ORIGINAL ARTICLE

Durvalumab With or Without Tremelimumab in Combination With Chemoradiotherapy in Patients With Limited-Stage SCLC: Results from the Phase 1 CLOVER Study

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Received 16 October 2024; revised 16 July 2025; accepted 27 July 2025
Available online - 5 August 2025

ABSTRACT

Introduction: The phase 1 CLOVER study (NCT03509012) evaluated durvalumab with or without tremelimumab in combination with concurrent chemoradiotherapy (cCRT) in patients with advanced solid tumors; here, we report findings from the limited-stage SCLC (LS-SCLC) cohort.

Methods: Patients with pathologically confirmed LS-SCLC whose disease could be encompassed within a radical radiation portal received durvalumab (arms 1 and 2) or durvalumab plus tremelimumab (arms 3 and 4) in combination with cCRT (cisplatin-etoposide and either standard radiotherapy [arms 1 and 3] or hyperfractionated radiotherapy [arms 2 and 4]). The primary end point was safety and tolerability. Preliminary efficacy and candidate biomarkers of response were assessed.

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Cite this article as: Cho BC, Ahn M-J, Nishio M, et al. Durvalumab with or without tremelimumab in combination with chemoradiotherapy in patients with limited-stage SCLC: results from the phase 1 CLOVER study. *J Thorac Oncol* XXXX;X:XXXXXX

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2025.100884

Results: Overall, 33 patients were enrolled: 12 in arm 1, 12 in arm 2, six in arm 3, and three in arm 4. No patients had dose-limiting toxicity. Grade 3 or 4 adverse events occurred in 79.2% of patients from arms 1 and 2 and 88.9% from arms 3 and 4; the most common were hematologic events. In arms 1, 2, 3, and 4, objective response rate was 66.7%, 66.7%, 83.3%, and 100.0%, disease control rate was 90.9%, 100.0%, 100.0%, and 100.0% at 18 weeks and 72.7%, 83.3%, 100.0%, and 100.0% at 48 weeks, and the median progression-free survival (PFS) (95% confidence interval) was 9.2 months (5.3–not estimable [NE]), 16.6 months (8.4–NE), not reached (16.6–NE), and 9.3 months (6.3–NE), respectively. In exploratory biomarker analyses, no difference in PFS by programmed cell death-ligand 1 expression level was observed; median PFS was numerically greater in high versus low tumor inflammation signature and *CD8A* expression subgroups.

Conclusions: Durvalumab in combination with cCRT, with or without tremelimumab, was tolerable and active in patients with LS-SCLC.

Keywords: Durvalumab; Tremelimumab; Chemoradiotherapy; Limited-stage SCLC; CLOVER

Introduction

Among patients diagnosed with SCLC, approximately one-third have limited-stage SCLC (LS-SCLC),[1] in which the tumor is confined to one hemithorax and can be encompassed within a single radiation field; these patients are generally suitable for treatment with curative intent.[2,3] Currently, the standard of care for most patients with LS-SCLC with good performance status is concurrent chemoradiotherapy (cCRT) using platinum-etoposide and either once- or twice-daily thoracic radiotherapy.[2] Despite high initial response rates with cCRT, most patients eventually relapse; median progression-free survival (PFS) is approximately 13 to 17 months and median overall survival (OS) is approximately 28 to 39 months,[4,5] with 5-year survival rates of only 29% to 34%,[4–6] highlighting the need for new treatment options to improve outcomes in patients with LS-SCLC.

Incorporating immune checkpoint inhibitors into the treatment of LS-SCLC is of particular interest, on the basis of evidence of immunomodulatory effects of radiotherapy and chemotherapy, which can enhance sensitivity of tumors to inhibitors of programmed cell death protein 1 (PD-1) or its ligand, programmed cell death-ligand 1 (PD-L1). Both chemotherapy and radiotherapy provoke immunogenic cell death, which increases the ability of the immune system to recognize and respond to a tumor by enhancing antigen release and presentation.[7–9] In addition, chemotherapy and radiotherapy have been found to up-regulate PD-L1 expression,[7,10,11] so the addition of a PD-1 or PD-L1 inhibitor may facilitate synergistic antitumor activity.

The clinical use of immune checkpoint blockade in SCLC was first validated in two phase 3 trials in extensive-stage SCLC (ES-SCLC), in which the combination of a PD-L1 inhibitor with first-line standard-of-care chemotherapy improved OS when compared with chemotherapy alone.[12–14] Phase 3 clinical trials in stage III NSCLC[15,16] and, more recently, in LS-SCLC[17] have also found that consolidation treatment with the PD-L1 inhibitor, durvalumab, improved survival outcomes in patients without disease progression following cCRT. The potential benefit of administration of immune checkpoint inhibitors concurrently with CRT, followed by consolidation treatment, was unclear at the time of study initiation; however, more recently, several phase 3 trials assessing this strategy in both unresectable stage III NSCLC[18,19] and LS-SCLC[20] found no improvement in survival outcomes. In addition, whether the clinical activity of PD-1 or PD-L1 pathway inhibitors can be enhanced by combination with inhibitors of the immune checkpoint cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) is unproven in LS-SCLC[21] and ES-SCLC.[22] The immune checkpoints PD-1 and CTLA-4 regulate immune responses by different, nonredundant mechanisms[23]; combining PD-(L)1 and CTLA-4 inhibitors may amplify antitumor T cell responses and provide additive or synergistic effects. Cumulatively, these data supported the rationale for investigating durvalumab, with or without the CTLA-4 inhibitor tremelimumab, combined with cCRT in patients with LS-SCLC.

The phase 1 CLOVER study (NCT03509012) evaluated the safety, tolerability, and preliminary efficacy of durvalumab, with or without tremelimumab, in combination with cCRT in patients with LS-SCLC, and durvalumab combined with cCRT in patients with unresectable, stage III NSCLC[24] or locally advanced head and neck squamous cell carcinoma.[25] Here, we present results from the LS-SCLC cohort of CLOVER. We also report results of exploratory biomarker analyses, focusing on biomarkers potentially associated with response to durvalumab, with or without tremelimumab, when combined with cCRT. A plain language summary of this article can be found in the Supplementary Material.

