



2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

PAI-1 as a Prognostic Biomarker and Mediator of Chemotherapy Resistance in Extensive-Stage Small Cell Lung Cancer

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INTRODUCTION

- The standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC) is combination **chemotherapy with immune checkpoint inhibitors**.
- Although most patients initially respond well to treatment, the majority eventually experience disease recurrence due to the development of **acquired chemoresistance**.^{1,2}

1) Blackhall F, et al. *BMJ Open* 2023;13:e052556.

2) Bonanno L, et al. *Front Immunol*. 2024;22:1353889.

INTRODUCTION

- We have previously demonstrated that **Plasminogen activator inhibitor-1 (PAI-1)** contributes to resistance to chemotherapy, molecular targeted therapy, and immune checkpoint inhibitors in non-small cell lung cancer.³⁻⁶
 - 3) T. Masuda, et al. *J Cell Mol Med.* 2019;23:2984-94.
 - 4) K. Tokumo, et al. *Cancers.* 2023;15:1092.
 - 5) T. Masuda, et al. *Biomed J.* 2025;49:100911.
 - 6) M. Sumii, et al. *Mol Cancer Ther.* 2026 ;25:435-447.
- The aim of this study was to investigate the role of PAI-1 in treatment response and the development of chemoresistance in small cell lung cancer.

METHODS -Clinical Investigation-

- We retrospectively analyzed 46 patients with **ES-SCLC** who initiated chemotherapy or chemoimmunotherapy at our institution between January 2014 and December 2024 and had pretreatment plasma samples available. **Plasma PAI-1 levels** were measured prior to treatment initiation, and their associations with treatment outcomes and survival were evaluated.
- The sum of tumor diameters was calculated based on the RECIST version 1.1 guidelines by summing the longest diameters of up to five target lesions, allowing a maximum of two lesions per organ.
- The number of metastatic lesions was counted. Patients with ≥ 6 metastatic lesions were classified as the high metastatic burden group, whereas those with ≤ 5 lesions were classified as the low metastatic burden group.

METHODS - Experimental Investigation-

- For translational investigation, SCLC cell lines SBC-3 and SBC-5 were used. Changes in **PAI-1 expression** following exposure to anticancer agents were assessed by RT-PCR, and the effects of the **PAI-1 inhibitor TM5614** on cell proliferation were evaluated.

RESULTS

1. Clinical Investigation

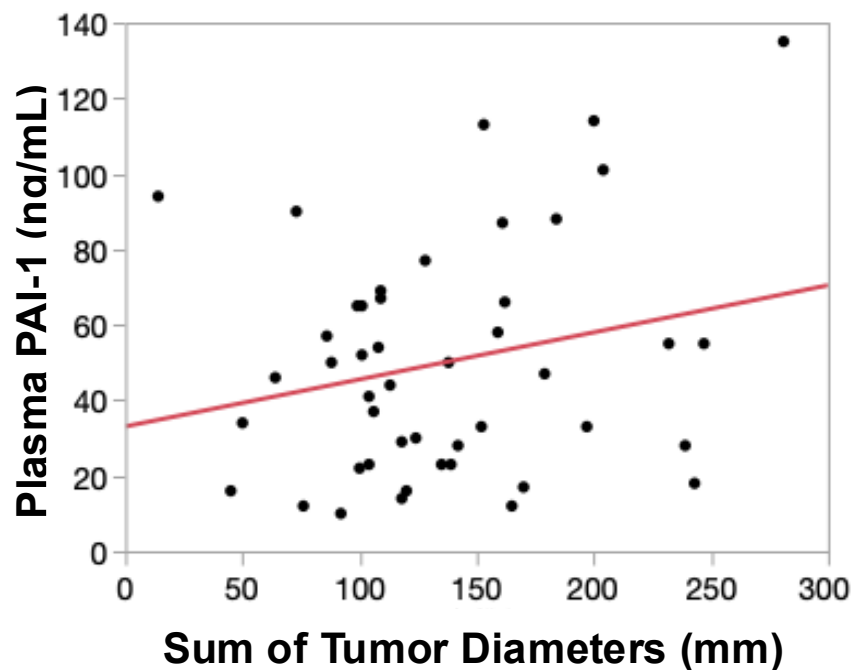
Table1. Patient characteristics

	n=46
Age, median (IQR)	73 (66–77)
Sex, male / female, n (%)	39 (85.1) / 7 (14.9)
BMI , median (IQR)	22.6 (20.8–24.6)
Smoking history, never / former / current, n (%)	2 (4.3) / 24 (52.2) / 20 (43.5)
Brinkman Index, median (IQR)	1000 (700–1365)
Performance Status, 0 / 1 / 2/ 3, n (%)	21 (45.7) / 17 (37.0) / 5 (10.9) / 3 (6.5)
Interstitial pneumonia, with / without, n (%)	13 (28.3) / 33 (71.7)
ICI administration, Yes / No, n (%)	19 (41.3) / 27 (58.7)
Plasma PAI-1 (ng/mL) , median (IQR)	47 (23–66)

