results

Patient Demographics

Between April 2016 and June 2018, a total of 20 patients with extensive-stage SCLC were enrolled (Table 1). The median age of the patients was 64 years (range 42–76). All patients had received prior chemotherapy and had disease progression at enrollment. Ten patients (50%) had two or more prior lines of therapy. Most patients (60%) had platinum resistant/refractory disease. All patients had received platinum plus etoposide as first-line treatment; 30% had received second-line or later treatment with topotecan, temozolomide or paclitaxel; and 15% had received prior immune checkpoint blockade.

All patients were evaluable for safety. A median of two cycles of treatment was administered (range 1–12

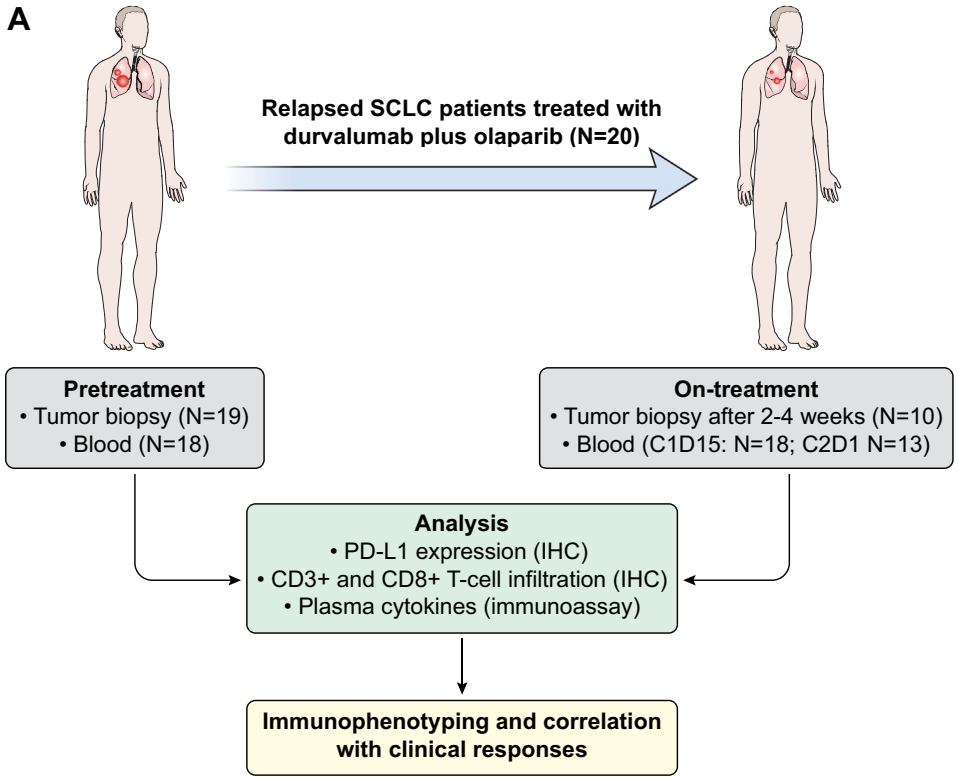


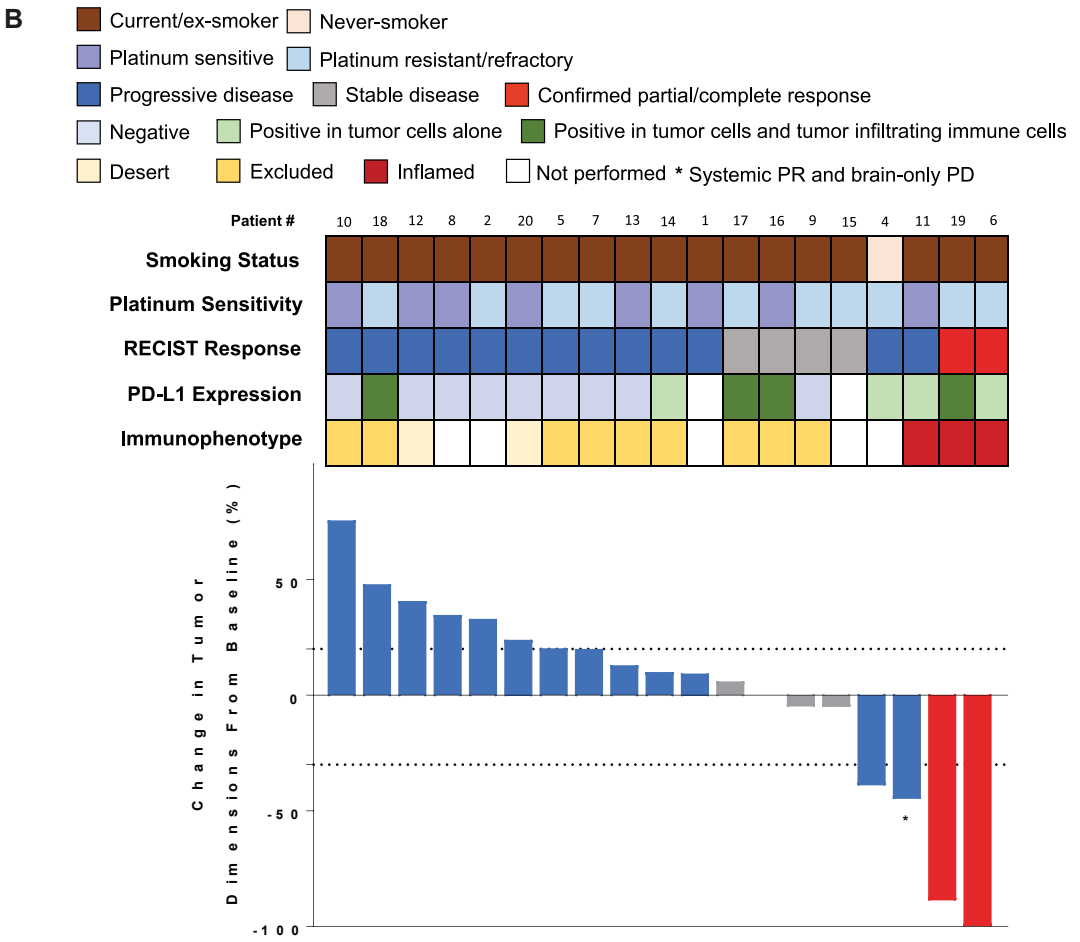
Figure 1. Efficacy of durvalumab plus olaparib in relapsed SCLC. (*A*) Study schema and biomarker analyses. (*B*) Waterfall plot showing change of tumor burden from baseline (investigator assessed [n = 19]). One patient was not evaluable for response because of rapidly PD before the first restaging scans. Bar length represents decrease or increase in target lesion size. Bar color is the best overall response (according to the Response Criteria in Solid Tumors [RECIST], version 1.1). Indicated by asterisk is a patient who discontinued treatment after one cycle for brain-only disease progression but had a partial response (PR) in the systemic disease-sites that lasted 6 months with no additional systemic therapy. Boxes above the waterfall plot indicate the smoking status, platinum sensitivity, RECIST response, programmed death ligand 1 (PD-L1) expression and immunophenotype of pretreatment tumors. (*C*) Spider plot of change in the sum of the unidimensional tumor measurements over time. The red lines represent confirmed responders, blue lines represent patients with PD, and gray lines represent patients with stable disease. Light brown squares indicate the time points at which patients discontinued treatment because of progressive disease in the brain. Plus sign indicates patients who are receiving treatment at data cutoff. Asterisk indicates the patient who discontinued treatment after one cycle for brain-only disease progression but who had a PR in the systemic disease-sites. One patient who was not evaluable is not included. IHC, immunohistochemistry.

cycles). A total of 19 patients were evaluable for response. One patient was not evaluable for response because of rapidly progressive disease (PD) before the first restaging scans. At the time of data cutoff on October 1, 2018, the median follow-up time was 11.1 months (range 4.0–29.8). Three patients are continuing to receive treatment.