Patients and Methods

Patients

Patients who were aged 18 years and older with treatment-naive, histologically or cytologically confirmed LS-SCLC (American Joint Committee on Cancer eighth edition stage I−III; T any, N any, M0), whose disease could be encompassed within a radical radiation portal. Additional key eligibility criteria were: WHO or Eastern Cooperative Oncology Group performance status of 0 or 1; provision of fresh or archival tumor biopsy at screening; at least one measurable lesion per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1); no previous exposure to immune-mediated therapy; body weight more than 30 kg; and adequate organ and bone marrow function including pulmonary function with forced expiratory volume in 1 second greater than 1 liter or 40% predictive value and transfer coefficient of the lung for carbon monoxide greater than 40% predicted within the 8 weeks before enrolment. Key exclusion criteria were the following: mixed SCLC and NSCLC per histological testing; ES-SCLC; planned radiation dose of greater than or equal to 20 Gy (V20) to greater than 35% of the total (left and right) volume of the lung and mean lung dose exceeding 20 Gy (relative biological effectiveness); planned radiation dose of greater than or equal to 50 Gy (V50) to greater than 25% of the heart volume; simultaneous primary malignancies or bilateral tumors; active or previous autoimmune or inflammatory disorders; paraneoplastic syndrome of autoimmune nature requiring systemic treatment; uncontrolled intercurrent illness; or history of active primary immunodeficiency.

All patients provided written informed consent. The study protocol and all amendments were approved by the relevant ethics committee or institutional review board and regulatory authorities, and the study was conducted in accordance with the International Conference on Harmonization good clinical practice guidelines, the Declaration of Helsinki, and applicable local regulations.

Study Design and Treatment

For patients with LS-SCLC, the CLOVER study consisted of four treatment arms, each including a dose-limiting toxicity (DLT) assessment part followed by an expansion part. For each arm, the target enrolment for DLT assessment was six patients. Investigators selected whichever open arm they felt was most appropriate (Supplementary Fig. 1). In arms 1 and 2, patients received durvalumab in combination with cCRT, consisting of standard cisplatin-etoposide and either standard radiotherapy (arm 1) or hyperfractionated radiotherapy (arm 2). Arms 3 and 4 opened only after establishing that the regimens in arms 1 and 2 were safe and tolerable; treatment in arm 3 was as for arm 1, and treatment in arm 4 was as for arm 2, with the addition of tremelimumab. Each arm could be expanded up to 30 additional patients, depending on a review of data from the DLT part by the Safety Review Committee. The Sponsor terminated the study early during enrolment of patients in the expansion part in arms 1 and 2 after completion of enrolment in the DLT part in arm 3, and during enrolment in the DLT part in arm 4. The Sponsor's decision to discontinue the study was not because of safety concerns in either the parent CLOVER study or other studies.

Patients received durvalumab 1500 mg (arms 1 and 2) or durvalumab 1500 mg plus tremelimumab 75 mg (arms 3 and 4) by means of intravenous (IV) infusion every 4 weeks. Tremelimumab was administered for four doses; durvalumab monotherapy continued every 4 weeks until disease progression. Cisplatin was administered at a dose of 60 to 80 mg/m^2 IV every 3 weeks (Q3W) on day 1, and etoposide was administered at 100 to 120 mg/m^2 IV Q3W on days 1 to 3 for 4 to 6 cycles, per local guidelines. Patients were allowed to switch to carboplatin (area under the curve 5 IV Q3W) if cisplatin was not tolerated. In the event of tolerability concerns, the total cisplatin dose per cycle could be split over days 1, 2, and 3 of each chemotherapy cycle in the expansion part only. External beam radiation started within the first or second cycle of chemotherapy. Patients in arms 1 and 3 received daily standard radiotherapy (2 Gy/fraction), given in five fractions per week (one fraction/day) over 6 to 7 weeks for a total of 60 to 70 Gy. Patients in arms 2 and 4 received hyperfractionated radiotherapy (1.5 Gy/fraction), given in 10 fractions per week (2 fractions/day, at least 6 hours apart) over 3 weeks for a total of 45 Gy.

Each treatment modality continued as planned unless there was unacceptable toxicity (including any adverse event [AE] that met the definition of a DLT), withdrawal of consent, or another protocol-defined discontinuation criterion was met. Prophylactic cranial irradiation (PCI) was permitted at the investigator's discretion after completion of cCRT for patients with a complete or partial response to initial treatment. After study treatment discontinuation, patients were followed up for survival until data cutoff (December 31, 2020).

Outcomes

The primary end point was the safety and tolerability of durvalumab (with or without tremelimumab) in combination with cCRT, assessed in terms of DLTs and AEs. A DLT was defined as a severe AE that had a reasonable possibility of being related to durvalumab or tremelimumab (alone or in combination with cCRT) and

occurred in the period from the first dose of durvalumab until 28 days after completion of radiotherapy. Full details of AEs considered to be DLTs are included in the supplement. Secondary end points included objective response rate (ORR), best objective response, duration of response (DoR), disease control rate (DCR), PFS (defined as time from first dose of durvalumab to date of objective tumor progression or death) rate at 12, 18, and 24 months, all on the basis of investigator assessment per RECIST v1.1, and OS. Exploratory objectives included the evaluation of candidate biomarkers associated with response, specifically PD-L1 expression, *CD8A* expression, and tumor inflammation signature (TIS) (an 18-gene signature that measures a preexisting but suppressed adaptive immune response within tumors[26]).

Assessments

Tumors were assessed by investigators using computerized tomography or magnetic resonance imaging of the chest and abdomen, according to RECIST v1.1. Assessments took place at baseline, at 4 weeks after the last dose of chemotherapy or radiotherapy, whichever occurred later (and no earlier than 12 weeks after the first dose of durvalumab), then at 24 weeks after the first dose of durvalumab, and subsequently every 8 weeks until 48 weeks after the first dose of durvalumab, and every 12 weeks thereafter until data cutoff, clinical progression, RECIST v1.1–defined progression, or for the duration of study treatment in patients treated through RECIST v1.1–confirmed disease progression. Patients were monitored for safety throughout the study, and AEs were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Survival status was assessed 4, 8, and 12 weeks after stopping treatment and every 12 weeks thereafter until data cutoff. Methods used to evaluate candidate biomarkers are provided in the supplement; for all biomarker analyses, data were pooled across treatment arms because of the small sample size.

