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STUDY PROTOCOL

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Phase II study of durvalumab (MEDI 4736) plus carboplatin and etoposide in elderly patients with extensive stage small cell lung cancer: Study protocol of turtle study (LOGIK 2003)

Hidenobu Ishii[1] | Koichi Azuma[1] | Takayuki Shimose[2] | Hiroshige Yoshioka[3] | Takayasu Kurata[3] | Naoki Shingu[4] | Masaki Okamoto[5] | Yosuke Kawashima[6] | Isamu Okamoto[7]

[1]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan

[2]Clinical Research Support Center Kyushu, Fukuoka, Japan

[3]Department of Thoracic Oncology, Kansai Medical University Hospital, Hirakata, Japan

[4]Division of Respiratory Medicine, Saiseikai Kumamoto Hospital, Kumamoto, Japan

[5]Department of Respirology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

[6]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan

[7]Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Correspondence
Koichi Azuma, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka, 830-0011, Japan.
Email: azuma@med.kurume-u.ac.jp

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Abstract

Background: Recently, the addition of antiprogrammed cell death-ligand 1 (PD-L1) monoclonal antibodies, including durvalumab and atezolizumab to platinum-based chemotherapy, has demonstrated clinical benefits in patients with untreated advanced small cell lung cancer (SCLC). However, these clinical trials comprised small populations of elderly patients with SCLC. Therefore, the safety of anti-PD-L1 immunotherapy plus platinum and etoposide in elderly patients remains unclear.

Methods: This prospective, multicenter, single-arm study was designed to evaluate the safety and efficacy of durvalumab plus carboplatin and etoposide in untreated elderly patients (aged > 75) with extensive stage (ES) SCLC. A total of 40 patients were recruited. Patients received up to four cycles of durvalumab 1500 mg and carboplatin at a dose equivalent to an area under the curve of 5 on day 1, and etoposide 80 mg/m^2 on days 1 to 3 every 3 weeks as induction treatment, followed by durvalumab maintenance treatment every 4 weeks. The primary endpoint was safety as measured by adverse events according to the Common Terminology Criteria for Adverse Events version 5.0, laboratory analyses, vital signs, and physical examination. Key secondary endpoints were objective response rate, median progression-free survival, 12-month overall survival rate, and the completion rate for four cycles of induction chemotherapy.

Discussion: The present study was designed to evaluate the safety of durvalumab plus carboplatin and etoposide in elderly patients with ES-SCLC.

KEYWORDS
SCLC, elderly patients, durvalumab, immunotherapy

INTRODUCTION

Lung cancer is the leading cause of death due to cancer worldwide.[1] In Japan, more than 60% of patients diagnosed with advanced lung cancer are over 75 years of age.[2] Small cell lung cancer (SCLC) is a histological subtype that accounts for ~15% of all lung cancer cases.[3] SCLC is a neuroendocrine carcinoma that exhibits rapid growth and early spread to distant sites, with 60%–70% of cases found to have extensive-stage (ES) disease at the time of diagnosis.[4]

In Japan, treatment with carboplatin at a dose equivalent to an area under the curve (AUC) of 5 plus etoposide 80 mg/m^2 has been commonly used in elderly patients with ES-SCLC,

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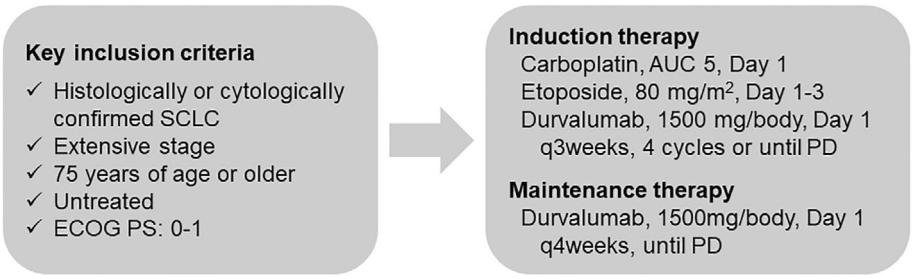

FIGURE 1 Schema of the study. SCLC, small cell lung cancer; PS, performance status; AUC, area under the curve; PD, progressive disease

following the results of a randomized phase III trial (JCOG 9702).[5] The JCOG 9702 trial compared carboplatin plus etoposide and split doses of cisplatin plus etoposide in ES-SCLC patients with advanced age or poor performance status and reported no significant differences in overall survival or toxicity. In the JCOG 9702 trial, carboplatin plus etoposide consisted of carboplatin at dose equivalent to an AUC of 5 on day 1 and etoposide 80 mg/m^2 on days 1 to 3.

