Design and Rationale for a Phase III, Randomized, Placebo-controlled Trial of Durvalumab With or Without Tremelimumab After Concurrent Chemoradiotherapy for Patients With Limited-stage Small-cell Lung Cancer: The ADRIATIC Study

Suresh Senan,[1] Isamu Okamoto,[2] Gyeong-won Lee,[3] Yuanbin Chen,[4] Seiji Niho,[5] Gabriel Mak,[6] Wenliang Yao,[6] Norah Shire,[6] Haiyi Jiang,[6] Byoung Chul Cho[7]

Abstract

Limited-stage (LS) small-cell lung cancer (SCLC) remains an area of high unmet medical need. The standard-of-care therapy comprises curative-intent platinum-based chemotherapy with concurrent radiotherapy (cCRT), which can be followed by prophylactic brain irradiation and then observation. However, most patients will relapse. Durvalumab (antiprogrammed cell death ligand-1) has enhanced the efficacy outcomes after cCRT for patients with unresectable, stage III non-small-cell lung cancer. Recently, durvalumab combined with platinum-etoposide demonstrated a significant survival benefit compared with platinum-etoposide as first-line treatment of patients with extensive-stage SCLC and has also shown antitumor activity as monotherapy and combined with tremelimumab (anticytotoxic T-lymphocyte–associated antigen-4) in pretreated patients with extensive-stage SCLC. ADRIATIC, a phase III, randomized, double-blind, placebo-controlled, multicenter, global study (ClinicalTrials.gov identifier, NCT03703297), is designed to investigate the efficacy of durvalumab, with or without tremelimumab, as consolidation therapy for patients with LS-SCLC without disease progression after cCRT. Approximately 600 patients with documented histologic or cytologic LS-SCLC, World Health Organization/Eastern Cooperative Oncology Group performance status 0 or 1, and no progression after 4 cycles of cCRT will be randomized (1:1:1) to treatment (durvalumab 1500 mg plus placebo every 4 weeks [q4w] for 4 cycles, followed by durvalumab 1500 mg q4w; durvalumab 1500 mg plus tremelimumab 75 mg q4w for 4 cycles, followed by durvalumab 1500 mg q4w; or dual placebo q4w for 4 cycles, followed by single placebo q4w) within 1 to 42 days of completing cCRT, stratified by stage and receipt of prophylactic brain irradiation. The primary endpoints are progression-free survival and overall survival. The secondary endpoints are overall survival and progression-free survival rates, objective response rate, and safety and tolerability. Recruitment began in September 2018.

Clinical Lung Cancer, Vol. 21, No. 2, e84-8 © 2020 Published by Elsevier Inc.

Keywords: Clinical study, Cytotoxic T-lymphocyte–associated antigen-4, Immunotherapy, Programmed cell death ligand-1, SCLC

[1]Department of Radiation Oncology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands
[2]Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[3]Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Jinju, Gyeongsang, Republic of Korea
[4]Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI
[5]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[6]AstraZeneca, Gaithersburg, MD
[7]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea

Submitted: Nov 21, 2019; Accepted: Dec 23, 2019; Epub: Dec 28, 2019

Address for correspondence: Suresh Senan, MBBS, PhD, Department of Radiation Oncology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, De Boelelaan 1118, Amsterdam 1182 DB, The Netherlands
E-mail contact: s.senan@amsterdamumc.nl

1525-7304/© 2020 Published by Elsevier Inc.
https://doi.org/10.1016/j.cllc.2019.12.006

Introduction

Small-cell lung cancer (SCLC) represents ~13% to 15% of all newly diagnosed lung cancer cases and is clinically the most aggressive form of lung cancer.[1] Approximately one third of patients with SCLC will present with limited-stage SCLC (LS-SCLC).[1] The curative-intent standard-of-care therapy for patients with LS-SCLC is platinum-based chemotherapy, which typically includes etoposide plus either cisplatin or carboplatin, with concurrent thoracic radiotherapy (concurrent chemoradiotherapy [cCRT]), followed by prophylactic cranial irradiation (PCI), if indicated, and then observation.[2] Although most patients will respond to initial cCRT, the majority experience disease relapse. The median overall survival (OS) has been 25 to 30 months, with a 5-year survival rate of 31% to 34%.[3] Recent data with immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway, combined with platinum-based chemotherapy, have demonstrated improved clinical outcomes as first-line treatment of patients with extensive-stage (ES)-SCLC, extending the median OS to > 12 months for the first time for this population.[4,5] In the second-line, postplatinum setting, the median OS has been only 5.4 months with topotecan,[6] emphasizing the importance of improving outcomes with first-line treatment for all stages of SCLC.