Efficacy

Of the 19 evaluable patients, one each had a confirmed complete response (CR) and a partial response (PR) and four patients had stable disease, including two instances of prolonged stable disease (≥8 months) (Fig. 1*B* and *C* and Supplementary Table 1). In all, 13 patients had PD. This included a patient who discontinued treatment after one cycle for brain-only disease progression but had a PR in the systemic disease sites that lasted 6 months with no additional systemic therapy, as well as another patient who had a PR at the first restaging but PD on the confirmatory scan. The investigator-assessed ORR was 10.5% (95% confidence interval [CI]: 1.3%–33.1%). The median PFS was 1.8 months (95% CI: 0.9–2.4 months), and the 6-month PFS probability was 20.0% (95% CI: 6.2%–39.3%) (Supplementary Fig. 1). The median OS was 4.1 months (95% CI: 2.4–9.2 months), and the 6-month OS rate was 37.1% (95% CI: 16.3–58.2%) (Supplementary Fig. 2). All told, clinical benefit was observed in four of 19 (21.1% [95% CI: 6.1%–45.6%]) evaluable patients who had confirmed CR, PR, or prolonged stable disease (≥8 months).

The patient with the CR (patient 6) had platinum-refractory disease that harbored a deleterious *BRCA1* mutation. The rapid clinical improvement in this patient was accompanied by a steep decline in circulating free



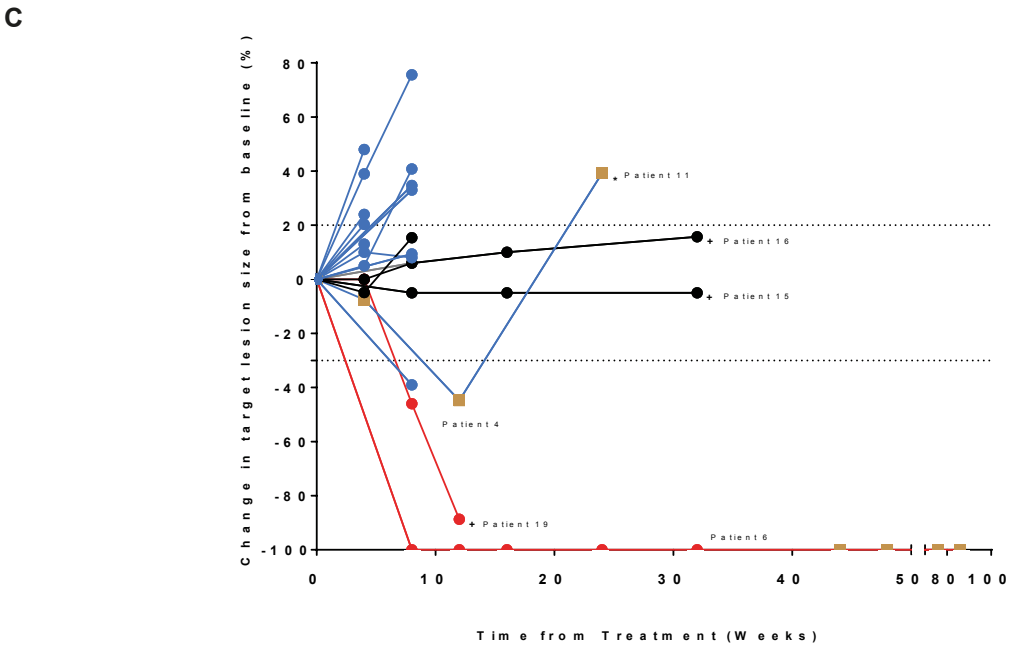


Figure 1. (*continued*).