Statistical Analysis

Safety data were summarized using the safety analysis set, comprising all patients treated with at least one dose of durvalumab (with or without tremelimumab). Efficacy assessments included all treated patients with a baseline tumor assessment and measurable disease at baseline (full analysis set [FAS]). Safety data are presented by pooling arms based on the experimental systemic treatment assignment, arms 1 and 2 (durvalumab) and arms 3 and 4 (durvalumab and tremelimumab). Preliminary efficacy data are reported by arm. Time-to-event end points for DoR, PFS, and OS were estimated by the Kaplan-Meier method. The incidence, time course, and management of the grouped term "pneumonitis or radiation pneumonitis" events were summarized in a post hoc analysis. The grouped term "pneumonitis or radiation pneumonitis" includes the following preferred terms: acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, idiopathic pneumonia syndrome, immune-mediated pneumonitis, interstitial lung disease, lung opacity, organizing pneumonia, pleuroparenchymal fibroelastosis, pneumonitis, pulmonary fibrosis, and radiation pneumonitis. All statistical analyses were descriptive and performed using the Statistical Analysis System version 9.4 (SAS Institute, Cary, North Carolina).

Results

Patients and Treatment

Between May 11, 2018, and March 27, 2020, the SCLC cohort enrolled 33 patients from 12 centers in Japan, South Korea, Taiwan, Spain, and the United States. Arms 1 and 2 (durvalumab plus cCRT with standard or hyperfractionated radiotherapy, respectively) each enrolled 12 patients across the DLT and expansion parts. Arm 3 (durvalumab plus tremelimumab plus cCRT with standard radiotherapy) enrolled six patients in the DLT part, and arm 4 (durvalumab plus tremelimumab plus cCRT with hyperfractionated radiotherapy) enrolled three patients in the DLT part. Early termination of the study meant that the DLT assessment part was completed in arms 1 to 3 but not in arm 4. Across all treatment arms, the median age was 60.0 years (range, 43–74), most patients were Asian (81.8%), male (72.7%), current or former smokers (81.8%), and had stage III disease (78.8%) (Table 1).

All patients received at least one dose of study treatment and were included in the safety analysis set. Patient disposition is presented in Supplementary Table 1. In arms 1 and 2, nine (37.5%) patients remained on durvalumab treatment at the time of data cutoff (December 31, 2020). Patients received a median (range) of 10.0 (1–32) doses of durvalumab in arm 1 and 12.5 (4–28) doses in arm 2. Four (44.4%) patients in arms 3 and 4 were still receiving durvalumab at data cutoff. Patients received a median (range) of 18 (3–24) doses of durvalumab in arm 3 and 8 (7–24) doses in arm 4. Five (83.3%) patients in arm 3 and three (100%) in arm 4 received the maximum four doses of tremelimumab. In general, patients received the planned 4 to 6 cycles of chemotherapy. In arms 1, 2, 3, and 4, 83.3%, 100%, 100%, and 100% of patients, respectively, received at least four cycles of chemotherapy (on the basis of

Table 1. Baseline Patient Demographics and Disease Characteristics (Full Analysis Set)

Patient Characteristic	Arms 1 and 2 Durvalumab + cCRT (n = 24)	Arms 3 and 4 Durvalumab + Tremelimumab + cCRT (n = 9)	Total (n = 33)
Median age (range), y	58.0 (43-71)	63.0 (59-74)	60.0 (43-74)
Age group, n (%)			
<65 y	21 (87.5)	6 (66.7)	27 (81.8)
≥65 to <75 y	3 (12.5)	3 (33.3)	6 (18.2)
Sex, n (%)			
Male	16 (66.7)	8 (88.9)	24 (72.7)
Female	8 (33.3)	1 (11.1)	9 (27.3)
Race, n (%)			
White	5 (20.8)	1 (11.1)	6 (18.2)
Asian	19 (79.2)	8 (88.9)	27 (81.8)
WHO or ECOG performance status, n (%)			
0	9 (37.5)	3 (33.3)	12 (36.4)
1	15 (62.5)	6 (66.7)	21 (63.6)
Smoking history, n (%)			
Current smoker	4 (16.7)	2 (22.2)	6 (18.2)
Former smoker	14 (58.3)	7 (77.8)	21 (63.6)
Never smoker	6 (25.0)	0	6 (18.2)
AJCC disease stage, n (%)			
I	1 (4.2)	0	1 (3.0)
II	4 (16.7)	2 (22.2)	6 (18.2)
III	19 (79.2)	7 (77.8)	26 (78.8)
Extent of disease,[a] n (%)			
Locally advanced - respiratory	24 (100.0)	9 (100.0)	33 (100.0)
Locally advanced - lymph nodes	21 (87.5)	9 (100.0)	30 (90.9)
PD-L1 status,[b] n (%)			
Positive	11 (45.8)	2 (22.2)	13 (39.4)
Negative	13 (54.2)	6 (66.7)	19 (57.6)
Missing	0	1 (11.1)	1 (3.0)

[a]Patients could have multiple sites of disease.
[b]PD-L1-positive defined as PD-L1 expression on greater than or equal to 1% tumor cells or greater than or equal to 1% immune cells.
AJCC, American Joint Committee on Cancer; cCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand-1.

cisplatin exposure); 41.7%, 33.3%, 33.3%, and 0%, respectively, received six cycles. One patient in arm 1 received no radiotherapy because their radiotherapy plan failed to meet study requirements; this patient subsequently discontinued all other study treatments. The other 11 patients in arm 1 and all patients in arm 3 received a total radiation dose of 60 to 70 Gy (conventional fractionation), per protocol. All patients in arms 2 and 4 received a total radiation dose of 45 Gy (hyperfractionation), per protocol. Fifteen (62.5%) patients in arms 1 and 2 and four (44.4%) in arms 3 and 4 received PCI after completing cCRT.

Safety

No patients had a DLT. All patients had at least one AE of any cause, which were grade 3 or 4 in 19 (79.2%) patients from arms 1 and 2 and eight (88.9%) from arms 3 and 4 (Table 2). In all arms, the most typically reported grade 3 or 4 AEs were hematologic events (Table 3). The most frequent were neutropenia (70.8%, n = 17), leukopenia (37.5%, n = 9) and anemia (25.0%, n = 6) in arms 1 and 2, and neutropenia (66.7%, n = 6), anemia (33.3%, n = 3), and febrile neutropenia, leukopenia, lymphopenia, and thrombocytopenia (each 22.2%, n = 2) in arms 3 and 4. Serious AEs and AEs leading to treatment discontinuation are detailed in Supplementary Tables 2 and 3. Serious AEs occurred in five (20.8%) patients in arms 1 and 2 and four (44.4%) in arms 3 and 4. The only serious AE occurring in more than one patient in either arms 1 and 2 or arms 3 and 4 was radiation pneumonitis (n = 2 in arms 3 and 4). AEs leading to treatment discontinuation occurred in two (8.3%) patients in arms 1 and 2 (pneumonitis and immunoglobulin A nephropathy, respectively) and two (22.2%) in arms 3 and 4 (pneumonitis and radiation pneumonitis, respectively). No AEs resulted in death. Four (16.7%) patients had immune-mediated AEs (imAEs) in arms 1 and 2, and three (33.3%) in arms 3 and 4. Grade 3 or 4 imAEs occurred in one (4.2%) patient in arms 1 and 2 (dermatitis or rash) and one