Durvalumab is a selective, monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80,[7] allowing T cells to recognize and kill tumor cells. In the phase III PACIFIC study (ClinicalTrials.gov identifier, NCT02125461), durvalumab reduced the risk of disease progression (PD) or death by 48% (stratified hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.42-0.65; $P < .001$; median, 16.8 vs. 5.6 months) and the risk of death by 32% (stratified HR, 0.68; 99.73% CI, 0.47-0.997; $P = .0025$; median, not reached vs. 28.7 months) compared with placebo, in patients with unresectable, stage III non-small-cell lung cancer (NSCLC) without PD after platinum-based chemoradiotherapy.[8,9] Durvalumab, with or without the anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody, tremelimumab,[10] is also currently in development for the treatment of LS-SCLC and ES-SCLC. In early-phase studies (ClinicalTrials.gov identifiers, NCT01693562, NCT02261220, NCT02937818), durvalumab, with or without tremelimumab, demonstrated durable clinical activity and a manageable safety profile for patients with pretreated ES-SCLC.[11-13] The addition of durvalumab, with or without tremelimumab, to etoposide plus either carboplatin or cisplatin (platinum-etoposide) is also being evaluated as first-line treatment for patients with ES-SCLC in the CASPIAN study (ClinicalTrials.gov identifier, NCT03043872). At the interim analysis, CASPIAN demonstrated a statistically significant and clinically meaningful improvement in OS for patients treated with durvalumab plus platinum-etoposide compared with platinum-etoposide alone (HR, 0.73; 95% CI, 0.59-0.91; $P = .0047$).[5] The clinical activity of durvalumab, with or without tremelimumab, observed in ES-SCLC suggests that these agents might also confer clinical benefits for patients with LS-SCLC.

The ADRIATIC study (ClinicalTrials.gov identifier, NCT03703297) will build on this background by investigating the efficacy and safety of durvalumab, with or without tremelimumab, as consolidation therapy for patients with LS-SCLC without PD after cCRT. In the present report, we have described the study design.

Materials and Methods

Study Design

ADRIATIC is a phase III, randomized, double-blind, placebo-controlled, multicenter, global study in patients with LS-SCLC. Approximately 600 patients from 17 countries across Asia, Europe, and North and South America will be randomized (1:1:1) to receive 1 of the following treatment regimens within 1 to 42 days of completing cCRT (and PCI treatment, if indicated by the local standard-of-care protocols): durvalumab monotherapy (1500 mg intravenously [IV] every 4 weeks [q4w]) combined with placebo (saline IV q4w) for 4 cycles, followed by durvalumab (1500 mg IV q4w); durvalumab (1500 mg IV q4w) combined with tremelimumab (75 mg IV q4w) for 4 cycles, followed by durvalumab (1500 mg IV q4w); or placebo (saline IV q4w) combined with a second saline solution IV q4w for 4 cycles each, followed by a single saline solution IV q4w (Figure 1). Treatment will continue until PD in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), intolerable toxicity, or a maximum of 24 months, whichever comes first. Randomization will be stratified by stage (I/II vs. III) using the TNM classification and receipt of PCI (yes vs. no) to ensure that study arms are balanced for prognostic factors.