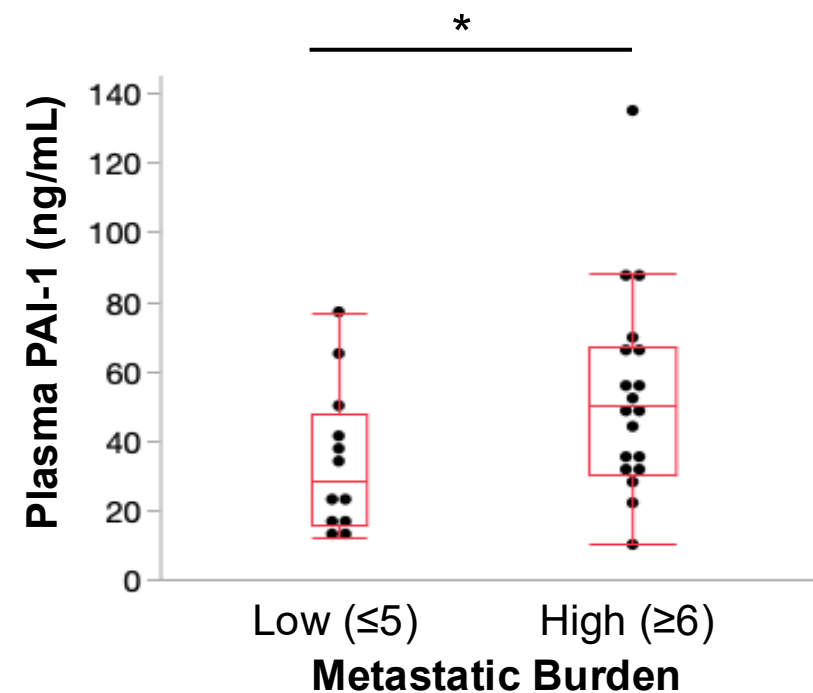
RESULTS

Figure 1. Association of Plasma PAI-1 Levels with Tumor Burden

(A) Sum of Tumor Diameters



(B) Metastatic Burden



* $p < 0.05$, Mann-Whitney U test

Plasma PAI-1 levels correlated with tumor size and were significantly higher in the high-metastatic-burden group than in the low-metastatic-burden group.

RESULTS

Table2. Univariate and Multivariable Cox Regression Analysis

(A) Progression-Free Survival; PFS

			Univariable analysis		Multivariable analysis	
			HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age	≥ 70		0.67 (0.32–1.39)	0.297	0.56 (0.27–1.15)	0.117
Sex	M		0.68 (0.27–1.68)	0.405		
PS	≥ 2		0.89 (0.37–2.14)	0.790	0.94 (0.35–2.50)	0.897
Brinkman Index	≥ 1000		0.65 (0.33–1.28)	0.216		
ICI administration	Yes		0.59 (0.30–1.16)	0.118		
Interstitial pneumonia	With		0.99 (0.48–2.06)	0.975		
Plasma PAI-1	≥ 55ng/mL		2.12 (1.09–4.15)	0.027	2.06 (1.04–4.05)	0.034
Sum of tumor diameters	≥ 122mm		1.12 (0.59–2.13)	0.724		
Number of metastatic lesions	≥ 6		1.56 (0.79–3.09)	0.202	1.28 (0.64–2.54)	0.490

High Plasma PAI-1 levels were an independent adverse prognostic factor for PFS.

