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Trial in Progress: Phase II Study of TM5614 With Chemoradiotherapy and Durvalumab in Unresectable LA-NSCLC

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Disclosure

Artificial Intelligence (AI) Use Disclaimer

During the preparation of this work, the authors used ChatGPT to improve the English grammar and readability of the manuscript. After using this tool, the authors carefully reviewed and edited the content as needed and take full responsibility for the content of the published article.

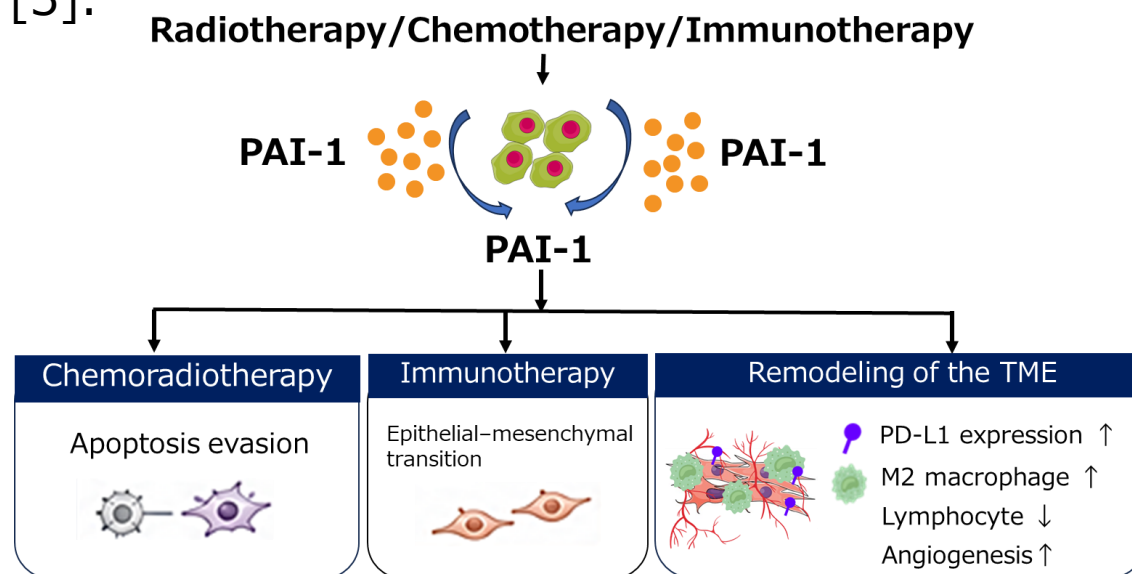
INTRODUCTION Standard Treatment and Unmet Needs in Locally Advanced NSCLC

Concurrent chemoradiotherapy (CRT) followed by 1 year of durvalumab consolidation is the standard treatment for patients with unresectable stage III non-small cell lung cancer (NSCLC). However, the 5-year progression-free survival (PFS) and overall survival (OS) rates are 33.1% and 42.9%, respectively, indicating that many patients are not cured [1,2].

Thus, strategies that enhance both local control by radiotherapy and systemic control by durvalumab are needed.

INTRODUCTION Role of Plasminogen Activator Inhibitor-1 (PAI-1) in Treatment Resistance

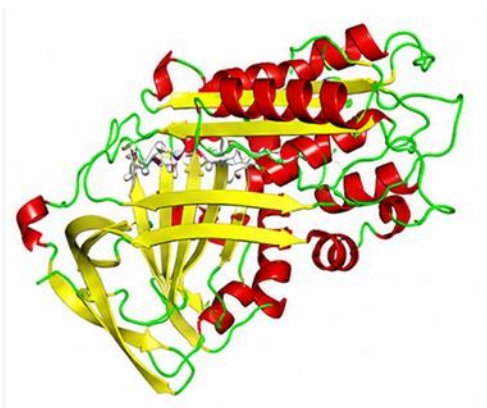
PAI-1 is a major regulator of fibrinolysis. We found that treatment-resistant NSCLC cells commonly upregulate **PAI-1** following chemotherapy, immunotherapy, and radiotherapy. Furthermore, **PAI-1** acts as a **hub molecule** that supports the **survival of resistant cells** by promoting apoptosis evasion, epithelial–mesenchymal transition, and remodeling of the tumor microenvironment (TME) [3].