Table 1. Patient Characteristics (N = 20)

Characteristic	Value
Sex, n (%)	
Female	11 (55)
Male	9 (45)
Median age, y (range)	64 (42-76)
ECOG performance status, n (%)	
0	1 (5)
1	18 (90)
2	1 (5)
Race, n (%)	
White	18 (90)
Asian	1 (5)
Black	1 (5)
Type of prior therapy, n (%)[a]	
Chemotherapy	20 (100)
Radiotherapy	9 (45)
Immunotherapy	3 (15)
Surgery	1 (5)
Investigational agents	4 (5)
Lines of prior systemic therapy, n (%)	
1	10 (50)
2	7 (35)
3	3 (15)
Prior chemotherapy type, n (%)	
Cisplatin/carboplatin plus etoposide	20 (100)
Topotecan	3 (15)
Paclitaxel	2 (10)
Temozolomide	1 (5)
Sensitivity to first-line therapy	
Platinum-sensitive	8 (40)
Platinum-resistant/refractory	12 (60)

[a]Patients could have received more than one type of prior therapy.
ECOG, Eastern Cooperative Oncology Group.

DNA (Fig. 2*A* and *B*). The patient discontinued treatment after 11 months for relapse limited to the brain. As of the last follow-up at 21 months after the start of treatment, the patient continued to have no evidence of systemic disease.

The patient with the confirmed PR (patient 19) had *EGFR*-mutant adenocarcinoma transformed to SCLC and was continuing to receive treatment, with the response maintained for 5 months at the time of data cutoff. Two patients, each of whom had previously received immune checkpoint inhibitors (patients 15 and 16, who previously had PD after 4 and 6 months of immune checkpoint inhibitor-combination, respectively), had prolonged stable disease ongoing at 8 months each. Finally, an additional patient (patient 11) discontinued treatment after one cycle for brain-only disease progression. This patient later had a systemic response that was maintained for 6 months until disease progression.

Safety

Treatment-related AEs are listed in Table 2. The most common AEs were anemia (80%), lymphopenia (60%), leukopenia (50%), and fatigue and thrombocytopenia (45% each). Nine patients (45%) had grade 3 or 4 treatment-related AEs: anemia, lymphopenia, thrombocytopenia, and hypophosphatemia. No neurological or immune-related AEs were observed except for an increased level of thyroid-stimulating hormone (25%), which was asymptomatic in all cases. One patient needed dose reduction of olaparib for grade 3 anemia. No additional dose modifications were required, and no patient discontinued treatment because of AEs.

PD-L1 Expression and Tumor-Infiltrating Immune Cells

Of the 19 patients, all except one (who was considered high-risk for biopsy because of clinical deterioration since screening) underwent biopsy to collect fresh pretreatment core biopsy specimens. Eight of the 18 patients (44%) with adequate tissue for evaluation had quantifiable PD-L1 expression in tumor cells or tumor-infiltrating immune cells (Supplementary Table 2); in most cases, it was limited to less than 20% of cells. An inflamed phenotype was usually accompanied by PD-L1 expression. PD-L1 was expressed in tumor or stroma in both of the patients with confirmed responses (patients 6 and 19) and in a patient with systemic response and brain-only PD (patient 11). However, PD-L1 expression was also noted in several tumors that did not respond. In contrast, tumor responses were observed in all instances when pretreatment tumors showed an inflamed phenotype (patients 6, 19, and 11) (see Fig. 1*A*). None of the noninflamed tumors responded to treatment.

To characterize the immunological events associated with tumor response or progression, during-treatment tumor biopsies were performed in 10 patients, of which nine provided adequate material (Supplementary Table 2). Responding tumors (those of patients 11 and 19) displayed a dense T-cell infiltrate in clusters and aggregates extending deeply into the tumor with extensive tumor cell necrosis accompanied by increased PD-L1 expression on tumor and tumor-infiltrating immune cells (Fig. 3*A*). In contrast, nonresponding tumors showed a lack of PD-L1 expression and displayed either an immune desert (minimal or no T-cell infiltration) (Fig. 3*B*) or immune-excluded pattern (T cells solely around the outer edge of the tumor) (Fig. 3*C*).