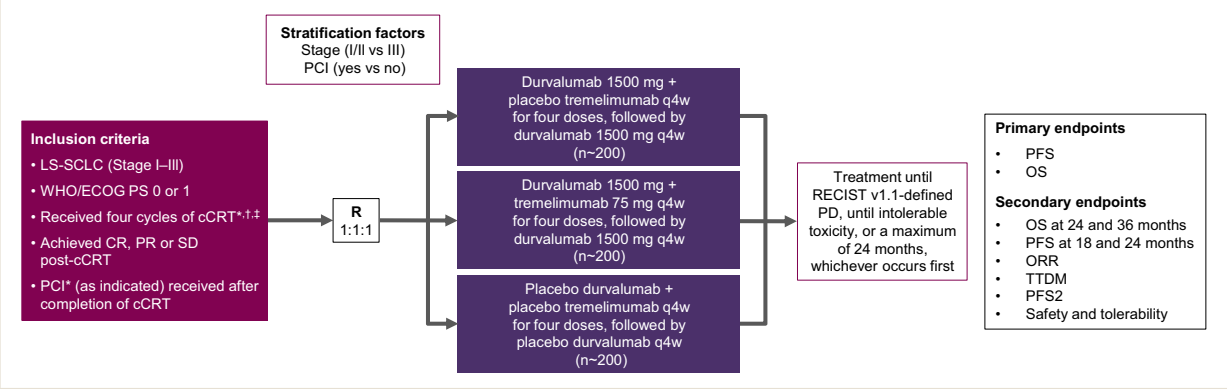
Key Eligibility Criteria

Patients must be ≥ 18 years old and have documented histologic or cytologic LS-SCLC, World Health Organization/Eastern Cooperative Oncology Group performance status 0 or 1, an estimated life expectancy of ≥ 12 weeks, and a complete response, a partial response, or stable disease after definitive, platinum-based cCRT (Table 1). The patients must have received cCRT before study entry, with the chemotherapy component consisting of 4 cycles of platinum and IV etoposide. Patients with disease control after receiving only 3 cycles of platinum-based chemotherapy might also be eligible at the discretion of the investigator. Radiotherapy must have been initiated no later than the end of cycle 2 of chemotherapy and should consist of either 60 to 66 Gy within 6 weeks (standard once-daily schedule) or 45 Gy within 3 weeks (hyperfractionated twice-daily schedule). PCI is permitted at the investigator's discretion and must be conducted after completion of cCRT and within 1 to 42 days of first study treatment. Patients will be excluded if they have ES-SCLC, mixed SCLC and NSCLC histologic features, any unresolved grade ≥ 2 adverse event (AE) after cCRT, any history of grade ≥ 2 pneumonitis (except for resolved infective pneumonitis), or active or previous documented autoimmune or inflammatory disorders or uncontrolled intercurrent illness.

Study Endpoints

The primary endpoints are progression-free survival (PFS), assessed by blinded independent central review per RECIST v1.1, and OS. The secondary endpoints include OS at 24 and 36 months, PFS at 18 and 24 months, objective response rate, time to death or distant metastasis (TTDM), time from randomization to second progression, and safety and tolerability. Additional secondary endpoints include symptoms and health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer

Figure 1 Study Design. *Concurrent Chemoradiotherapy (cCRT) and Prophylactic Cranial Irradiation (PCI) Must Be Completed Within 1 to 42 Days Before Randomization and Treatment Initiation. †Three Cycles of Platinum-based Chemotherapy Is Permitted if Disease Control Was Achieved and No Additional Benefit Can Be Expected From an Additional Cycle as Determined by the Investigator. ‡The Radiotherapy Component Must Have Been Initiated No Later Than the End of Cycle 2 of Chemotherapy and Consist of Either 60 to 66 Gy Over 6 weeks (Standard Once-daily Schedule) or 45 Gy Over 3 Weeks (Hyperfractionated Twice-daily Schedule)



Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; LS-SCLC = limited-stage small-cell lung cancer; ORR = objective response rate; OS = overall survival; PCI = prophylactic cranial irradiation; PD = progressive disease; PFS = progression-free survival; PFS2 = interval from randomization to second progression; PR = partial response; PS = performance status; q4w = every 4 weeks; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease; TTDM = time to death or distant metastasis; WHO = World Health Organization.

quality-of-life questionnaires (QLQ-C30, version 3, and QLQ-LC13), pharmacokinetics, and immunogenicity. Tissue samples will be collected for exploratory analyses of, but not limited to, PD-L1 expression and the tumor mutational burden.