Table 2. Safety Summary (Safety Analysis Set)

AE, n (%)	Arms 1 and 2 Durvalumab + cCRT (n = 24)	Arms 3 and 4 Durvalumab + Tremelimumab + cCRT (n = 9)
Any cause	24 (100.0)	9 (100.0)
Grade 3 or 4	19 (79.2)	8 (88.9)
With outcome of death	0	0
Serious	5 (20.8)	4 (44.4)
Leading to dose delay or interruption	14 (58.3)	9 (100.0)
Leading to treatment discontinuation[a]	2 (8.3)	2 (22.2)
Immune-mediated[b]	4 (16.7)	3 (33.3)
Grade 3 or 4 immune-mediated	1 (4.2)	1 (11.1)

Note: Includes AEs that started before the first treatment and worsened with the first dose, or with an onset date on or after the date of the first dose and up to and including 90 days after the date of the last dose of study medication or until the start of the first subsequent therapy (whichever came first).
[a]Any AE resulting in permanent discontinuation of durvalumab, tremelimumab, chemotherapy, or radiotherapy.
[b]Defined as an event that was associated with drug exposure and consistent with an immune-mediated mechanism of action, in which there was no clear alternate cause, and that required the use of either systemic steroids or other immunosuppressants, endocrine therapy (for specific endocrine events), or both. There were no fatal immune-mediated AEs.
AE, adverse event; cCRT, concurrent chemoradiotherapy.

(11.1%) in arms 3 and 4 (pneumonitis) (Supplementary Table 4). There were no fatal imAEs.

Post hoc analyses revealed that any-grade pneumonitis or radiation pneumonitis (grouped term) occurred in 11 (45.8%) patients in arms 1 and 2, and seven (77.8%) in arms 3 and 4 (Supplementary Table 5). Grade 2 or higher (i.e., symptomatic) pneumonitis or radiation pneumonitis occurred in four (16.7%) patients in arms 1 and 2 (all grade 2) and five (55.6%) in arms 3 and 4 (including two [22.2%] patients with grade 3 events). There were no grade 4 or 5 pneumonitis or radiation pneumonitis events in any arm. The median time to first onset of pneumonitis or radiation pneumonitis after first dose of durvalumab (days [range]) was 141 (106–253) in arms 1 and 2, and 143 (64–219) in arms 3 and 4 (Supplementary Table 5). Seven (29.2%) patients in arms 1 and 2 and six (66.7%) in arms 3 and 4 received systemic corticosteroids to manage pneumonitis or radiation pneumonitis (Supplementary Table 6). Pneumonitis or radiation pneumonitis led to the discontinuation of immunotherapy in one (4.2%) patient in arms 1 and 2, and two (22.2%) in arms 3 and 4 (Supplementary Table 7).

Efficacy

All 33 patients were included in the FAS. Response data are presented in Table 4. Confirmed ORR (95% confidence interval [CI]) was 66.7% (34.9–90.1) in both arms 1 and 2 (eight partial responses in each arm), 83.3% (35.9–99.6) in arm 3 (one complete response and four partial responses), and 100.0% (29.2–100.0) in arm 4 (three partial responses). Among patients with a confirmed response, the median DoR (months [95% CI]) was 5.3 (3.1–not estimable [NE]) in arm 1, 13.4 (5.4–NE) in arm 2, NE (NE–NE) in arm 3, and 6.0 (3.0–NE) in arm 4. Patient response profiles are illustrated in Supplementary Figure 2. The estimated percentage of patients remaining in response at 12 months was 35.0% in arm 1, 62.5% in arm 2, 100.0% in arm 3, and 33.3% in arm 4. The DCR at 18 weeks was 90.9% in arm 1, and 100.0% in arms 2, 3, and 4; the DCR at 48 weeks was 72.7% in arm 1, 83.3% in arm 2, and 100.0% in arms 3 and 4.

PFS data are displayed in Figure 1. At data cutoff, 7 out of 12 patients in arm 1 and 6 out of 12 patients in arm 2 had experienced disease progression or had died, whereas 1 of 6 patients in arm 3 and 2 of 3 patients in arm 4 had experienced disease progression (with no deaths); median duration of PFS follow-up in censored patients (months [range]) was 9.0 (0.0–27.6) in arm 1, 17.7 (3.2–24.6) in arm 2, 19.4 (15.4–22.3) in arm 3, and 22.0 (22.0–22.0) in arm 4. Median PFS (months [95% CI]) was 9.2 (5.3–NE) in arm 1 (Fig. 1*A*), 16.6 (8.4–NE) in arm 2 (Fig. 1*B*), not reached (NR) (16.6–NE) in arm 3 (Fig. 1*C*), and 9.3 (6.3–NE) in arm 4 (Fig. 1*D*). The estimated 12-, 18-, and 24-month PFS rates for all arms are provided in Figure 1.

At data cutoff, 3 out of 12 patients in arm 1 and 1 out of 12 patients in arm 2 had died, whereas there were no deaths in arms 3 and 4; the median duration of OS follow-up in censored patients (months [range]) was 11.5 (8.6–29.6) in arm 1, 21.7 (10.7–29.9) in arm 2, 20.9 (17.5–24.0) in arm 3, and 16.4 (13.2–22.8) in arm 4. Median OS (95% CI) was NR (14.0–NE) in arm 1 and NR (NE–NE) in arms 2, 3, and 4. The 12-month OS rate (95% CI) was 91.7% (53.9–98.8) in both arm 1 and arm 2, and 100% in both arms 3 and 4.

Exploratory Biomarker Analyses

PD-L1. A total of 32 patients were evaluable for PD-L1 expression; 13 patients had PD-L1 greater than or equal to 1% on either tumor cells or immune cells, and 19 patients had PD-L1 less than 1% on both tumor and immune cells. There was no apparent association between PFS and PD-L1 status (hazard ratio [HR] = 1.24 [95% CI: 0.46–3.34]); because of the small number of PFS events per subgroup by PD-L1 expression, the CI is wide, and the *p* value for this analysis is not reported (Supplementary Fig. 3).

