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RESEARCH ARTICLE

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Efficacy and safety of TM5614 in combination with paclitaxel in the treatment of paclitaxel-resistant cutaneous angiosarcoma: Phase II study protocol

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Abstract

Cutaneous angiosarcoma (CAS) is an endothelial cell-derived, highly aggressive type of vascular tumour. Although chemoradiotherapy with paclitaxel (PTX) is recognized as a first-line therapy for CAS, second-line therapy for CAS remains controversial, and there is no standard therapy for taxane-resistant CAS. Plasminogen activator inhibitor-1 (PAI-1) is associated with poor clinical outcomes, and elevated levels of PAI-1 in both tissue and serum are correlated with poor response to therapy in various cancers, including skin cancers. Since PAI-1 protects endothelial cells from Fas ligand-mediated apoptosis, PAI-1 inhibition might induce apoptosis of endothelial cell-derived tumours such as CAS. This is a single-arm, open-label, multi-institutional, Phase 2 clinical trial to assess the efficacy and safety of PTX in combination with TM5614 (PAI-1 inhibitor) in patients with PTX-resistant CAS. PTX will be administered for 28 weeks, with oral administration of TM5614. The primary endpoint of this study will be the overall response rate (ORR) at 28 weeks after starting treatment (central image evaluation). The secondary endpoint will include the ORR at 28 weeks after starting treatment (investigator evaluation), ORR at 8 weeks and 16 weeks after initiation of treatment (central

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and investigator evaluation), progression-free survival, overall survival, disease control rate and safety profiles. Assuming the null hypothesis of a response rate of 13.6% and an alternative hypothesis of 45%, a minimum of 15 patients are required to achieve a two-sided, Type I error of 5% and power of 70% based on the exact binomial distribution. Data quality control will be conducted by a combination of centralized (remote) and on-site monitoring. This study will contribute to the development of novel combination therapy for PTX-resistant CAS patients, which remains an unmet clinical need.

KEYWORDS
clinical trials, PAI-1, PAI-1 inhibitors, PTX, taxane-resistant CAS

1 | INTRODUCTION

Cutaneous angiosarcoma (CAS) is an endothelial cell-derived, highly aggressive type of vascular tumour histologically characterized by detachment of tumour cells into the vascular lumen.[1] Previous clinical studies have suggested the importance of paclitaxel (PTX) in maintenance therapy for CAS.[2,3] Although chemoradiotherapy with a taxane is recognized as a first-line therapy for CAS,[3,4] second-line therapy for CAS remains controversial and there is no standard therapy for taxane-resistant CAS.[5]

PAI-1 is associated with poor clinical outcomes in various cancers.[6,7] For example, as we previously reported, elevated levels of PAI-1 in both tissue and serum from melanoma patients decrease the number of tumour-infiltrating lymphocytes, leading to poor response to anti-PD-1 Abs monotherapy.[7] Moreover, the clinical study of TM5614 (a PAI-1 inhibitors)-based combination therapy for other cancers, such as anti-PD-1 antibody resistant unresectable melanoma (jRCT2021210029) and chronic myeloid leukaemia (jRCT2031190071), is ongoing.[8,9] Furthermore, PAI-1 protects endothelial cells (ECs) from Fas ligand-mediated apoptosis, which is induced by EC activation, EC detachment, hypoxia or exposure to vascular endothelial growth factor (VEGF).[10] Since CAS is an endothelial cell-derived vascular tumour,[1] PAI-1 derived from tumour cells in CAS might induce the proliferation of tumour cells, as well as pro-angiogenic effects in the tumour microenvironment of CAS, leading to the progression of CAS. From the above findings, we have designed a clinical trial to evaluate the efficacy and safety of PTX plus a PAI-1 inhibitor, TM5614, in Japanese patients with PTX-resistant CAS.

