Study Protocol

Treatment rationale and protocol design: an investigator-initiated phase II study of combination treatment of nivolumab and TM5614, a PAI-1 inhibitor for previously treated patients with non-small cell lung cancer

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Background: There is no established standard 3rd line treatment for patients with advanced non-small cell lung cancer (NSCLC). Although cytotoxic chemotherapeutic agents that are not used as 1st or 2nd line treatment are administrated as 3rd line treatment, their anti-tumor efficacy is insufficient. Anti-programmed death ligand-1 (PD-L1)/programmed death-1 (PD1) treatment is more effective and less toxic than chemotherapy in anti-PD-L1/PD-1 treatment-naïve patients with NSCLC. Therefore, anti-PD-L1/PD-1 therapy is considered an appropriate 3rd line treatment. However, the anti-tumor efficacy is limited in patients previously treated with anti-PD-L1/PD-1 antibody. Today, new drugs are needed to increase the efficacy of anti-PD-L1/PD-1 antibodies.

Methods: This open-label, single-arm, investigator-initiated phase II study is designed to evaluate combination treatment of nivolumab and TM5614, a plasminogen activator inhibitor (PAI-1) inhibitor as 3rd or more line treatment in NSCLC patients who underwent standard treatment. The primary endpoint is the objective response rate and the secondary endpoints are progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety. Recruitment began in September 2023 and is expected to continue for approximately three years.

Discussion: Currently, there is no standard 3rd line treatment for advanced NSCLC, and we hope that the findings of this study will facilitate more effective treatments in this setting. Ethics and dissemination: the study protocol conformed to the ethical principles outlined in the Declaration of Helsinki. All patients will provide written informed consent prior to enrollment. Results will be published in a peer-reviewed publication.

Trial Registration: This study is registered to Japan Registry of Clinical Trials with number: jRCT2061230039 (19/July/2023).

Keywords: Non-small cell lung cancer (NSCLC); anti-programmed death-1 antibody; plasminogen activator inhibitor-1 (PAI-1); TM5614; nivolumab

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Introduction

Lung cancer is the most common cause of cancer-related death (1), and is classified into two broad histological types: non-small cell lung carcinoma (NSCLC) and small-cell lung carcinoma. A standard treatment for patients with advanced NSCLC, a performance status of 0–1, and no driver mutations is platinum-based doublet chemotherapy and anti-programmed death ligand-1 (PD-L1)/programmed death-1 (PD1) antibody (2). However, the 2-year progression-free survival (PFS) rate is only 22%, and few patients show a complete response (CR) (3). Although platinum doublet chemotherapy with anti-PD-1 antibody and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody is available, no remarkable improvement in treatment outcomes has been observed (4,5). The standard 2nd line treatment is docetaxel and ramucirumab, whose PFS is reported to be only 4.5 months, hence their efficacy is insufficient (6). Additionally, a standard 3rd line treatment has not yet been established.

Currently, single-agent chemotherapeutic drugs, including nab-paclitaxel, which are not used until 2nd line treatment, are administrated as 3rd line treatment, but their response rate ranges from 5% to 20%, and the incidence of severe adverse events ranges from 30–50% (7-13). In contrast, a phase III study showed that the response rates of anti-PD-1 antibodies, such as nivolumab, pembrolizumab, and docetaxel, were approximately 20% (for the two former drugs) and 9%, respectively, and the efficacy of anti-PD-1 antibody was superior to that of docetaxel in anti-PD-1 treatment-naive patients. Furthermore, the incidence of severe adverse events is lower with anti-PD-1 treatment than with docetaxel treatment (14,15). Therefore, anti-PD-1 therapy is an appropriate candidate for 3rd line treatment. However, the response rate to nivolumab was only 8.5% in patients previously treated with anti-PD-1/PD-L1 antibody (16). Thus, to improve the anti-tumor efficacy of anti-PD-1/PD-L1 treatment in patients previously treated with anti-PD-1/PD-L1, new drugs, such as anti-CTLA-4 antibody, are being developed. However, anti-CTLA-4 antibodies are associated with increasing lethal immune-related side effects, such as pneumonitis and hypercytokinemia, as well as medical costs. Therefore, new treatment agents with fewer side effects and lower medical costs are required to increase the efficacy of anti-PD-1/PD-L1 antibodies in patients previously treated with anti-PD-1/PD-L1 antibodies.