Study Assessments

Objective tumor assessments will be performed by blinded independent central review and investigator assessment using RECIST v1.1. The assessments will be conducted at screening and every 8 weeks for the first 72 weeks after randomization, followed by every 12 weeks up to week 96 and then every 24 weeks thereafter until RECIST v1.1-defined PD, with 1 additional follow-up scan, if clinically feasible. AEs will be graded using the Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

The full analysis set (all randomized patients) will be used for all efficacy analyses, including patient-reported outcomes. The safety and tolerability data will be presented by treatment groups using the safety analysis set (all patients who have received > 1 dose of study treatment). Stratified log-rank tests will be used for the primary, secondary, and sensitivity analyses of PFS, the primary and secondary analyses of OS, and the analyses of TTDM, time from randomization to second progression, and time to HRQoL, symptom and function deterioration. Kaplan-Meier estimates will be used to assess the landmark PFS and OS rates and the sensitivity analyses of OS. A logistic regression model will be used for all ORR analyses and symptom improvement rates. The baseline demographic data, AEs, and HRQoL and function improvement rates will be summarized using descriptive statistics.

Ethical Considerations

The study is being conducted in accordance with the protocol and the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines. The independent ethics committee/institutional review board at all participating sites has approved the study protocol. All patients will provide written informed consent before study enrollment. It will be possible to obtain data underlying the findings described in the final report for this study in accordance with AstraZeneca's data sharing policy (available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure).

Conclusions

New treatment options are required for patients with LS-SCLC. The phase III ADRIATIC study is designed to assess the efficacy and safety of durvalumab, with or without tremelimumab, as consolidation therapy for patients with LS-SCLC without evidence of PD after platinum-based cCRT. The rationale for this study is supported by evidence from PACIFIC, which demonstrated enhanced efficacy outcomes with durvalumab after cCRT in patients with unresectable, stage III NSCLC.[8,9] The results from PACIFIC have also suggested that cCRT might have a priming effect on tumors for a response to anti-PD-1/PD-L1 therapy.[8,9,14,15] Additionally, recent data demonstrating improved clinical outcomes with immune checkpoint blockade targeting the PD-1/PD-L1 pathway for patients with ES-SCLC, including as first-line treatment,[4,5] have suggested that these therapies might have a role in earlier stages of disease. Finally, future opportunities to optimize the use of immune checkpoint blockade for patients with LS-SCLC, including exploratory analyses to investigate correlations between

Table 1 Key Inclusion and Exclusion Criteria

Key Criteria
Inclusion
Written informed consent
Age $\geq$ 18 years at screening
Documented histologic or cytologic evidence of LS-SCLC (stage I-III; stage I or II must be medically inoperable)
WHO/ECOG performance status of 0 or 1 at enrollment and randomization
Received first-line cCRT (as defined)
Received 4 cycles of chemotherapy containing platinum and IV etoposide concurrent with RT administered as per local standard of care regimens, which must be completed within 1-42 days before randomization and the first dose of investigational product
Received a total dose of RT of 60-66 Gy over 6 wk for standard QD RT schedules or 45 Gy over 3 wk for hyperfractionated BID RT schedules
RT must have begun no later than the end of cycle 2 of chemotherapy
Three cycles of platinum-based chemotherapy concurrent with RT is permitted if disease control was achieved and no additional benefit can be expected from an additional cycle of chemotherapy as determined by the investigator
Patients must have achieved CR, PR, or SD, without PD after definitive, platinum-based cCRT
PCI can be delivered per investigator discretion and local standard of care and must be conducted after cCRT has completed and within 1-42 days before randomization and first dose of investigational product
Availability of tumor tissue
Adequate organ and bone marrow function and estimated life expectancy of $\geq$ 12 wk
Exclusion
Mixed SCLC and NSCLC histologic features
Extensive-stage SCLC
Received regimens other than etoposide and platinum as consolidation chemotherapy after RT completion
Received sequential chemoradiotherapy for LS-SCLC
PD during cCRT
Patients with any history of grade $\geq$ 2 pneumonitis (except for resolved infective pneumonitis)
Active or previous documented autoimmune or inflammatory disorders or uncontrolled intercurrent illness
History of another primary malignancy, leptomeningeal carcinomatosis or primary immunodeficiency, or active infection
Any unresolved toxicity (CTCAE grade $\geq$ 2) from previous chemoradiotherapy
Active infection, including tuberculosis, HIV, hepatitis B and C

Abbreviations: BID = twice daily; cCRT = concurrent chemoradiotherapy; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; IV = intravenous; LS = limited-stage; NSCLC = non–small-cell lung cancer; PCI = prophylactic cranial irradiation; PD = disease progression; PR = partial response; QD = once daily; RT = radiotherapy; SCLC = small-cell lung cancer; SD = stable disease; WHO = World Health Organization; wk = weeks.

biomarker expression and the response to treatment, will be based on advances in our understanding of the disease. Recruitment for the phase III ADRIATIC study began in September 2018 and is ongoing.