2 | METHODS/DESIGN

2.1 | Objectives, trial design and study setting

This study is a single-arm, open-label, multi-institutional, Phase 2 clinical trial to assess the efficacy and safety of PTX in combination with TM5614 (a pPAI-1 inhibitor) in patients with PTX-resistant CAS. The recruitment of study participants will start on 1 September 2023 and will continue until a total of 15 participants are registered. The study will be conducted at six centres: Tohoku University Hospital, Jichi Medical University, Dermatology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Nagoya City University, Kyushu University and National Cancer Center Hospital. All study participants are required to provide written, informed consent. PTX dosage and administration at enrolment or the last dose will be maintained, and TM5614 will be orally administered daily for 28 weeks. TM5614 will start at a dosage of 120 mg, whether the dose of TM5614 can be increased will be confirmed after 4 weeks of administration, and if confirmed, the dose will be increased to 180 mg.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

1. Age: 18 years or older.
2. Patients (or surrogates) who have provided written, informed consent to participate in this clinical trial.
3. Histologically confirmed, incurable, unresectable CAS.
4. Patients with incurable CAS who have a history of chemotherapy treatment with PTX for CAS and continue to receive PTX. Patients with progressive disease (PD) whose condition worsens on PTX maintenance therapy, defined as having any of the following findings:
- ≥ 10% increase in tumour size, and changes in tumour imaging that do not meet the definition of partial response (PR)
- Development of new lesions.
- Development of new mural nodules or increase in diameter of pre-existing mural nodules.
5. Patients confirmed to have either or both of the following within 14 days prior to enrolment
- One or more measurable lesions defined by the Response Evaluation Criteria in Solid Tumours (RECIST) guideline ver. 1.1.
- Patients with one or more superficial lesions with a maximum size of 10 mm or more that can be measured by colour photography.
6. ECOG performance status 0–1.
7. Life expectancy ≥90 days.
8. Women willing to use double contraception and who agree not to breastfeed for at least 5 months after final administration. Men

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willing to use double contraception for at least 7 months after final administration.

9. Sufficient organ functions, fulfilling all of the following conditions:

- White blood cell count ≥2000/mm^3.
- Absolute neutrophil count ≥1500/mm^3.
- Platelet count ≥100,000/mm^3.
- Haemoglobin ≥9.0 g/dL.
- AST and ALT ≤3 times the upper limit of the reference value of the institution. In the case of liver metastasis, ≤5 times the upper limit of the reference value of the institution.

2.2.2 | Exclusion criteria

1. Patients with (or having a history of) a severe hypersensitivity reaction to taxane anticancer drugs.
2. Patients for whom side effects from prior treatment or the effects of surgical therapy remain and are judged by the investigator or investigator to affect the safety assessment of the investigational drug.
3. Patients with double cancers. However, completely resected basal cell carcinoma, carcinoma in situ, intramucosal cancer or superficial bladder cancer, or patients with other cancers that have not recurred for more than 5 years prior to provision of consent to participate in this study can be enrolled.
4. Patients with central nervous system metastasis. However, patients who are asymptomatic and do not require treatment can be registered.
5. Patients with (or having a history of) interstitial lung disease, pulmonary fibrosis, or radiation pneumonitis diagnosed by diagnostic imaging. However, for radiation pneumonitis, patients with confirmed stabilization due to fibrosis, and patients in whom there is no concern about relapse can be registered.
6. Patients with diverticulitis or symptomatic gastrointestinal ulcer disease.
7. Patients with pericardial fluid, pleural effusion or ascites requiring continuous treatment.
8. Patients whose tumour-related pain cannot be stably controlled.
9. Patients with a history of transient ischemic attack or cerebrovascular attack within 180 days prior to enrolment in the study.
10. Patients with a history of thrombosis or thromboembolism (pulmonary artery embolism or deep vein thrombosis). However, such patients for whom 90 days or more have passed since the last occurrence and for whom there is no concern about relapse can be registered.
11. Patients participating in other clinical trials within 30 days prior to enrolment.
12. Patients with the following cardiovascular diseases:

- Patients with a history of myocardial infarction 6 months before registration.
- Patients with symptomatic arrhythmias requiring treatment.

13. Patients who received radiation therapy within 28 days prior to enrolment in this study. However, irradiation for the purpose of mitigation and irradiation 15 days before registration are permitted.
14. Patients with a positive HIV antibody test, HBs antigen test, or HCV antibody test. Patients who are negative on the HBsAg test but positive on either the HBs antibody test or the HBc antibody test and whose HBV-DNA quantification is higher than the detection sensitivity.
15. Patients with a bleeding tendency.
16. Patients with bleeding that is difficult to control.
17. Patients with hemoptysis.
18. Patients who are pregnant, lactating or may be pregnant.
19. Other patients who are not eligible for this clinical trial as determined by the investigator.