Plasminogen activator inhibitor-1 (PAI-1) is a glycoprotein with a molecular weight of 47-kDa produced by vascular endothelial cells, macrophages, and platelets and is an inhibitor of the fibrinolytic system (17). In contrast, PAI-1 is reported to be involved in the proliferation and apoptosis of cancer cells and tumor angiogenesis, resulting in tumor progression in lung, breast, cervical cancers and malignant mesothelioma (18-20). In addition, we showed that PAI-I is involved in chemotherapeutic resistance through the activation of cancer-associated fibroblasts and epithelial-mesenchymal transition in lung cancer cells (21). We have also found that PAI-1 is associated with resistance of lung cancer cells to PD-1 antibody treatment.

TM5614, a PAI-1 inhibitor, was selected from more than 1,400 novel derivatives explored by in silico drug discovery based on the crystal structure of human PAI-1. TM5614 is a small-molecule drug developed in academia (Tohoku University) through discovery, optimization, good non-clinical laboratory practice studies, and good manufacturing practice (GMP) regarding compliant synthesis and formulation (22,23). TM5614 has been found to be well tolerated in Phase I studies in healthy subjects. In addition, the antitumor efficacy of the combination treatment with TM5614 and an anti-PD-1 antibody has been observed to be higher than that of an anti-PD-1 antibody treatment in an *in vivo* study using a mouse lung cancer model. Our studies revealed that TM5614 improved the tumor immune-microenvironment, such as an increase in cytotoxic T cells and a decrease in tumor-

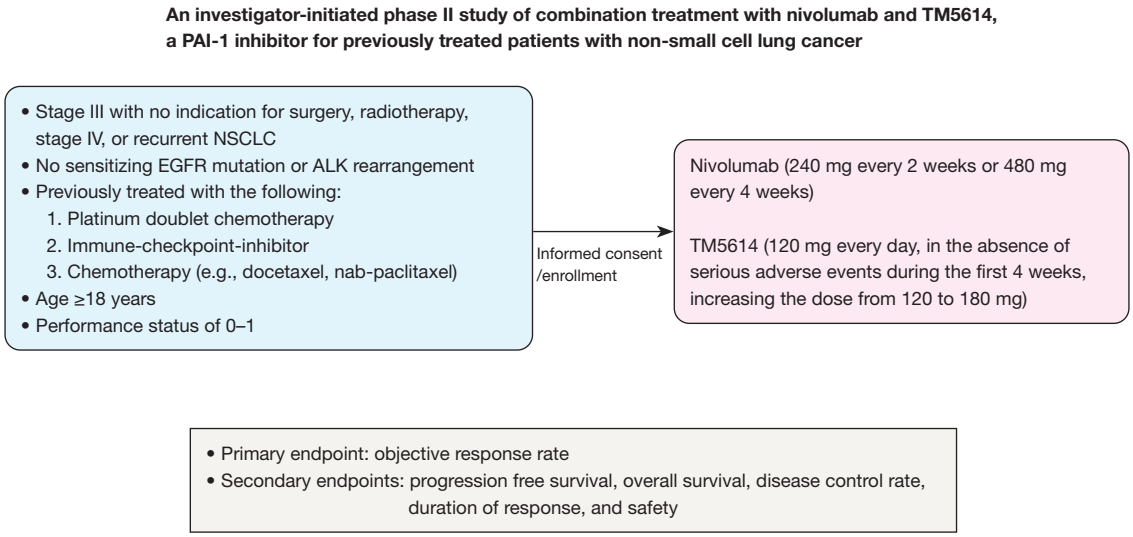

Figure 1 Study flow chart. PAI-1, plasminogen activator inhibitor-1; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

associated macrophages and PD-L1 expression of cancer cells. Furthermore, a phase II study examining the efficacy of TM5614 combined with a tyrosine kinase inhibitor in patients with chronic myelogenous leukemia was completed (24) and a phase III study is ongoing. In addition, a phase II study was conducted to investigate the combination treatment with nivolumab and TM5614 in patients with melanoma (jRCT2021210029). To date, no safety issues have been reported. Based on these observations, TM5614 is being used in addition to nivolumab in the present study. We present this article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1858/rc).