Changes in PD-L1 expression and T-cell infiltration are described in Supplementary Table 2. Of the five patients having tumors with no pretreatment PD-L1 expression, two (patients 9 and 12) remained negative for PD-L1 expression after treatment; in three (patients 10, 13, and 20), PD-L1 expression was seen on tumor cells after treatment with no expression on tumor-infiltrating immune cells. In all five cases, no significant

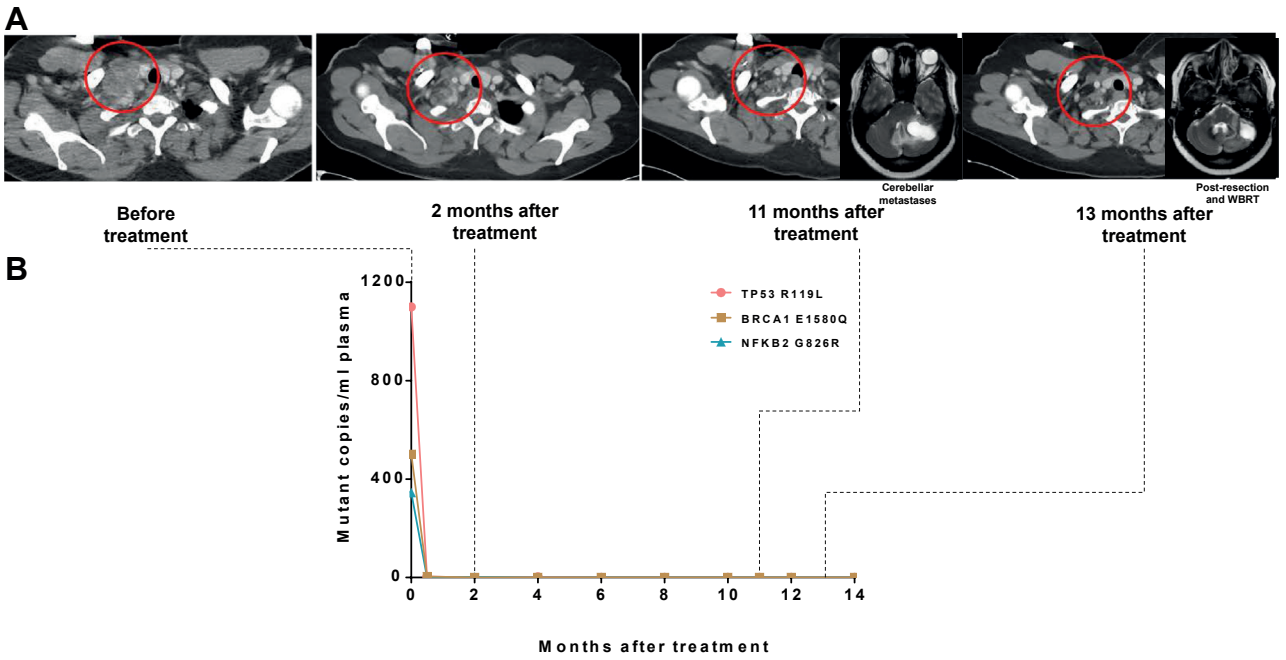


Figure 2. Representative responses. (*A*) Computed tomography images and (*B*) dynamic changes in circulating free DNA at the corresponding time points in a patient with a complete response (patient 6). The right supraclavicular lymph node is indicated by red circles. *TP53*, tumor protein p53 gene; *BRCA1*, BRCA1 associated protein 1 gene; *NFKB2*, nuclear factor kappa B subunit 2 gene.