RESULTS

Table2. Univariate and Multivariable Cox Regression Analysis

(B) Overall Survival; OS

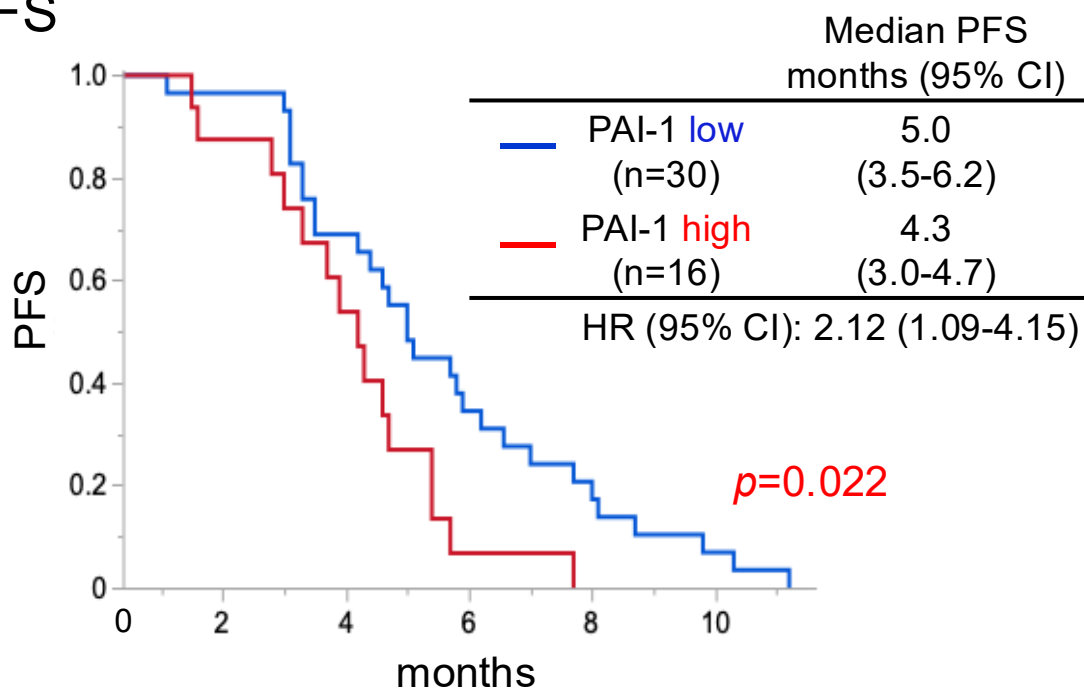
			Univariable analysis		Multivariable analysis	
			HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age	≥ 70		0.89 (0.37–2.15)	0.800	0.68 (0.29–1.64)	0.396
Sex	M		0.50 (0.18–1.35)	0.174		
PS	≥ 2		1.81 (0.68–4.86)	0.236	2.43 (0.86–7.08)	0.094
Brinkman Index	≥ 1000		1.50 (0.69–3.29)	0.301		
ICI administration	Yes		0.72 (0.34–1.50)	0.382		
Interstitial pneumonia	With		1.25 (0.52–2.98)	0.616		
Plasma PAI-1	≥ 55ng/mL		2.43 (1.19–4.96)	0.002	2.72 (1.28–5.79)	0.009
Sum of tumor diameters	≥ 122mm		2.79 (1.29–6.00)	0.007		
Number of metastatic lesions	≥ 6		1.76 (0.82–3.78)	0.145	1.94 (0.90–4.19)	0.090

High Plasma PAI-1 levels were an independent adverse prognostic factor for OS.

RESULTS

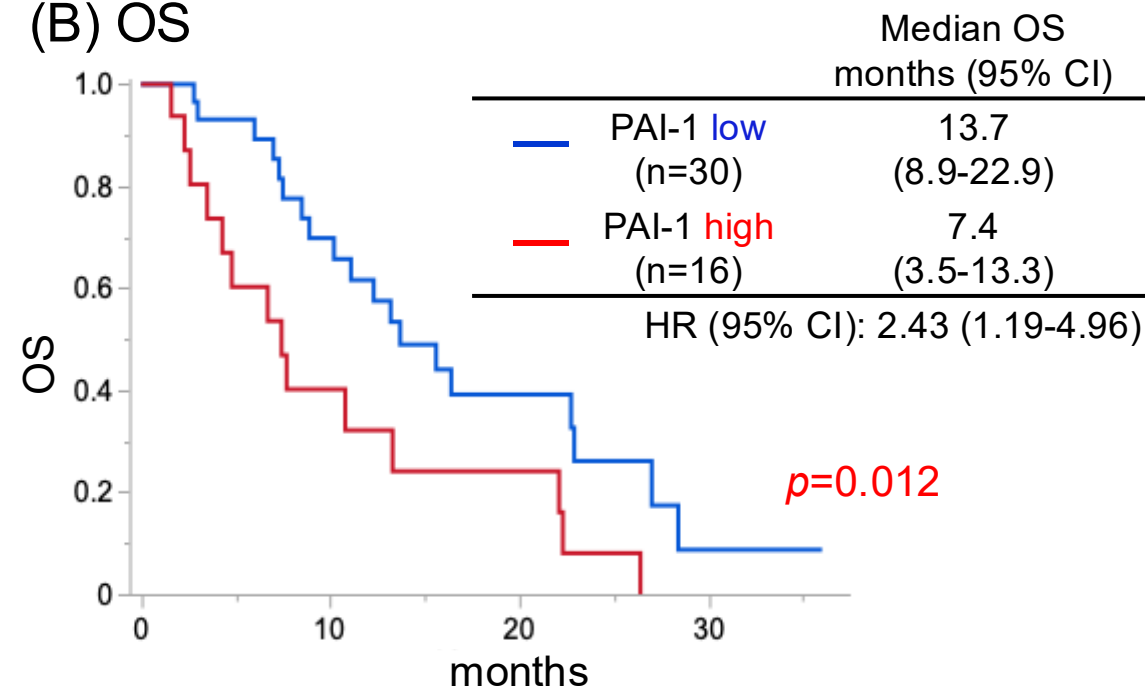
Figure2. Association of Plasma PAI-1 Levels with Prognosis