Methods

Study design and objective

This open-label, single-arm, investigator-initiated phase II study will evaluate the efficacy and safety of combination treatment with nivolumab and TM5614, a PAI-1 inhibitor as 3rd or more line therapy for patients with NSCLC who were previously treated with platinum doublet chemotherapy, anti-PD-1/PD-L1 treatment, and one more cytotoxic chemotherapy. *Figure 1* shows a flowchart of the study. Six hospitals have agreed to participate in this study.

Endpoints

The primary endpoint is the objective response rate. The secondary endpoints are PFS, overall survival (OS), disease control rate, duration of response (DOR), and safety. The exploratory endpoint is the optimal cut-off value of pretreatment plasma PAI-1 levels to discriminate radiological tumor response or disease control from disease progression.

Key eligibility criteria

Key inclusion and exclusion criteria are listed in *Tables 1*,*2*.

Estimation of sample size

The response rate to cytotoxic chemotherapy used as 3rd or more line treatment has been previously reported to be approximately 5–20% (7-13). All patients to be enrolled in this study received anti-PD-L1/PD-1 antibody treatment previously. Thus, the response rate in our study is likely to be lower than that of a previous study. Additionally, a previous study showed that the response rate to nivolumab in patients previously treated with an anti-PD-L1/PD-1 antibody was 8.5% (16). In that study, patients who achieved disease control with anti-PD-L1/PD-1 antibody

Table 1 Key inclusion criteria

Inclusion criteria
(I) Age of ≥18 years at the time of informed consent
(II) Provision of written informed consent
(III) Histologically confirmed stage III with no indication for curative surgery, radiotherapy, stage IV, or recurrent NSCLC
(IV) No sensitizing epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements in patients with non-squamous carcinoma
(V) No or unknown *ROS-1* rearrangement, *BRAF* (*V600E*) gene mutation, *MET* exon 14 skipping mutation, *RET* rearrangement, or *NTRK* rearrangement
(VI) Disease progression during or after the most recent treatment and history of treatment
(VII) Patients who received the following treatments
• Platinum doublet chemotherapy
• Immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab, nivolumab, and ipilimumab)
• Chemotherapy (e.g., pemetrexed, docetaxel, nab-paclitaxel, S-1)
(VIII) Measurable lesions based on RECIST Ver.1.1
(IX) Eastern Cooperative Oncology Group performance status of 0–1
(X) Estimated life expectancy of >3 months
(XI) Adequate organ function within 7 days prior to registration

NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2 Key exclusion criteria

Exclusion criteria
(I) Active autoimmune disease that has required systemic treatment using corticosteroids or other immunosuppressive medication
(II) History of serious immune-related adverse events caused by anti-PD-1/anti-PD-L1 antibodies
(III) Patients receiving continuous systemic administration (oral or intravenous) of steroids or other immunosuppressive drugs exceeding 10 mg/day of prednisolone equivalent
(IV) Multiple cancers
(V) Central nervous system metastases (symptomatic or requiring treatment)
(VI) Carcinomatous meningitis
(VII) Evidence of interstitial pneumonia
(VIII) Uncontrollable pleural effusion, ascites, or pericardial fluid
(IX) Underwent radiotherapy within 2 weeks before the first nivolumab and TM5614
(X) Evidence of severe or uncontrolled systemic disease

PD-1, programmed death-1; PD-L1, programmed death ligand 1.

for 6 months and whose last administration of anti-PD-L1/PD-1 antibody was more than 60 days earlier were enrolled. These criteria were excluded from our study. Thus, we set the response rate threshold at 6.0%. The expected response rate was set at 20% based on the efficacy of TM5614 and the previously reported response rate of cytotoxic chemotherapy used as third or further lines (9,11). The sample size was determined using an exact binomial test based on a threshold response rate of 6.0%, an expected response rate of 20.0% in the present study, one-sided

alpha value of 0.05, and a power of 0.8. Based on these parameters, 39 patients will be enrolled in this study. We will include 39 patients in the full analysis set.

Treatment

Patients will receive intravenous nivolumab (240 mg every 2 weeks or 480 mg every 4 weeks) and oral administration of TM5614 (120 mg every day, in the absence of serious adverse events during the first 4 weeks, increasing the dose from 120 to 180 mg), until they experience radiologic disease progression, treatment-related adverse events of unacceptable severity, withdrawal of consent, or termination of treatment at the discretion of the investigator.