Recently, the addition of antiprogrammed cell death-ligand 1 (PD-L1) monoclonal antibodies to platinum-based chemotherapy has demonstrated clinical benefits in patients with untreated ES-SCLC.[6,7] The IMpower 133 trial was a phase III trial that demonstrated significantly increased overall and progression-free survival with the addition of atezolizumab to carboplatin plus etoposide in ES-SCLC patients. The IMpower 133 trial comprised only 10% of patients aged over 75 years. The regimen doses used in the IMpower 133 trial were carboplatin at a dose equivalent to an AUC of 5 and etoposide 100 mg/m^2, which are higher doses than commonly used in clinical practice. The CASPIAN trial was a randomized phase 3 trial conducted to determine the efficacy and safety of durvalumab plus platinum-etoposide followed by maintenance therapy with durvalumab compared to platinum-etoposide alone, with a significant increase in overall survival observed in the durvalumab plus platinum-etoposide group. In the CASPIAN trial, the platinum agent used was either carboplatin or cisplatin according to the clinical judgment of the investigator, and a range of doses were used for each drug including carboplatin, cisplatin, and etoposide.

Although the IMpower 133 and CASPIAN trials reported improved survival with the addition of anti-PD-L1 monoclonal antibodies to chemotherapy in ES-SCLC patients regardless of patient age, these clinical trials included a small proportion of elderly patients and used high or variable treatment doses. Therefore, we designed a phase II clinical trial of durvalumab plus carboplatin and etoposide using doses appropriate for the treatment of elderly patients with ES-SCLC (Figure 1).

METHODS

Study design

This was a multicenter, single-arm phase II study designed to evaluate the safety and efficacy of first-line durvalumab plus carboplatin and etoposide treatment in elderly patients with ES-SCLC. The trial was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the central review board of Clinical Research Network Fukuoka (CRB7180004). The trial has been registered with the Japan Registry of Clinical Trials (jRCTs071210050).

Eligibility criteria

Inclusion criteria

1. Histologically or cytologically confirmed SCLC
2. Aged ≥75-years-old
3. ES-SCLC
4. No prior systemic chemotherapy for ES-SCLC
5. Patients who had received prior treatment for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months from the time of ES-SCLC diagnosis
6. No serious tumor-related complications
7. Brain metastases must be asymptomatic
8. ECOG performance status of 0 to 1
9. Measurable lesions
10. No prior thoracic radiotherapy or chemotherapy for any other cancers within a year of enrollment
11. Adequate organ function
12. Written, informed consent

Exclusion criteria

1. Synchronous or metachronous (within a year) malignancies
2. Active infection requiring systemic therapy
3. Body temperature ≥ 38°C
4. Psychiatric disease
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures
6. History of autoimmune disease: Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy or controlled type I diabetes mellitus on an insulin regimen were eligible
7. Patients requiring systemic steroid therapy (≥10 mg/day of prednisolone)

8. Unstable angina within 3 weeks or history of myocardial infarction within 6 months
9. Interstitial pneumonia or pulmonary fibrosis. Patients with a medical history of radiation pneumonitis which was stable without treatment were eligible

Treatment

Patients received chemotherapy with up to four cycles of durvalumab 1500 mg on day 1, carboplatin at a dose equivalent to an AUC of 5 on day 1, and etoposide 80 mg/m^2 on days 1 to 3 every 3 weeks as induction treatment. Subsequent maintenance treatment with durvalumab 1500 mg was administered every 4 weeks until disease progression or the development of unacceptable toxicity.

Endpoints

The primary endpoint was safety, as measured by adverse events according to the Common Terminology Criteria for Adverse Events version 5.0, laboratory analyses, vital signs, and physical examination. The secondary endpoints were objective response rate, median progression-free survival, 12-month overall survival rate, completion rate for four cycles of induction chemotherapy with durvalumab plus carboplatin and etoposide, functional assessment of cancer therapy–lung (FACT-L) scale score, and instrumental activities of daily living (IADL) scale.

Statistical analysis

The primary objective of this study was to evaluate the safety of the protocol treatment in elderly patients with ES-SCLC. The present study was not designed to be confirmatory with a predetermined statistical threshold. Therefore, a sample size of 40 patients was set as the target number of patients to be enrolled over a period of 18 months. The statistical power required to detect adverse events was evaluated for 35 patients, assuming five ineligible patients. Adverse events with an incidence rate of 5% or more were expected to be observed in one or more patients with a probability of 83.4%.

DISCUSSION

The number of elderly patients with cancer, including SCLC, continues to increase. As elderly patients typically have comorbid diseases affecting multiple organs, elderly patients are at increased risk of toxicity related to systemic. The incidence of grade 3 or 4 neutropenia was 24% in all patients who participated in the CASPIAN trial and 95% in the JCOG 9702 trial of carboplatin plus etoposide in elderly ES-SCLC patients.[5,7] The Guidelines for Diagnosis and Treatment of the Lung Cancer, the Clinical Practice Guidelines in Oncology, the National Comprehensive Cancer Network Guidelines ver. 3,[8] and the European Society for Medical Oncology clinical practice guidelines[9] recommend the use of atezolizumab or durvalumab in combination with a platinum-based agent plus etoposide regardless of patient age. However, the safety of these combination therapies in elderly patients remains uncertain as the IMpower 133 and CASPIAN trials comprised small proportions of elderly patients with SCLC. The present study was designed to evaluate the safety of durvalumab plus carboplatin and etoposide in elderly patients with ES-SCLC.

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ORCID

Koichi Azuma https://orcid.org/0000-0001-5040-5856

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