Acknowledgments

Medical writing support, which was in accordance with Good Publication Practice guidelines, was provided by Craig Turner, MSc, of Cirrus Communications, an Ashfield company (Macclesfield, UK), and was funded by AstraZeneca.

Disclosure

S.S. has received research grants and personal fees (advisory boards and speaker fees) from AstraZeneca and personal fees (advisory boards) from Merck and Celgene, all outside the submitted work. I.O. has received research grants from Boehringer-Ingelheim during the conduct of the study; research grants and personal fees from AstraZeneca, Taiho Pharmaceutical, Chugai Pharma, Boehringer-Ingelheim, Ono Pharmaceutical, MSD Oncology, Lilly, and Bristol-Myers Squibb; research grants from Astellas Pharma, Novartis, and AbbVie; and personal fees from Pfizer, all outside the submitted work. Y.C. has received research grants from AstraZeneca, ISPEN, Roche, and Bristol-Myers Squibb; personal fees (consultancy, speakers' bureau) from AstraZeneca, Genentech, Bristol-Myers Squibb, Novartis, and Takeda; personal fees (speakers' bureau) from Merck, Eli Lilly, and Guardant Health; and personal fees (consultancy) from Pfizer and Array Biopharma, all outside the submitted work. S.N. has received research grants from Merck Serono; research grants and personal fees (honoraria) from AstraZeneca, Pfizer, MSD, and Eli Lilly; and personal fees (honoraria) from Chugai, Taiho, Bristol-Myers Squibb, Novartis, Boehringer-Ingelheim, Shionogi, and Yakult, all outside the submitted work. B.C.C. has received research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, and MSD; has provided consultancy for Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and MSD; has stock ownership in TheraCanVac Inc, Gencurix Inc, and Bridgebio Therapeutics; and has received royalties from Champions Oncology. G.M. and N.S. are full-time employees of AstraZeneca. W.Y. and H.J. are full-time employees of AstraZeneca and have stock ownership in AstraZeneca. The remaining author declares that they have no competing interests.

References

1. Oronsky B, Reid TR, Oronsky A, Carter CA. What's new in SCLC? A review. *Neoplasia* 2017; 19:842-7.
2. Früh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 24(suppl 6):vi99-105.
3. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol* 2017; 18:1116-25.
4. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018; 379:2220-9.
5. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019; 394:1929-39.
6. Ardizzoni A, Hansen H, Dombernowsky P, et al. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. *J Clin Oncol* 1997; 15:2090-6.
7. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res* 2015; 3:1052-62.
8. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; 377:1919-29.
9. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018; 379:2342-50.
10. Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anti-cytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. *Expert Opin Biol Ther* 2008; 8:1583-93.
11. Goldman JW, Dowlati A, Antonia SJ, et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer. *J Clin Oncol* 2018; 36(suppl), abstract 8518.
12. Cho D, Mahipal A, Dowlati A, et al. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer. *J Clin Oncol* 2018; 36(suppl), abstract 8517.
13. Bondarenko I, Juan-Vidal O, Pajkos G, et al. Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant extensive disease-small cell lung cancer from cohort A of the phase 2 BALTIC study. *Ann Oncol* 2018; 29(suppl 8):viii596-602.
14. McCall NS, Dicker AP, Lu B. Beyond concurrent chemoradiation: the emerging role of PD-1/PD-L1 inhibitors in stage III lung cancer. *Clin Cancer Res* 2018; 24: 1271-6.
15. Ko EC, Formenti SC. Radiotherapy and checkpoint inhibitors: a winning new combination? *Ther Adv Med Oncol* 2018; 10, 1758835918768240.