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STUDY PROTOCOL

Forthcoming Phase II Study of Durvalumab (MEDI4736) Plus Chemotherapy for Small Cell Lung Cancer with Brain Metastases

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Background: The standard of care for extensive-stage small cell lung cancer (ES-SCLC) is an immune checkpoint inhibitor (ICI) combined with platinum-etoposide (PE) chemotherapy. At initial diagnosis, about 25% of ES-SCLC patients have brain metastases, which are associated with a poor prognosis. The decision as to whether to treat brain metastases with local therapies such as surgery or radiotherapy before initiation of systemic chemoimmunotherapy is based on symptoms due to the brain lesions and the general condition of the patient. Subset analysis of the CASPIAN study showed that combination therapy with PE plus durvalumab (MEDI4736) is promising for ES-SCLC with brain metastases. However, data required in daily clinical practice, such as intracranial response rate and duration of intracranial response, are insufficient for such patients.

Patients and Methods: We have designed a single-arm phase II trial of durvalumab plus PE for patients aged ≥20 years with chemotherapy-naïve ES-SCLC and at least one brain metastasis ≥5 mm in size that has not been previously treated. Patients receive durvalumab intravenously combined with four cycles of PE. Enrollment of 50 patients over 2 years at 25 oncology facilities in Japan is planned. The primary endpoint is intracranial response rate.

Conclusion: This is the first prospective study to evaluate the effects of an ICI with PE specifically in ES-SCLC patients with brain metastases. If it demonstrates intracranial efficacy, this regimen will be a potential treatment option for such individuals, and radiation therapy or surgery for brain metastases can be avoided or postponed.

Keywords: immune checkpoint inhibitor, PD-L1, intracranial metastasis, intracranial response rate, platinum-etoposide

Introduction

Lung cancer is the leading cause of cancer-related mortality in many countries.[1] Primary lung cancer is classified as small cell lung cancer (SCLC) or non–small cell lung cancer (NSCLC), which differ in outcome and sensitivity to chemotherapy and radiotherapy, with SCLC accounting for ~15% of all primary lung cancer cases. The standard frontline treatment for extensive-stage (ES) SCLC had been platinum-etoposide (PE) chemotherapy for three decades until immunotherapy showed robust clinical activity in recent Phase III trials, with an immune checkpoint inhibitor (ICI) combined with PE now being the standard therapy for ES-SCLC.[2–4] However, the prognosis of ES-SCLC remains poor and further progress in treatment development is needed.

About 25% of cases of ES-SCLC are complicated by brain metastasis at the time of initial diagnosis.[5–7] Such metastasis is associated with a poor prognosis and a reduced quality of life, and its control has therefore been a long-standing clinical goal. Radiotherapy is an important treatment option for brain metastases but can give rise to complications such as cognitive decline and symptomatic radiation necrosis.[8,9] Brain metastases of SCLC also respond to chemotherapy, but the effect is transient in

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many cases, with a persistent intracranial response not to be expected.[10,11] In the case of ICIs, favorable responses of brain metastatic lesions of other cancer types (malignant melanoma and NSCLC), including a persistent intracranial response, have been demonstrated.[12–14] Subgroup analysis of patients with brain metastases in the CASPIAN study of combination therapy with durvalumab (a monoclonal antibody to programmed cell death–ligand 1 [PD-L1]) and PE versus PE alone for individuals with ES-SCLC yielded point estimations of the hazard ratios for overall survival (OS) and progression-free survival (PFS) of 0.69 and 0.73, respectively, showing that such combination therapy was also promising for this subgroup.[3] However, no prospective data have been available with regard to the intracranial efficacy of such combination therapy for SCLC patients with untreated brain metastases. Patients with brain metastases accounted for only 10% of subjects in the CASPIAN study, highlighting the fact that data required for actual clinical practice, such as the size-reducing effect of the combination therapy for brain metastatic lesions (intracranial tumor response) and response duration, are insufficient. An intracranial response to systemic treatment can improve quality of life and avoid the need for radiotherapy or brain surgery in individuals with brain metastases. It is therefore important to assess the intracranial efficacy of such treatment in SCLC patients with untreated brain metastases.

With this background indicating that combination therapy with durvalumab and PE might exert a persistent antitumor effect on brain metastatic lesions of SCLC, we have designed a single-arm study to evaluate the efficacy of such combination therapy for untreated brain metastases in SCLC patients.