2.3 | Ethics approval and consent to participate

This study will be conducted in accordance with the principles expressed in the Declaration of Helsinki, good clinical practice guidelines, and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The protocol version 1.2 was approved by the Institutional Review Board of Tohoku University Hospital in April 2023 and the institutional review board of the following participating centres: Cancer Institute Hospital of Japanese Foundation for Cancer Research, Nagoya City University Graduate School of Medical Sciences, Kyushu University, Jichi Medical University, and National Cancer Center Hospital. Written, informed consent will be obtained from all enrolled participants.

2.4 | Endpoints/outcome measures

The primary endpoint of this study will be the overall response rate (ORR) at 28 weeks after starting treatment (central image evaluation) based on RECIST version 1.1 criteria. Imaging response will be evaluated at Week 24, and if response criteria are met, it will be confirmed again at Week 28. The secondary endpoint will include the ORR at 28 weeks after starting treatment (investigator evaluation), ORR at 8 weeks and 16 weeks after initiation of treatment (central and investigator evaluation), progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and adverse events graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. For this study, PFS is defined as the time from initiation of treatment in the clinical trial to disease progression or death from any cause, and OS is defined as the time from initiation of treatment in the clinical trial to death from any cause.

Safety verification will be assessed by the incidence of adverse events. Dose-limiting toxicity (DLT) is defined as an adverse event for which a causal relationship to TM5614 cannot be ruled out,

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making re-administration of TM5614 difficult. If DLT is observed in 2 cases, registration will be discontinued, and continuation of this trial will be re-considered.

2.5 | Schedule of the study and interventions

The trial schedule is composed of three periods: screening, treatment and post-observation periods. The screening period starts from the date of consent acquisition to the day before the first administration of the study drug. During this screening period, inclusion and exclusion criteria for the study participants will be evaluated. During the treatment period, appropriate doses of PTX will be administered intravenously over 120 min, for 28 weeks, with oral administration of TM5614 at a dose of 120 mg once a day (0–4 weeks) and 180 mg once a day (5–28 weeks). Study participants will be assessed for tumour response using imaging. During the post-observation period, adverse events will be reported 28 days after the last dose of PTX. To determine OS, all subjects will be followed up until death, withdrawal of consent or the end of the study.

2.6 | Criteria for discontinuation of treatment

The administration of PTX plus TM5614 will be discontinued in patients who experience at least one of the following[1]: radiographic disease progression according to RECIST version 1.1 criteria, progression of superficial lesions measured by colour photography, or apparent disease progression with clinical symptoms[2]; when there is a request for discontinuation from the patient or a legally authorized person[3]; if the patient turns out to be clearly ineligible for the present clinical trial[4]; when administration of PTX is discontinued[5]; when the investigator determines that it is difficult to continue the clinical trial due to the occurrence of adverse events[6]; if the efficacy and safety evaluation committee recommends discontinuation of the clinical trial[7]; if the patient becomes pregnant; or[8] the investigator or physician decides to discontinue administration of the drug.

2.7 | Data collection

Data quality control will be conducted by a combination of centralized (remote) and on-site monitoring, according to each procedure's standardized protocols. Centralized monitoring will be conducted by the coordinating investigator, the coordinating office and the data centre conducting the data collection. The data centre will verify the progress of the clinical trial, the visits of each patient, protocol compliance and the occurrence of adverse events. A centralized monitoring report will be created by the data centre and submitted to the coordinating investigator, who will ensure that the study is conducted properly and safely based on the centralized monitoring report and will take appropriate measures when necessary.

On-site monitoring will ensure that the study is conducted in compliance with the protocol and good clinical practice guidelines, as well as assess the electronic case report forms. The data manager will check for inconsistencies. The quality assurance auditor will assess the quality of the study independently according to the quality assurance plan. Moreover, the auditor will assess whether the study is conducted in compliance with the protocol and good clinical practice guidelines.

2.8 | Sample size calculation

Assuming the null hypothesis of a response rate of 13.6% (ORR of eribulin methylate for taxane-resist CAS[11]) and the alternative hypothesis of a response rate of 45%, a minimum of 15 patients are required to achieve a two-sided, Type I error of 5% and power of 70% based on the exact binomial distribution.

2.9 | Statistical analysis

Statistical analyses and reporting will be conducted in accordance with the Consolidated Standards of Reporting Trials guidelines, with the primary analyses based on the intention-to-treat principle without imputing any missing observations. All efficacy analyses will be based primarily on the full dataset, defined as including all patients who have received at least one dose of PTX and TM5614, and were treated in accordance with the study protocol. A safety analysis will be conducted using data from the safety analysis population. For baseline variables, summary statistics will be calculated as frequencies and proportions for categorical data and means and standard deviations for continuous variables.