Table 3. AEs of Any Cause Occurring in At Least 10% of Patients Across Arms 1 and 2 or in ≥2 Patients Across Arms 3 and 4 (Safety Analysis Set)

	Arms 1 and 2 Durvalumab + cCRT (n = 24)		Arms 3 and 4 Durvalumab + Tremelimumab + cCRT (n = 9)	
AE,[a] n (%)	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any	24 (100.0)	19 (79.2)	9 (100.0)	8 (88.9)
Neutropenia	23 (95.8)	17 (70.8)	7 (77.8)	6 (66.7)
Anemia	15 (62.5)	6 (25.0)	5 (55.6)	3 (33.3)
Nausea	15 (62.5)	0	4 (44.4)	0
Esophagitis	13 (54.2)	0	5 (55.6)	0
Pneumonitis or radiation pneumonitis[b]	11 (45.8)	0	7 (77.8)	2 (22.2)
Decreased appetite	12 (50.0)	0	5 (55.6)	0
Thrombocytopenia	10 (41.7)	1 (4.2)	4 (44.4)	2 (22.2)
Leukopenia	10 (41.7)	9 (37.5)	3 (33.3)	2 (22.2)
Constipation	9 (37.5)	0	3 (33.3)	0
Alopecia	8 (33.3)	0	2 (22.2)	0
Rash	4 (16.7)	1 (4.2)	5 (55.6)	0
Cough	4 (16.7)	0	4 (44.4)	0
Pruritus	4 (16.7)	0	4 (44.4)	0
Pyrexia	7 (29.2)	0	1 (11.1)	0
Radiation skin injury	6 (25.0)	0	1 (11.1)	0
Asthenia	3 (12.5)	0	3 (33.3)	1 (11.1)
Dysphagia	4 (16.7)	0	2 (22.2)	0
Dyspepsia	2 (8.3)	0	3 (33.3)	0
Fatigue	4 (16.7)	0	1 (11.1)	0
Febrile neutropenia	3 (12.5)	2 (8.3)	2 (22.2)	2 (22.2)
Hiccups	4 (16.7)	0	1 (11.1)	0
Insomnia	4 (16.7)	0	1 (11.1)	0
Myalgia	2 (8.3)	0	3 (33.3)	0
Oropharyngeal pain	2 (8.3)	0	3 (33.3)	0
Upper respiratory tract infection	4 (16.7)	0	1 (11.1)	0
Vomiting	4 (16.7)	0	1 (11.1)	0
Back pain	3 (12.5)	0	1 (11.1)	0
Diarrhea	3 (12.5)	0	1 (11.1)	0
Dysgeusia	3 (12.5)	0	1 (11.1)	0
Headache	4 (16.7)	0	0	0
Hypomagnesemia	4 (16.7)	0	0	0
Odynophagia	3 (12.5)	0	1 (11.1)	0
Pneumonia	3 (12.5)	2 (8.3)	1 (11.1)	0
Productive cough	3 (12.5)	0	1 (11.1)	0
Abdominal pain	3 (12.5)	0	0	0
Alanine aminotransferase increased	1 (4.2)	0	2 (22.2)	0
Gastritis	3 (12.5)	0	0	0
Lymphopenia	1 (4.2)	1 (4.2)	2 (22.2)	2 (22.2)
Amylase increased	0	0	2 (22.2)	1 (11.1)
Delirium	0	0	2 (22.2)	0
Maculopapular rash	0	0	2 (22.2)	0

Note: Includes AEs that started before the first treatment and worsened with the first dose, or with an onset date on or after the date of the first dose and up to and including 90 days after the date of the last dose of study medication or until the start of the first subsequent therapy (whichever came first).
[a]AEs are listed in order of frequency across all arms.
[b]Pneumonitis or radiation pneumonitis (grouped term) includes reported preferred terms of pneumonitis and radiation pneumonitis.
AE, adverse event; cCRT, concurrent chemoradiotherapy.

TIS and *CD8A* Expression. RNA sequencing was performed on tumor tissue samples from 18 patients. Five patients had high TIS and *CD8A* expression (using the top quartile cutoffs of 4.59 and 2.83, respectively); 13 patients had low TIS and *CD8A* expression. There were too few events to calculate the HR and associated *p* value for PFS by *CD8A* gene expression and TIS subgroups. Median PFS was NR (95% CI: 1.4–NE) in the high TIS subgroup and was 9.3 months (95% CI: 6.3–NE) in the low TIS subgroup (Fig. 2). The results for *CD8A* gene expression were similar to those for TIS; in the high versus low *CD8A* expression subgroups, the median PFS was NR

Table 4. Summary of Confirmed Tumor Response (Full Analysis Set)

Outcome	Arm 1 Durvalumab + cCRT (Standard RT) (n = 12)	Arm 2 Durvalumab + cCRT (Hyperfractionated RT) (n = 12)	Arm 3 Durvalumab + Tremelimumab + cCRT (Standard RT) (n = 6)	Arm 4 Durvalumab + Tremelimumab + cCRT (Hyperfractionated RT) (n = 3)
Objective response rate, n (%)	8 (66.7)	8 (66.7)	5 (83.3)	3 (100.0)
95% CI	34.9-90.1	34.9-90.1	35.9-99.6	29.2-100.0
Best objective response, n (%)				
Complete response	0	0	1 (16.7)	0
Partial response	8 (66.7)	8 (66.7)	4 (66.7)	3 (100.0)
Stable disease ≥16 wk	2 (16.7)	1 (8.3)	1 (16.7)	0
Progressive disease	1 (8.3)	1 (8.3)	0	0
Not evaluable	1 (8.3)	2 (16.7)	0	0
Median duration of response, mo	5.3	13.4	NE	6.0
95% CI	3.1-NE	5.4-NE	NE-NE	3.0-NE
Remaining in response, %				
12 mo	35.0	62.5	100.0	33.3
18 mo	35.0	46.9	100.0	33.3
Disease control rate at 18 wk,[a] n/N (%)	10/11 (90.9)	12/12 (100.0)	6/6 (100.0)	3/3 (100.0)
95% CI	58.7-99.8	73.5-100.0	54.1-100.0	29.2-100.0
Disease control rate at 48 wk,[a] n/N (%)	8/11 (72.7)	10/12 (83.3)	6/6 (100.0)	3/3 (100.0)
95% CI	39.0-94.0	51.6-97.9	54.1-100.0	29.2-100.0

Note: Responses were investigator-assessed per Response Evaluation Criteria in Solid Tumors version 1.1.
[a]Defined as the percentage of patients with best objective response of complete or partial response in that period, or who have exhibited stable disease for a minimum interval of 17 weeks or 47 weeks (as applicable). Assessed in patients with at least one postbaseline RECIST version 1.1 assessment.
cCRT, concurrent chemoradiotherapy; CI, confidence interval; NE, not estimable; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors.