Patients and Methods

Study Design and Objective

This study (SPEED, LOGiK2001) was designed as a multicenter, single-arm phase II trial to evaluate the efficacy and safety of durvalumab (MEDI4736) plus PE chemotherapy with the primary endpoint of intracranial response rate in treatment-naïve ES-SCLC patients with brain metastases (Figure 1).

Endpoints

The primary endpoint of the trial is the proportion of patients achieving an intracranial response (partial response or complete response) as defined by the modified Response Evaluation Criteria in Solid Tumors (modified RECIST).[12,13] Secondary endpoints are intracranial PFS, extracranial response rate (RR), extracranial PFS, systemic RR, systemic PFS, OS, and safety.

Treatment Plan

Patients receive durvalumab (1500 mg/body intravenously every 3 weeks) combined with PE chemotherapy (intravenously every 3 weeks for four cycles). PE chemotherapy regimens consist of cisplatin (80 mg/m^2) or carboplatin (area under the concentration-time curve [AUC] of 5 mg mL^{-1} min) plus etoposide (80 to 100 mg/m^2). After the four cycles of induction

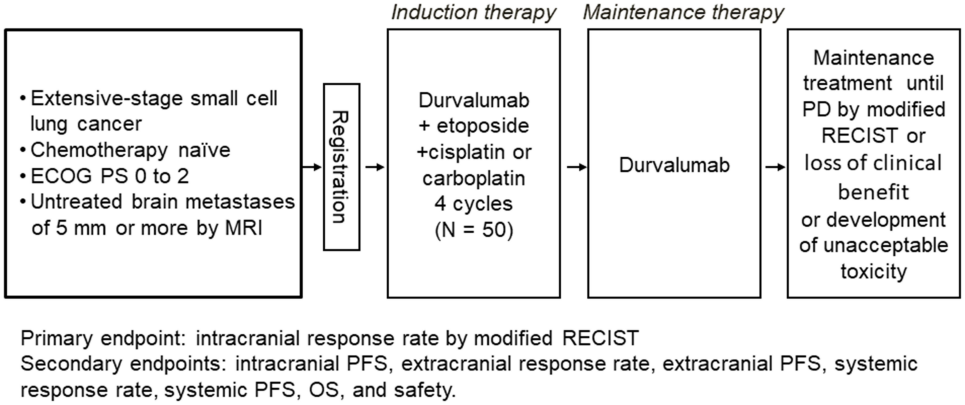

Figure 1 Design of the SPEED study.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; OS, overall survival.

therapy, maintenance treatment with durvalumab (1500 mg/body intravenously every 4 weeks) continues until disease progression, loss of clinical benefit, or development of unacceptable toxicity.

Key Eligibility Criteria

Chemotherapy-naïve individuals 20 years of age or older with histologically or cytologically confirmed SCLC and at least one brain metastasis ≥5 mm in size that has not been treated previously are eligible for the study. Patients can be enrolled if they are asymptomatic with regard to brain metastasis or have mild symptoms that have been controlled for at least 1 week with therapy for brain edema including steroid equivalent to prednisolone at ≤40 mg/day, but those with brain metastases that require urgent radiation or emergency surgery are excluded. Eligibility stipulates an Eastern Cooperative Oncology Group performance status of 0 to 2 as well as adequate lung, bone marrow, liver, and kidney function.

Patients who meet any of the following criteria are not eligible to participate in the study: diagnosis of autoimmune disease; major surgery within 7 days before registration; a history of other cancer within the previous 2 years; pregnancy; serious psychosis or psychotic symptoms; serious uncontrolled medical conditions including diabetes; concurrent unstable angina or a history of myocardial infarction within the previous 12 months; and positive status for active hepatitis B or hepatitis C. Individuals requiring systemic corticosteroids (>10 mg daily prednisone or equivalent) for treatment of conditions other than brain edema and those taking immunosuppressive medication are also not eligible.