The primary endpoint for efficacy will be the proportion of responders, considering a response threshold of 13.6% (H_0, null hypothesis) and an expected response rate of 45% (H_1, alternative hypothesis). The 95% confidence intervals will be calculated according to the binomial distribution of the response rate. Confidence interval limits will be assessed against the response threshold. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute). All statistical analyses will be described in detail in the statistical analysis plan, which will be fixed prior to database lock.

2.10 | Confidentiality

All study-related information will be stored securely on-site and identified only by a coded number to ensure participant confidentiality. All records that contain names or other personal identifiers will be stored separately from the study records identified by code numbers. All local databases will be secured with password-protected access systems. Data generated by this trial will be considered confidential by the investigators, except for the data to be included in the publications.

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2.11 | Patient and public involvement

Neither patients nor the public were involved in the design of this study.

3 | DISCUSSION

CAS is a rare and highly aggressive type of vascular tumour.[1] Since the number of patients entered in most previous clinical trials was small owing to its rarity, the recommended protocol for CAS is limited.[5] Since CAS expresses multiple angiogenic growth factors, including plasminogen activator inhibitor-1 (PAI-1), leading to increased expressions of pro-angiogenetic factors,[12] VEGF and VEGFR inhibitors or multi-tyrosine kinase inhibitors (TKIs) are potential drug targets in CAS.[13–15] Although several Phase II trials of antiangiogenic TKIs for AS have been reported, the results were not satisfactory.[15] For example, a recent multicentre, Phase 2 study evaluating pazopanib for incurable angiosarcoma reported a median PFS of 14.4 weeks and a 3-month PFS of 54.6% (95% CI: 36.0%–82.9%).[16] In another clinical trial, the median PFS was 4.3 months with pazopanib for chemotherapy-resistant angiosarcoma.[17] In another report, the objective response rate (ORR) of bevacizumab monotherapy was 8%, and the median PFS was 3 months.[18] Notably, even bevacizumab in combination with PTX, a standard drug for the treatment of CAS, did not improve the ORR of PTX monotherapy (28% combination vs 46% PTX), PFS (6.6 vs. 6.6 months), or OS (19.5 vs. 15.9 months).[19] These findings suggest that other angiogenesis-promoting factors are needed as targets to improve the systemic therapy for CAS.

Plasminogen activator inhibitor-1 (PAI-1) has been validated to be highly expressed in various types of tumours including melanoma,[6] and various pro-tumorigenic functions of PAI-1 in cancer progression and metastasis have been widely reported,[20] even in skin cancers.[7,12] For example, both the expression of PAI-1 on tumour cells and serum levels of PAI-1 correlate significantly with the efficacies of anti-PD-1 Abs in advanced melanoma patients.[7] In a CAS cohort, the expression of PAI-1 on tumour cells significantly correlated with OS in CAS patients.[12] Indeed, PAI-1 increases the expression and production of IL-23p19 on ISO-HAS-B human angiosarcoma cells to promote favourable tube networks, suggesting that PAI-1 promotes the pro-angiogenic effect in the development of CAS.[12] These reports suggested that a PAI-1 inhibitor, TM5614, might improve the anti-tumour effects of standard therapy of CAS, such as PTX, and in this report, we present the protocol of a multicentre, single-arm clinical trial involving the use of PTX plus TM5614 in Japanese patients with PTX-resistant CAS.

AUTHOR CONTRIBUTION

T. Fujimura, Y. Fujisawa, S. Matsushita and T. Miyata designed the research study. T. Fujimura, K. Yoshino, M. Nakamura, H. Kato, T. Ito, T. Maekawa, Y. Fujisawa, S. Matsushita, R. Amagai, E, Yamazaki, M. Takahashi, E, Tamabuchi, A. Hashimoto, Y. Kambayashi, and N. Yamazaki contributed to fix research protocol. T. Fujimura, Y. Fujisawa, and Y. Asano wrote the paper. T. Fujimura, N. Yamazaki, T. Miyata and Y. Asano supervised the study.

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CONFLICT OF INTEREST STATEMENT

T.M. declares research funding from Astellas Pharma Inc., Daiichi-Sankyo Biotech Co. Ltd., and Kowa Company, and holds stocks from Renascience Inc.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed at the time of submission.

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