(95% CI: 1.4−NE) versus 9.3 months (95% CI: 6.3−NE) (Supplementary Fig. 4).

Discussion

The LS-SCLC cohort of the phase 1 CLOVER study assessed safety, tolerability, and preliminary efficacy of durvalumab with or without tremelimumab in combination with cCRT in patients with previously untreated LS-SCLC. Most patients (24/33) received treatment with durvalumab and cCRT. Nine patients received durvalumab plus tremelimumab with cCRT, eight of whom successfully received the maximum four cycles of tremelimumab. Demographics and baseline characteristics of the study population were generally as expected, although there was a notably higher percentage of never-smokers (approximately 18%) than is usual in patients with SCLC. This observation may be attributable to the relatively high proportion of Asian patients (82%) in the CLOVER LS-SCLC cohort; previous reports found a greater proportion of never-smokers in South Korean and Chinese patients with SCLC (13−23%)[27–31] than has been reported in international studies with predominantly White patients (2.5%−9%).[12,14,32–34]

There were no unexpected safety findings in the LS-SCLC cohort, and no DLTs in arms 1 to 3. Early termination of the study precluded a full DLT assessment in arm 4. Most patients received at least four cycles of chemotherapy and completed scheduled radiotherapy, suggesting that the addition of durvalumab with or without tremelimumab to cCRT did not generally affect treatment adherence and was associated with manageable toxicity. Overall safety was consistent with the known AE profiles for each component of the study treatment, whether given alone or in combination.[4,14,35–39] In patients with LS-SCLC, cCRT is known to be associated with esophagitis (in particular with hyperfractionated radiotherapy) and, critically, pneumonitis or radiation pneumonitis.[4,40] In CLOVER, esophagitis was reported in approximately 50% of patients, with all cases at grade 1 or 2 and none leading to treatment discontinuation. Pneumonitis/radiation pneumonitis occurred in 45.8% of patients in arms 1 and 2; the rate in arms 3 and 4 was higher (77.8%). Median time to onset was similar across arms. Pneumonitis or radiation pneumonitis cases were primarily grade 1 or 2 in severity (grade 3 occurred only in two patients in arms 3 and 4), and events were manageable, with only one treatment discontinuation in arms 1 and 2 and two treatment discontinuations in arms 3 and 4; no events had a fatal outcome.

Interpretation of efficacy data from the SCLC cohort of CLOVER is limited by the phase 1 study design, with no comparator arm, and by the smaller-than-planned number of

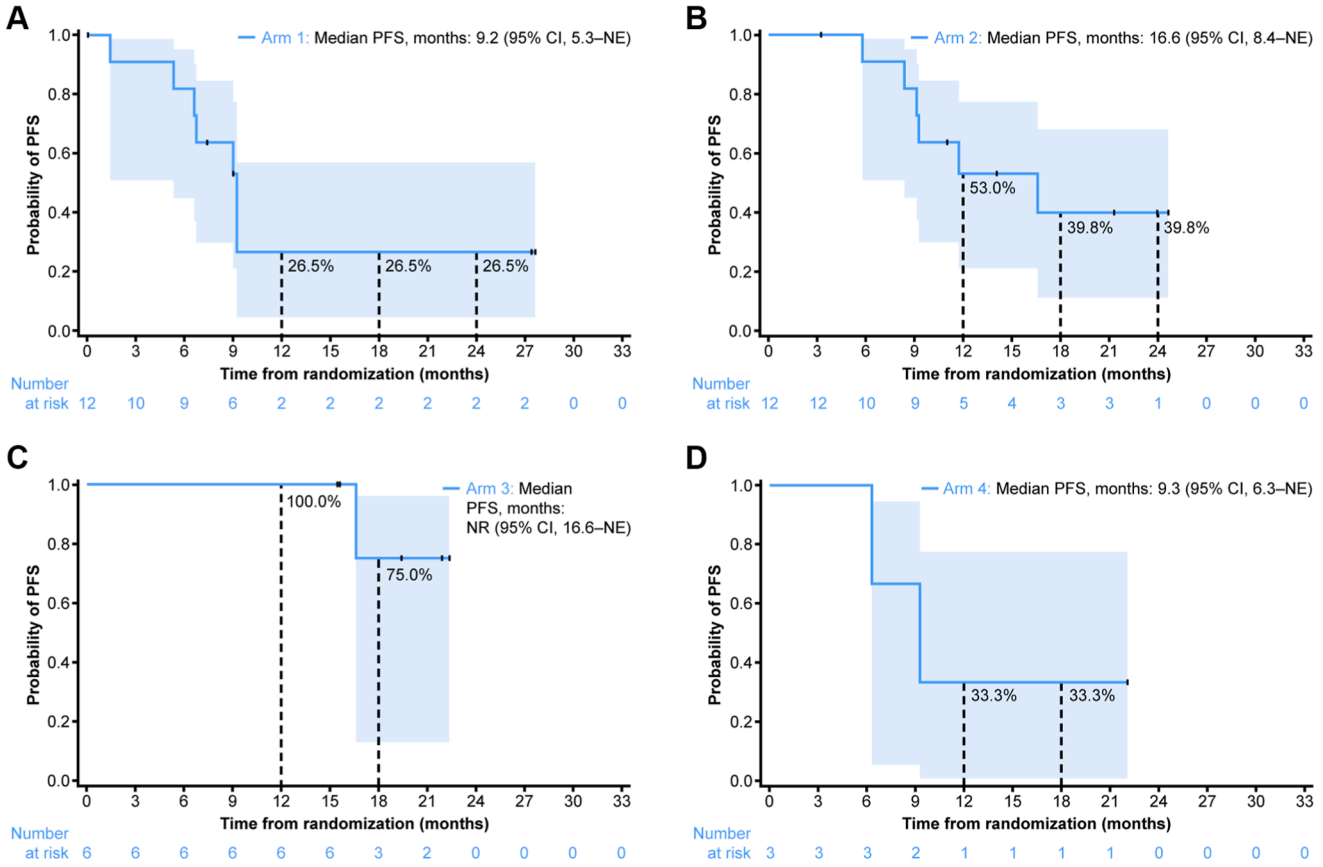

Figure 1. Kaplan-Meier estimates of PFS in (A) arm 1, (B) arm 2, (C) arm 3, and (D) arm 4 (full analysis set). CI, confidence interval; NE, not estimable; NR, not reached; PFS, progression-free survival.