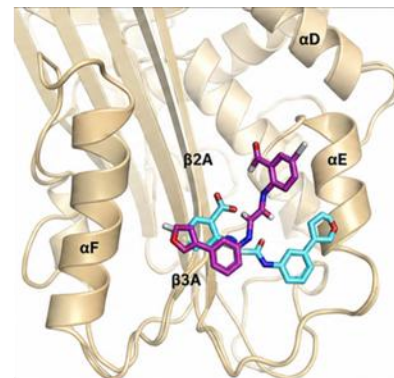
INTRODUCTION PAI-1 Inhibitor, TM5614

TM5614 is an orally available, academia-developed small-molecule PAI-1 inhibitor identified through in silico drug discovery and optimized from more than 1,400 novel derivatives.

Unstable PAI-1 (prone to degradation)



Stabilized by binding to vitronectin



TM5614 inserts into the vitronectin-binding site within PAI-1 and competes with vitronectin.

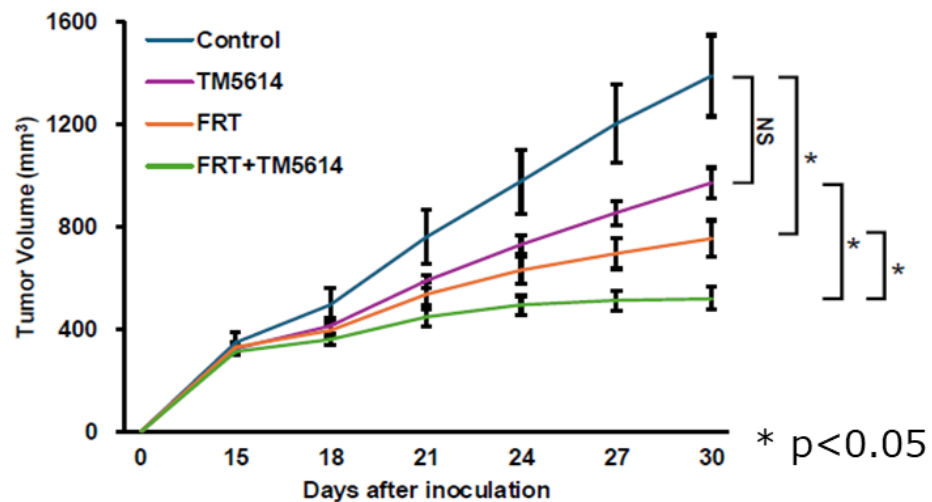


Promotes PAI-1 degradation

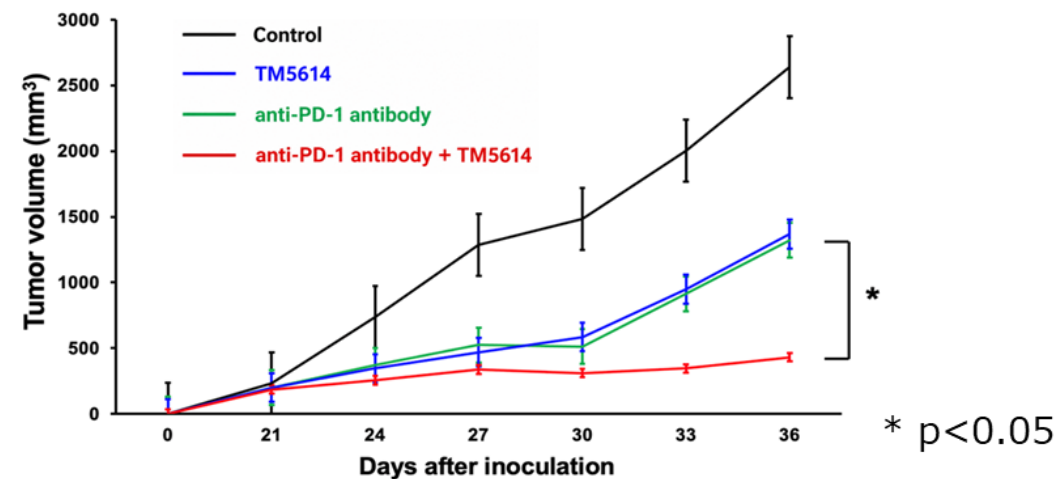
INTRODUCTION Antitumor Activity of TM5614, a PAI-1 Inhibitor

In our preclinical NSCLC models, TM5614 enhanced the antitumor effect of radiotherapy and anti-programmed cell death-1 (PD-1) therapy [4]