Table 2. Treatment-Related Adverse Events (Maximum Grade, All Cycles) (N = 20 Patients)

	Grade				
Adverse Event	1	2	3	4	Total (%)
Anemia	7	7	2		16 (80)
Lymphocyte count decreased	3	4	3	2	12 (60)
White blood cell decreased	6	4			10 (50)
Platelet count decreased	7	1	1		9 (45)
Fatigue	7	2			9 (45)
Hypothyroidism	5				5 (25)
Vomiting	4				4 (20)
Nausea	3				3 (15)
Diarrhea	3				3 (15)
Neutrophil count decreased	2				2 (10)
Anorexia	2				2 (10)
Constipation	2				2 (10)
Gastroesophageal reflux disease	2				2 (10)
Hypophosphatemia		1	1		2 (10)
Alanine aminotransferase increased	1				1 (5)
Alkaline phosphatase increased	1				1 (5)
Dysgeusia	1				1 (5)
Dyspepsia		1			1 (5)
Headache	1				1 (5)
Hypomagnesemia	1				1 (5)

changes in the T-cell infiltration pattern were observed; T cells were limited to the stroma and peritumoral area both before and after treatment. Of four tumors with pretreatment PD-L1 expression on tumor cells or tumor-infiltrating immune cells, three cases showed substantial increase in the number and intensity of PD-L1–positive cells, which in two instances were associated with clinical response (in patients 11 and 19).

Cytokines

Treatment resulted in increased concentrations of inflammatory cytokines, notably IFN gamma, interleukin-6, and interleukin-10, which is indicative of a systemic immune activation (Supplementary Fig. 3). Cytokine levels at baseline and change with treatment were not significantly associated with clinical response.

Discussion

Patients with SCLC continue to have one of the worst survival rates of all patients with cancer. Response to immune checkpoint blockade is relatively low despite a high tumor mutational burden. This study was conducted on the basis of preclinical data suggesting a beneficial interaction between DDR inhibition and immune checkpoint blockade and an extension of our previous work that defined the safety and tolerability of the combination of durvalumab and olaparib.[19] To our