patients resulting from premature closure of the study. However, the efficacy results of arms 1 and 2 are broadly similar to those reported in a single-arm phase 2 Korean study in which 50 patients with LS-SCLC received durvalumab plus platinum-etoposide for four cycles, with thoracic radiotherapy started with cycle 3 of chemoimmunotherapy, followed by consolidation durvalumab; median PFS was 14.4 months, and the 24-month PFS rate was 42.0%.[41] Data from further studies are required to improve our understanding of the optimal timing of immunotherapy and cCRT regimens in LS-SCLC, and randomized studies will provide the most valuable insights. The randomized phase 2 STIMULI study failed to show PFS superiority of consolidation immunotherapy with nivolumab (anti–PD-1) plus ipilimumab (anti–CTLA-4) versus observation after cCRT plus PCI.[21] However, STIMULI closed early because of slow accrual, and toxicity in the experimental arm resulted in a median time to treatment discontinuation of only 1.7 months, limiting interpretation of efficacy data. The phase 3, double-blind, placebo-controlled ADRIATIC study (NCT03703297) is evaluating consolidation treatment with durvalumab (with or without tremelimumab) in patients with LS-SCLC who have not progressed after cCRT; the primary end points are OS and PFS (by blinded independent central review) for durvalumab monotherapy versus placebo. In the first planned interim analysis from ADRIATIC, consolidation durvalumab exhibited statistically significant and clinically meaningful improvement in both OS and PFS compared with placebo (median OS 55.9 versus 33.4 months; HR = 0.73 [98.321% CI: 0.54–0.98]; $p = 0.01$; median PFS 16.6 versus 9.2 months; HR = 0.76 [97.195% CI: 0.59–0.98]; $p = 0.02$).[17] However, results from the second planned interim analysis of the phase 2/3 NRG Oncology/Alliance LU005 study (NCT03811002), which is evaluating cCRT with or without atezolizumab started simultaneously with thoracic radiotherapy and continued for up to 12 months, were negative.[20,42] The addition of atezolizumab to cCRT did not improve the primary end point of OS when compared with cCRT alone (HR = 1.11 [95% CI: 0.85–1.45]).[20] Finally, the phase 3 KEYLYNK-013 study (NCT04624204) is comparing cCRT plus either pembrolizumab (groups A and B) or placebo (group C), followed, in the absence of disease progression, by consolidation with pembrolizumab plus placebo (group A), pembrolizumab plus olaparib (group B), or placebo (group C); the dual primary end points are PFS and OS.[43] The primary completion date for this study is October 2027.

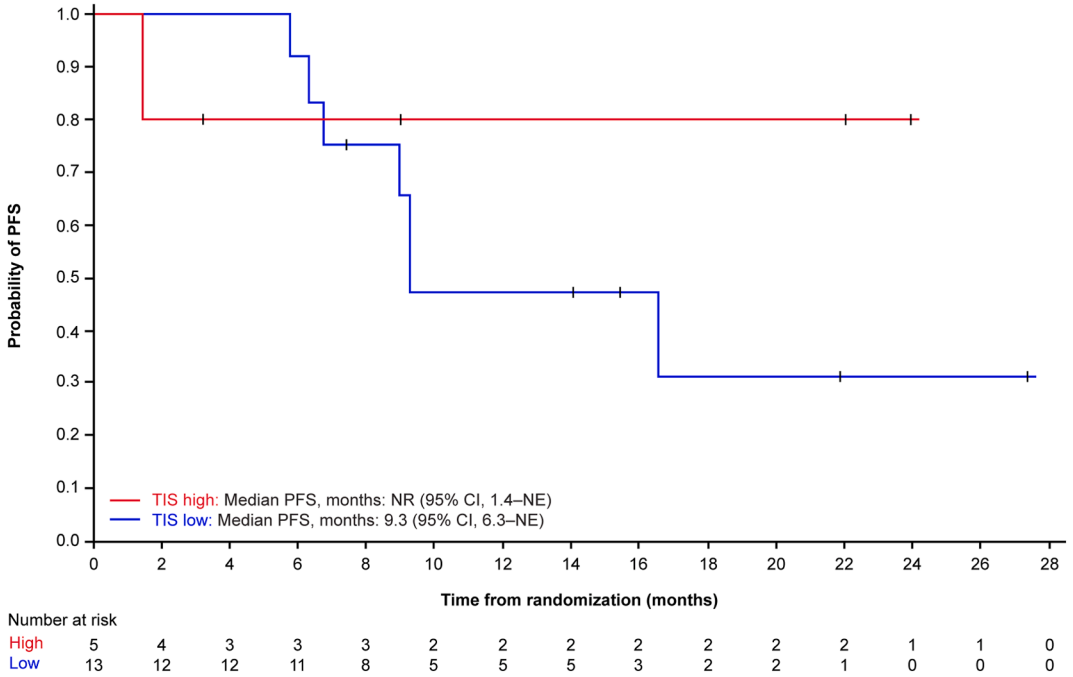

Figure 2. Kaplan-Meier estimates of progression-free survival by TIS (TIS evaluable population; n = 18). Patients were grouped into high or low TIS using the top quartile boundary as a cutoff. CI, confidence interval; NE, not estimable; NR, not reached; PFS, progression-free survival; TIS, tumor inflammation signature.