Evaluation of Response and Safety

The primary endpoint of the trial is the proportion of patients achieving an intracranial response (partial response or complete response) as defined by modified RECIST, consisting of RECIST (version 1.1) modified to allow up to five target brain metastases with a maximum diameter of ≥5 mm (and more than twice the slice thickness of a magnetic resonance imaging [MRI] scan). Key secondary endpoints are the proportion of patients achieving an overall response, defined as those who show a partial response or complete response for extracranial or systemic disease as determined by modified RECIST; PFS, defined as the time from the start of treatment to disease progression (based on modified RECIST for brain and systemic disease) or death, whichever occurs first; OS, defined as the time from the start of treatment to death; and safety and toxicity as measured by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). An MRI scan of the brain, computed tomography (CT) scans of the chest and abdomen, and either a bone scan or a positron emission tomography scan are required before initiation of study treatment. Patients undergo tumor assessment with an MRI scan of the brain and CT scans of the body at baseline, every 6 weeks during the first 24 weeks, every 8 weeks during the next 24 weeks, and every 12 weeks thereafter.

Statistical Design

The expected intracranial RR was set at 68% on the basis of the assumption that the study treatment would result in a response in the brain similar to the systemic response observed in the CASPIAN trial. Given the increased risk of cognitive impairment associated with the application of radiotherapy to the brain, the study regimen might be considered effective if half of the treated patients can avoid or delay cranial irradiation or brain surgery. On the other hand, if a size reduction for brain metastases cannot be achieved in at least half of the treated patients, preceding radiotherapy may be desirable. The threshold for the intracranial RR was therefore set at 50% in this study. Given this assumption, the study was designed to have a power of 80% and a one-sided level of alpha error of 0.05, resulting in a requirement for 46 patients. Allowing for ineligibility of patients for analysis, we plan on enrolling 50 patients at 25 oncology facilities in Japan.

Ethical Considerations

This study is being conducted in accordance with the precepts established in the Declaration of Helsinki and Clinical Trials Act of Japan. The study protocol was approved by the central certified review board (CRB) of Clinical Research Network Fukuoka (certification number: CRB7180004) in April 2021, before initiation of patient enrollment. The CRB of Clinical Research Network Fukuoka was established independently of the participating institutions and reviews clinical trials from various centers. This trial has been registered in the Japan Registry for Clinical Trials as jRCTs071210036. All participants in this trial have provided written informed consent.

Discussion and Conclusion

As far as we are aware, this trial is the first prospective study to focus on the intracranial response to an ICI combined with PE chemotherapy in patients with untreated brain metastases derived from SCLC. If the study demonstrates intracranial activity for durvalumab combined with PE chemotherapy in this patient population, then this regimen will become a potential treatment option for such individuals and radiation therapy or surgery for the brain metastases can be avoided or postponed. Study enrollment began in June 2021 and is to continue for 2 years, with 23 of the planned 50 patients having been enrolled as of 17 July 2022.

Data Sharing Statement

The data sets generated and analyzed during the current study will be available from the corresponding author Isamu Okamoto on reasonable request.

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Disclosure

Dr. Shiraishi has received research grants from Chugai Pharma as well as honoraria from Chugai Pharma, Eli Lilly, Ono Pharmaceutical, AstraZeneca, and Taiho Pharmaceutical, all outside the submitted work. Dr. Tsuchiya-Kawano has received honoraria from AstraZeneca, Bristol-Myers Squibb, Taiho Pharmaceutical, Chugai Pharma, Ono Pharmaceutical, and Kyowa Kirin, all outside the submitted work. Dr. Ishii has received honoraria from AstraZeneca, Chugai Pharma, Ono Pharmaceutical, Bristol-Myers Squibb, MSD Oncology, and AMCO, all outside the submitted work. Dr. Daga has received honoraria from AstraZeneca, Chugai Pharma, and Eli Lilly, all outside the submitted work. Dr. Ito has received honoraria from TAKEDA, Boehringer-Ingelheim, Eli Lilly, Chugai Pharma, AstraZeneca, Pfizer, Taiho Pharmaceutical, Ono Pharmaceutical, MSD, and Daiichi-Sankyo, all outside the submitted work. Dr. Okamoto has received research grants and personal fees from AstraZeneca, Taiho Pharmaceutical, Chugai Pharma, Boehringer-Ingelheim, Ono Pharmaceutical, MSD Oncology, Eli Lilly, and Bristol-Myers Squibb; research grants from Astellas Pharma, Novartis, and AbbVie; and personal fees from Pfizer, all outside the submitted work. The remaining authors have declared no competing interests in this work.

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