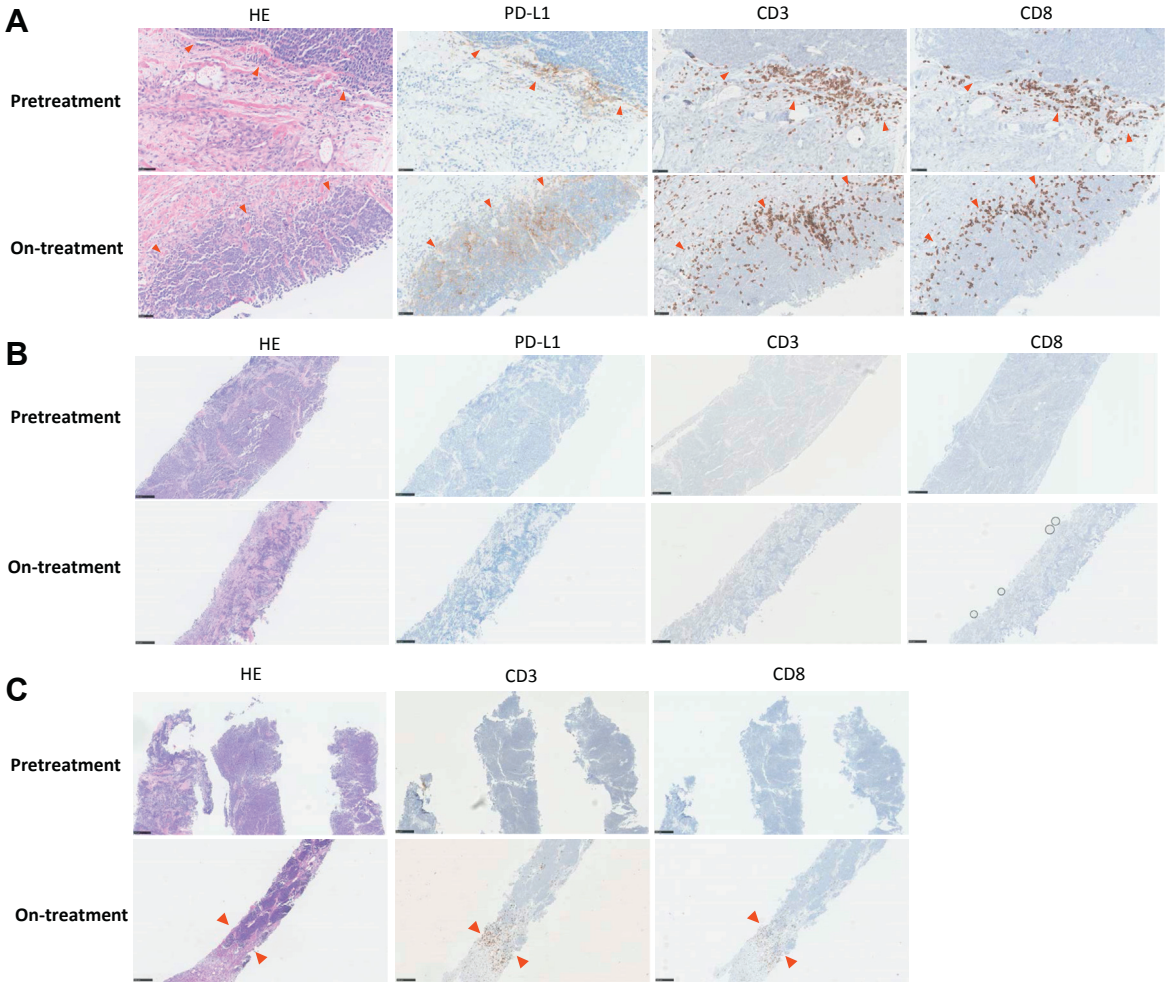


Figure 3. Biomarker status and responses. SCLC immunophenotypes visualized on pretreatment and during-treatment (2–4 weeks later) biopsy specimens stained immunohistochemically for the presence of programmed death ligand 1 (PD-L1) and CD3-positive and CD8-positive T cells. (*A*) Immune inflamed phenotype in a patient with transformed SCLC (patient 19) and an ongoing partial response. Pretreatment and during-treatment biopsy specimens stained immunohistochemically for the presence of PD-L1, CD3-positive, and CD8-positive T cells (original magnification ×40). (*B*) Immune desert phenotype in a patient who had progressive disease (patient 20). Pretreatment and during-treatment tumors show no T-cell infiltration or PD-L1 expression (original magnification ×10). (*C*) Immune-excluded phenotype in a patient (patient 9) with arrows indicating the tumor-stroma margin with T-cell infiltration after treatment (original magnification ×10). HE, hematoxylin and eosin.

knowledge, this is the first published report to evaluate immune checkpoint inhibitors with PARP inhibitor in patients with relapsed SCLC.

The study did not meet its primary end point, and the ORR of 10.5% failed to reject the null hypothesis of 35%. The confirmed ORR is similar to that of the PD-1 inhibitor nivolumab alone in this setting.[2] Clinically meaningful antitumor activity was observed in 21% of patients (confirmed CR, PR, or prolonged stable disease lasting ≥8 months), and no unexpected safety signals were detected. Two of three patients who had previously received immune checkpoint inhibitors had prolonged stable disease and were continuing to receive treatment at 8 months at the time of data cutoff.

The objective responses in this study occurred in patients with identifiable genomic alterations. The patient with a CR had a deleterious somatic *BRCA1* mutation. It is possible that the DDR defect sensitized the tumor to PARP inhibition, yet the depth and durability of tumor regression suggest a contribution from an immune-mediated response. An association between DDR gene alterations and improved responses to immune checkpoint inhibitors has been reported in urothelial cancers[20] and melanoma.[21] The frequency of DDR alterations in SCLC and whether there is an association between DDR alterations and immune checkpoint inhibitor response need further study. The prolonged ongoing response in a patient with *EGFR*-mutant NSCLC

that transformed to SCLC is notable in light of a recent report that found no responses among 17 patients with transformed SCLC who received immune checkpoint inhibitor alone.[22] The results of this study are in line with the findings from a phase II basket study in which olaparib was administered as monotherapy for 4 weeks followed by combination with durvalumab in patients with relapsed SCLC at least 12 weeks after platinum-based therapy.[23] Among 38 patients, two (5%) had responses and the 12-week disease control rate was 29%.