Radiotherapy



Immunotherapy



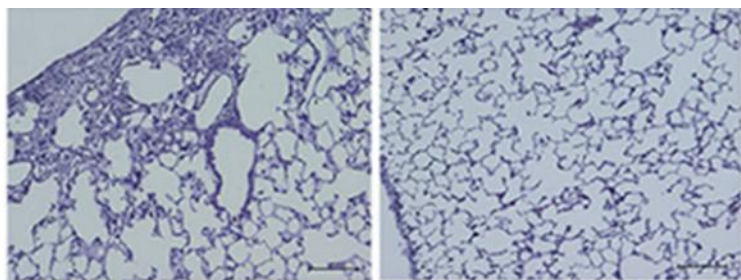
INTRODUCTION PAI-1–Mediated Radiation Pneumonitis and Pulmonary Fibrosis

Pneumonitis is another important limitation of durvalumab consolidation. Grade ≥ 2 pneumonitis has been reported in approximately 35% in real-world practice [5-6].

PAI-1 promotes fibroblast activation and radiation-induced pulmonary fibrosis [7], while a phase II study of **TM5614** in COVID-19 pneumonia suggested a protective effect against worsening lung injury [8].



H&E
stain
($\times 200$)



Wild type mouse

PAI-1 KO mouse

Radiation exposure induces radiation pneumonitis and pulmonary fibrosis in mice, whereas lung fibrosis is suppressed in PAI-1 knockout mice.

Thus, **TM5614** may improve antitumor efficacy while mitigating pulmonary toxicity.

INTRODUCTION Clinical activity of TM5614

	Phase	Treatment	Status
NSCLC	Phase II	TM5614+Nivolumab	Active, not recruiting
Melanoma	Phase III	TM5614+Nivolumab	Recruiting
CML	Phase III	Imatinib	Recruiting
Angiosarcoma	Phase II	TM5614+Paclitaxel	Active, not recruiting

TM5614 showed clinical activity in previously treated NSCLC in the third-line or later setting. Results will be presented at JLCS 2026.

INTRODUCTION Safety profile of TM5614

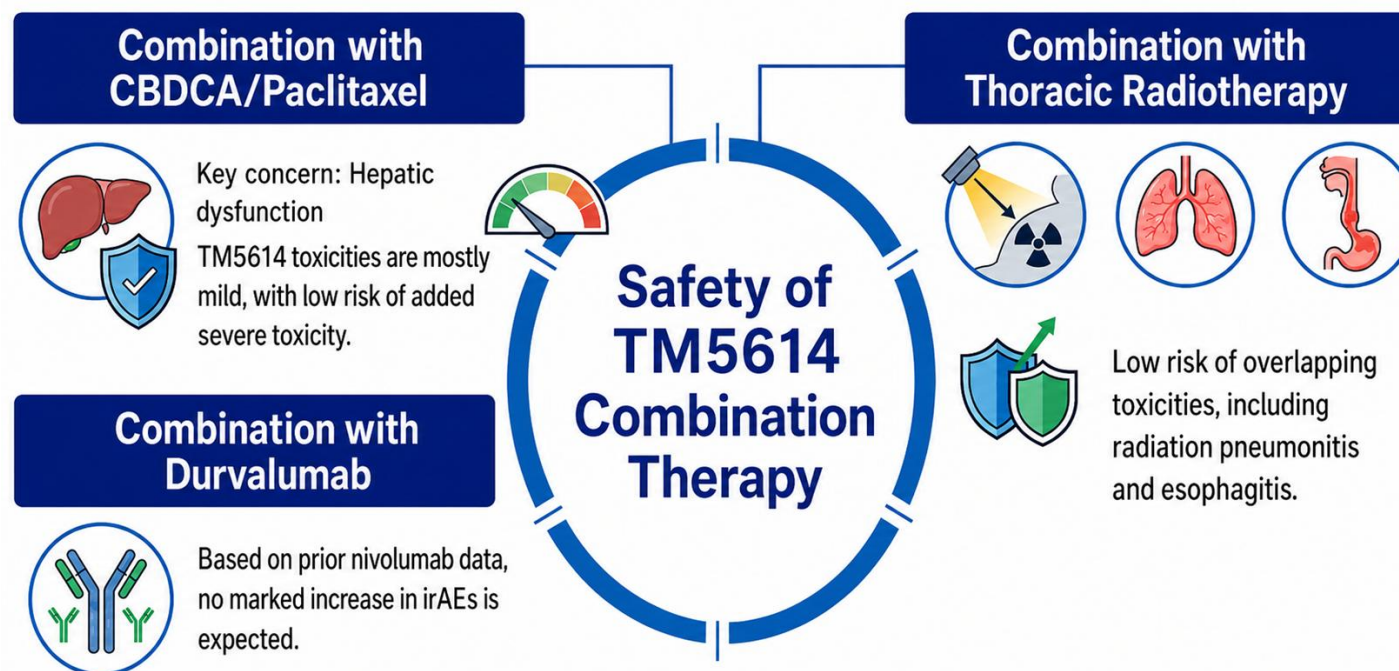
- ~230 patients treated with TM5614 in the Phase I and II trials.