(A) PFS



PAI-1 low	30	28	22	11	6	3
PAI-1 high	16	14	9	2	0	0

(B) OS



PAI-1 low	30	27	19	11	7	5	2	1
PAI-1 high	16	10	7	4	4	2	0	0

Patients with high PAI-1 levels had significantly shorter PFS and OS than those with low PAI-1 levels.

RESULTS

Summary of Result 1

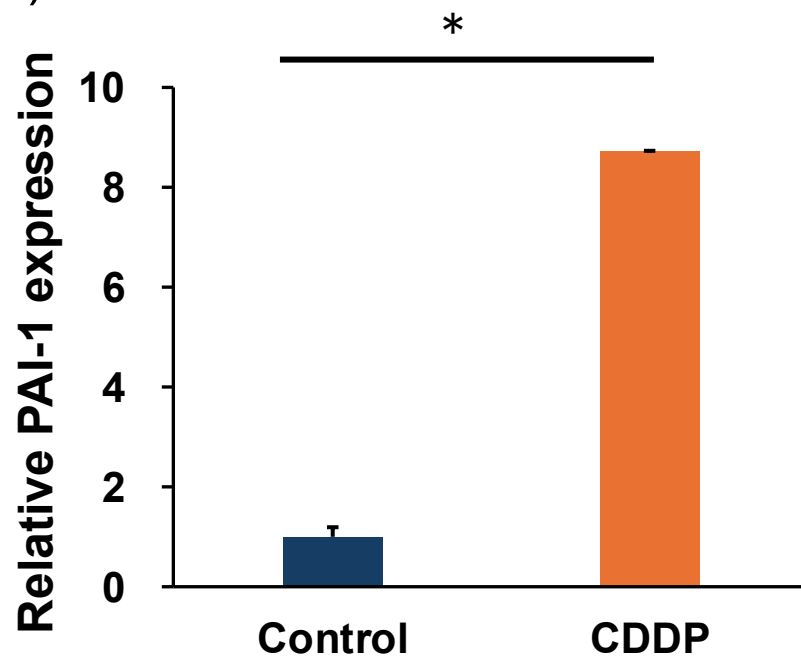
- **Pretreatment plasma PAI-1 levels showed a weak positive correlation with the sum of tumor diameters and were significantly higher in patients with a high metastatic burden.**
- **High pretreatment plasma PAI-1 was an independent predictor of poor PFS and OS.**
- **Patients with high plasma PAI-1 levels had significantly shorter first-line PFS and OS than those with low PAI-1 levels.**