Defining biomarkers predictive of response in SCLC is challenging because in this disease, biopsies are generally not performed at relapse and biopsy specimens usually provide limited tissue for analyses. Further, the relevance of the tumor immune phenotype to the response of SCLC was previously unknown. Consistent with the published literature, we observed that PD-L1 expression was in most cases limited to a minority of tumor cells and or tumor-infiltrating immune cells.[24] In our cohort, a large proportion of tumors (64%) exhibited the excluded phenotype; by contrast, only 21% and 14% of tumors exhibited the inflamed and desert phenotypes, respectively. Tumor responses were observed in all cases in which pretreatment tumors were T-cell–inflamed. Tumor CD8-positive T-cell infiltration has been linked to antitumor activity in patients with advanced melanoma[25] and NSCLC[26] treated with immune checkpoint inhibitors. Our observation extends these findings to relapsed SCLC and suggests that a preexisting CD8-positive T-cell response may be predictive of benefit from immune checkpoint inhibitor-based therapies in SCLC. If confirmed in larger cohorts, these findings may help identify those patients with SCLC who are most likely to benefit from immune checkpoint inhibitor–based therapies.

To our knowledge, this study is the first to assess immune phenotypes in serial SCLC biopsy specimens obtained during treatment. Biopsy specimens were obtained from the same lesion to minimize biological variability. Several observations are worth highlighting: first, the regressing lesions had a preexisting immune response and after treatment showed dense T-cell infiltration, suggesting that preexisting immunity is further amplified during treatment when responses do occur. Second, several nonresponding tumors had minimal or no tumor-infiltrating immune cells before and after treatment, likely reflecting the absence of preexisting tumor-specific T cells. Downregulation of human leukocyte antigen class I, which reduces the number of T-cell targets among the potential pool of aberrantly expressed tumor antigens, has been documented in SCLC[27] and may perhaps be operational here. Third, some of the nonresponding tumors showed a pattern wherein the immune cells did not penetrate the tumor but were instead restricted to the stroma, likely reflecting the presence of immunosuppressive mechanisms within the tumor. Finally, treatment with the combination did not result in substantial induction of PD-L1 in the nonresponding phenotypes or induction of an immune response where there was no preexisting immune response. It is unlikely that the lack of PD-L1 induction was due to sampling time points, as patients received continuous twice-daily dosing of olaparib that should have resulted in continuous PARP inhibition.

Potential limitations of this trial are its small sample size and its single-arm design with no monotherapy comparator groups, thereby preventing direct comparison of the combination with either agent alone. Lack of a comparator group also limits our ability to attribute the relative contribution of both drugs to the clinical and biomarker response. The relevance of the genomic profile to responses cannot be assessed in this study because such information is not available for nonresponding patients. Conclusions regarding the tumor microenvironment are limited by the sample size and the core biopsy size, which limits our understanding of the heterogeneity of immune responses among tumor sites. Nevertheless, the findings highlight the importance of serial biological profiling of SCLC over time at different treatment decision points. The combination of PARP inhibition and immune checkpoint blockade is being investigated in multiple tumor types, including prostate, ovarian, NSCLC, and breast cancers (NCT02734004, NCT02657889, NCT03330405, and NCT02484404). Preliminary results suggest that the improved combinatorial activity may be tissue specific.[28]

In conclusion, although the trial did not meet its primary end point, examination of pretreatment and during-treatment biopsy specimens provides important insights into selection of patients with SCLC for immune checkpoint inhibitor–based approaches. Rational development of immunotherapy combinations remains a challenge, particularly so in SCLC, where tissue availability presents a major obstacle to progress. Optimal immunotherapy in SCLC may need to enhance not only T-cell function but also antigen presentation and may also need to target the immunosuppressive mechanisms in the tumor microenvironment.[29]

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.04.026.

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