Patient registration

After confirming eligibility and obtaining a signed informed consent form, each patient will be registered and will receive treatment. Patient recruitment began in September 2023. It is expected to continue until December 2024. The observational period will be one year from the time of the final registration.

Follow-up and assessment

Patients must undergo various pretreatment evaluations, including a computed tomography (CT) or magnetic resonance imaging scan of the brain, CT scans of the chest and abdomen, a bone scan or positron emission tomography scan, and electrocardiography. Patients will be followed up for at least one year from the time of enrollment. Patients will undergo tumor assessments at baseline, every 4 weeks for 3 cycles, every 8 weeks after 4 cycles. Tumor response and/or radiologic disease progression will be evaluated based on RECIST Ver.1.1. (25). Adverse events are recorded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0. (26).

Statistical analysis

The primary endpoint is the objective response rate. The objective response rate [CR + partial response (PR) proportion] will be calculated, and the one-side 95% confidence interval calculated using the Clopper-Pearson method. The secondary endpoints are PFS, OS, disease control rate, DOR, and safety. PFS is defined as the time from treatment initiation to the occurrence of death, progression of disease (PD). Overall survival (OS) is defined as the time from the initiation of treatment to death. DOR is defined as the time from the date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD or to death due to any cause. The Kaplan-Meier method will be used to analyze PFS, DOR and OS. Ninety-five percent confidence intervals of survival function or median survival times will be calculated using Greenwood's formula or Brookmeyer and Crowley's method, respectively. The disease control rate (CR + PR + SD proportion) and 95% confidence interval will also be calculated. Adverse events observed during the protocol treatment are being summarized by type and grade. The optimal cut-off value of pretreatment serum PAI-1 level was determined through receiver operating characteristic curve analysis.

Ethics and informed consent

The trial received ethical approval from the institutional review board of Hiroshima University Hospital, Hiroshima, Japan (date of approval; 3/July/2023, the approval No. 50047) and was approved by the ethics committee of each participating institution. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients will provide written informed consent prior to enrollment.

Trial registration

This study is registered to Japan Registry of Clinical Trials with number: jRCT2061230039 (19/July/2023).

Discussion

There has not been an established standard 3rd line treatment for advanced NSCLC, and cytotoxic chemotherapeutic agents are administered. However, their response rates range from 5% to 20% and the incidence of severe adverse events ranges from 30–50% (7-13). Therefore, more effective and safer treatments are required. Currently, platinum doublet chemotherapy, anti-PD-L1/PD-1 antibody, and cytotoxic chemotherapy including docetaxel are the standard 1st and 2nd line treatment (2). Thus, cancer cells from patients whose disease progressed during these treatments acquired resistance to chemotherapy and anti-PD-1/PD-L1 antibody treatment. PAI-1 is involved in resistance of lung cancer cells to

chemotherapy (21). In addition, PAI-1 is associated with resistance to anti-PD-1 antibody treatment in lung cancer cells, and the antitumor efficacy of combination treatment with TM5614, a PAI-1 inhibitor, and an anti-PD-1 antibody was higher than that of anti-PD-1 antibody treatment in an *in vivo* study using mouse model. Based on these observations, TM5614, a PAI-1 inhibitor, is considered a reasonable third-line treatment drug in combination with nivolumab for 3rd line treatment after chemotherapy and anti-PD-1/PD-L1 antibody treatment.

There is a limitation in this study. This study is single arm study. Thus, we need to validate the results of this phase II study in a future trial with a larger sample to compare the treatment with the standard treatment.

To the best of our knowledge, the present study is the first clinical trial to investigate the efficacy and safety of nivolumab and TM5614, a PAI-1 inhibitor as 3rd or more line therapy for patients with advanced or recurrent NSCLC after standard treatment. We hope that these findings will facilitate a more effective and safe treatment in this setting.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial received ethical approval from the institutional review board of Hiroshima University Hospital, Hiroshima, Japan (date of approval; 3/July/2023, the approval No. 50047) and was approved by the ethics committee of each participating institution. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients will provide written informed consent prior to enrollment.

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