Our exploratory biomarker analyses aimed to provide some insight into defining patients who may derive the greatest benefit from combining immunotherapy and cCRT. PD-L1 expression has been found to predict response to PD-(L)1 inhibitors in other tumor types,[44] but does not seem to be predictive in SCLC.[45–47] As yet, little is known about PD-L1 as a biomarker in LS-SCLC. Consistent with findings from the phase 3 CASPIAN, IMpower133, and KEYNOTE-604 studies in ES-SCLC,[33,48,49] and the ADRIATIC study in LS-SCLC,[47] our results in patients with LS-SCLC appeared to show no difference in PFS by PD-L1 expression level. Although results are preliminary and limited by small subgroup sizes, we found that the median PFS was numerically greater in both high TIS and high *CD8A* expression subgroups than in the respective low subgroups. This is consistent with previously published findings that an "inflamed" subtype of SCLC (SCLC-I; characterized by high expression of immune checkpoints, major histocompatibility complex class I, and genes associated with immune cell infiltration, including *CD8A*) is associated with a better response to immune checkpoint inhibitors than other SCLC subtypes.[50,51]

In conclusion, the phase 1 CLOVER study showed that durvalumab in combination with cCRT, with or without tremelimumab, was associated with manageable toxicity that typically did not limit treatment received, and is active in patients with LS-SCLC; results from ongoing randomized studies will help further clarify the value of adding checkpoint inhibitor immunotherapy to cCRT in this population.

CRediT Authorship Contribution Statement

Byoung Chul Cho: Conceptualization, Formal analysis, Investigation, Resources, Data curation, Visualization, Supervision, Writing - review and editing.

Myung-Ju Ahn: Investigation, Writing - review and editing.

Makoto Nishio: Investigation, Data curation, Writing - review and editing.

Haruyasu Murakami: Investigation, Writing - review and editing.

Dong Wan-Kim: Investigation, Writing - review and editing.

Sang-We Kim: Investigation, Resources, Writing - review and editing.

Sana D. Karam: Investigation, Data curation, Writing - review and editing.

Ana Estival: Investigation, Writing - review and editing.

Chia-Chi Lin: Investigation, Writing - review and editing.

Jose Manuel Trigo: Investigation, Data curation, Writing - review and editing.

Rosa Alvarez: Validation, Formal analysis, Investigation, Writing - review and editing.

Chih Liang Wang: Investigation, Resources, Writing - review and editing.

Mingchao Xie: Formal analysis, Visualization, Writing - review and editing.

Sonia Iyer: Conceptualization, Methodology, Visualization, Supervision, Writing - original draft, Writing - review and editing.

Jon Armstrong: Formal analysis, Writing - review and editing.

Priti Chugh: Formal analysis, Supervision, Writing - review and editing.

Haiyi Jiang: Conceptualization, Methodology, Formal analysis, Supervision, Writing - review and editing.

Julie E. Bauman: Conceptualization, Methodology, Investigation, Supervision, Writing - review and editing.

Data Availability Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Disclosures

Dr. Chul Cho reports employment with Yonsei University Health System; ownership of stocks/shares with TheraCanVac Inc., Gencurix Inc., BridgeBio Therapeutics, KANAPH Therapeutic Inc., Cyrus therapeutics, Interpark Bio Convergence Corp., and J INTS BIO; membership on an advisory council or committee with KANAPH Therapeutic Inc., BridgeBio Therapeutics, Cyrus therapeutics, Guardant Health, Oscotec Inc., J INTS Bio, Therapex Co., Ltd., Gilead, and Amgen; membership on the board of directors for J INTS BIO; received consulting fees from Abion, BeiGene, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol Myers Squibb, CJ, CureLogen, Cyrus therapeutics, Ono, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI-Cell, Guardant, HK Inno-N, Imnewrun Biosciences Inc., Janssen, Takeda, MSD, Medpacto, Blueprint medicines, RandBio, and Hanmi; grants or funds from MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, GIInnovation, GI-Cell, Abion, AbbVie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Oncology, CJ bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, BridgeBio Therapeutics, Yuhan, ImmuneOncia, Illumina, KANAPh therapeutics, Therapex, JINTSbio, Hanmi, CHA Bundang Medical Center, and Vertical Bio AG; royalties from Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH (PDX, PDO, PDC Licensing Contract – not patent); and is a founder of DAAN Biotherapeutics. Dr. Ahn reports receiving honoraria and consulting fees from AstraZeneca, Roche, MSD, Merck, Takeda, ONO, Novartis, Lilly, Amgen, and Yuhan; and consulting fees from Alpha Pharmaceuticals. Dr. Nishio reports receiving honoraria from Ono Pharmaceuticals, Chugai Pharmaceutical, Taiho Pharmaceutical, Bristol Myers Squibb, Daiichi Sankyo, Lilly, AstraZeneca, MSD, AbbVie, Takeda, Pfizer, Boehringer Ingelheim, Novartis, Nippon Kayaku, Merck, and Janssen. Dr. Murakami reports receiving honoraria from Chugai Pharma, Daiichi Sankyo, AstraZeneca, Takeda, Amgen, Ono Pharmaceutical, Bristol Myers Squibb Japan, MSD, Pfizer, Novartis, Lilly Japan, Taiho Pharmaceutical, Eisai, Nihonkayaku, and GAIA BioMedicine. Dr. Wan-Kim reports receiving grants paid to their institution from Alpha Biopharma, Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, BridgeBio Therapeutics, Chong Keun Dang, Daiichi Sankyo, GlaxoSmithKline (GSK), Hanmi, InnoN Janssen, Merck, Merus, Mirati Therapeutics, MSD, Novartis, ONO Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan; and medical writing assistance from Amgen, AstraZeneca, Boehringer Ingelheim, BridgeBio Therapeutics, Chong Keun Dang, Daiichi Sankyo, GSK, Janssen, Merus, Mirati Therapeutics, MSD, Merck, Novartis, Pfizer, Roche, Takeda, and Yuhan. Dr. Kim reports membership on an advisory council or committee for Terapex; received consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Janssen, and Takeda; and grants or funds from Yuhan.

Dr. Karam reports receiving grants or funds from AstraZeneca, Roche, Amgen, and Genentech. Dr. Estival reports receiving honoraria from MSD, AstraZeneca, Bristol Myers Squibb, Merck, GSK, Takeda, Roche, and Pharmamar; and consulting fees from Takeda, MSD, and Roche. Dr. Lin reports receiving honoraria from Boehringer Ingelheim, Eli Lilly, Novartis, and Roche; and consulting fees from AbbVie, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Merck KGaA, Novartis, and PharmaEngine. Dr. Iyer reports ownership of stock/shares with AstraZeneca Oncology. Mr. Armstrong, Dr. Chugh, and Dr. Jiang report ownership of stock/shares with AstraZeneca. The remaining authors declare no conflict of interest.

Acknowledgments

The study was funded by AstraZeneca. We thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support for the development of this manuscript, under the

direction of the authors, was provided by Helen Kitchen, of Ashfield MedComms (Macclesfield, UK), an Inizio company, and funded by AstraZeneca.

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.2025.100884.

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