- **Treatment-related serious adverse events**

Melanoma: hepatic dysfunction, n=3 → recovered

NSCLC: hepatic dysfunction, n=1;

cholangitis, n=1; pneumonitis, n=1 → all recovered



AIM

- We designed a multicenter phase II investigator-initiated trial of TM5614 administered during concurrent CRT followed by durvalumab consolidation in unresectable stage III NSCLC.
- We hypothesize that continuous PAI-1 inhibition will improve PFS by **enhancing radiosensitivity and antitumor immunity** while **reducing treatment-related pulmonary toxicity**.

STUDY DESIGN

Multicenter, open-label, single-arm, phase II investigator-initiated trial



- Between 18 and 80 years
- Unresectable stage III disease
- ECOG PS 0-1
- Measurable disease by RECIST v1.1
- No activating EGFR mutation and ALK rearrangement

Treatment

Chemoradiotherapy



**Carboplatin
(AUC 2)**



**Paclitaxel
(40mg/m²)**

Weekly, up to 6 cycles



Thoracic radiotherapy
60Gy (30fr)



TM5614 180mg/day (oral)
Continuous treatment during CRT and durvalumab

Consolidation



**Durvalumab
1500mg**

every 4 weeks
Up to 1 year

ENDPOINTS

The primary endpoint

- 1-year PFS rate from CRT initiation.

Secondary endpoints

- Response rate, Disease control rate
- PFS, OS, 1-year OS rate
- PFS and OS from consolidation initiation
- Response rate, Disease control rate of CRT
- Transition to consolidation therapy
- Safety, Adverse events, grade ≥ 2 pneumonitis
- Longitudinal changes in pulmonary function.

Exploratory endpoints

- Associations of pretreatment plasma PAI-1 levels and longitudinal changes in PAI-1 with efficacy and treatment-related adverse events.



**Plasma sampling
for PAI-1
(concentration)**



Before initiation
of study
treatment



Before initiation of
durvalumab consolidation
therapy



At the end of
protocol
treatment

STUDY TIMELINE, INSTITUTIONS, SAMPLE SIZE

Enrollment period
April 2026-Mar 2028
(24 Months)



Follow-up period
April 2028-Jun 2029
(15 months)



- 12 institutions in Japan
- 1 institution with decentralized clinical (DCT) operation

Sample Size Determination

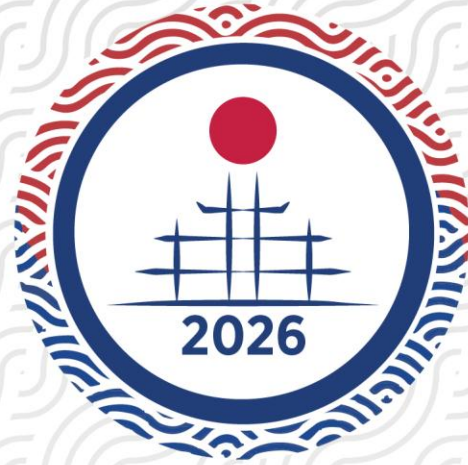
- **The primary endpoint:** 1-year PFS rate from CRT initiation.
- The threshold 1-year PFS rate was set at 50%.
- The expected 1-year PFS rate was set at 70%
- With a threshold rate of 50%, expected rate of 70%, one-sided significance level of 0.10, and 80% power, the required sample size was

ACKNOWLEDGEMENTS

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| [3] Biomed J. 2026 Feb;49(1):100911. | [4] Mol Cancer Ther 2026;25:435–447. |
| [5] Cancer Sci 2024;115:1273-82. | [6] Cancers (Basel) 2022;14. |
| [7] Exp Ther Med 2018;16:3070-6. | [8] Sci Rep 2024;14:165. |



Thank You.