RESULTS

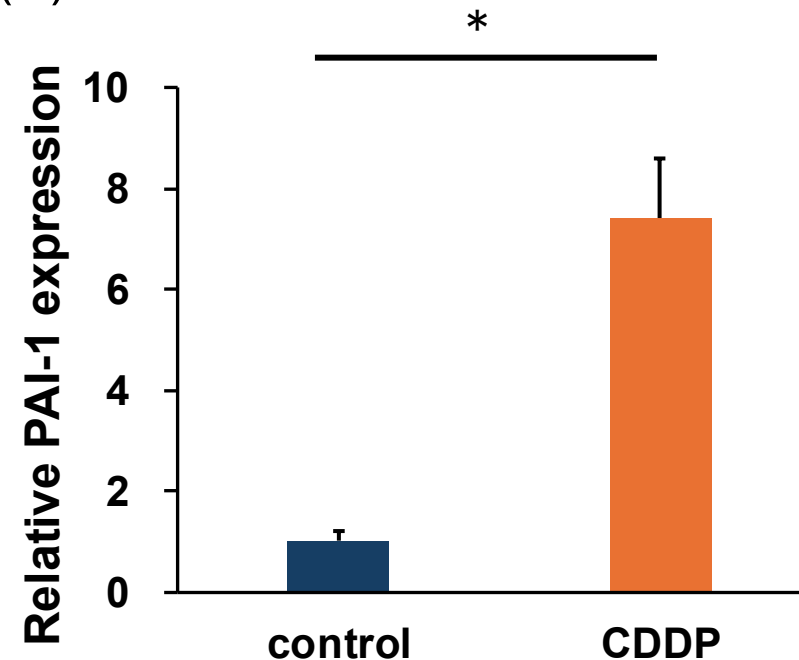
2. Experimental Investigation

Figure3. PAI-1 mRNA expression (qRT-PCR)

(A)SBC-3



(B)SBC-5



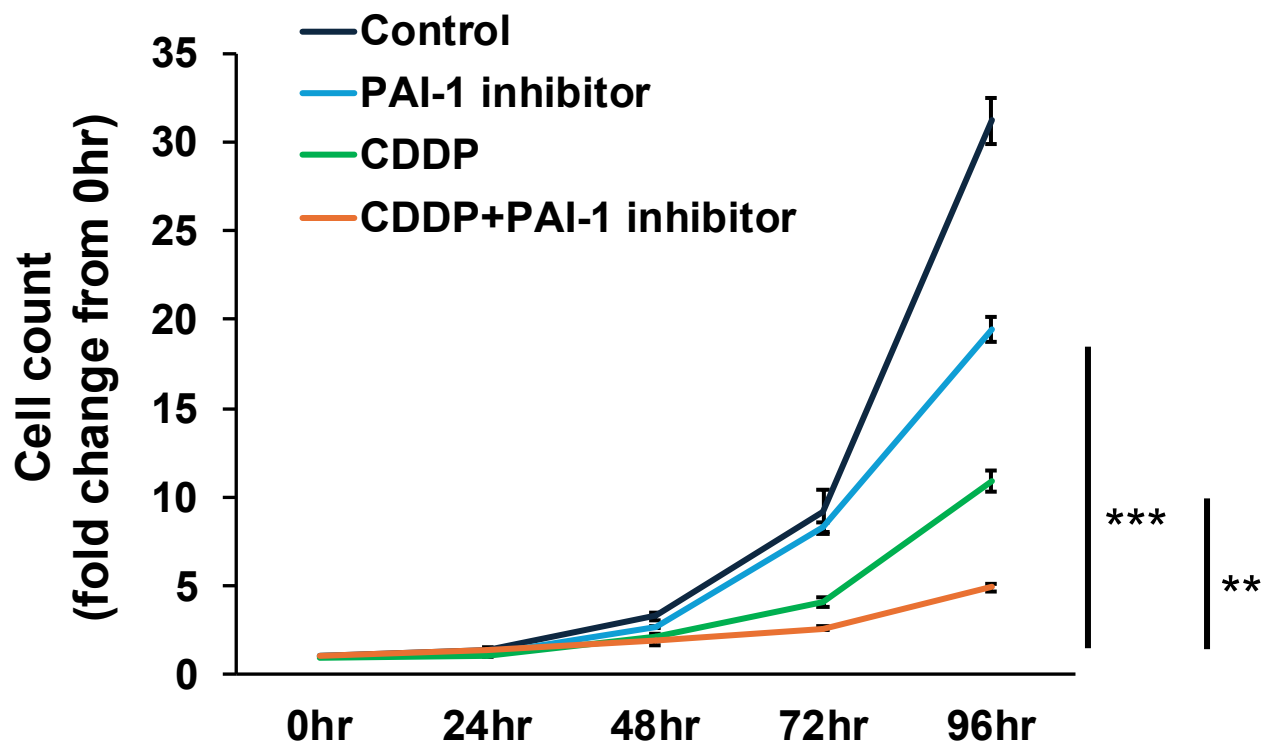
* $p < 0.05$, Student T test

PAI-1 mRNA expression was increased in the cisplatin-treated group.

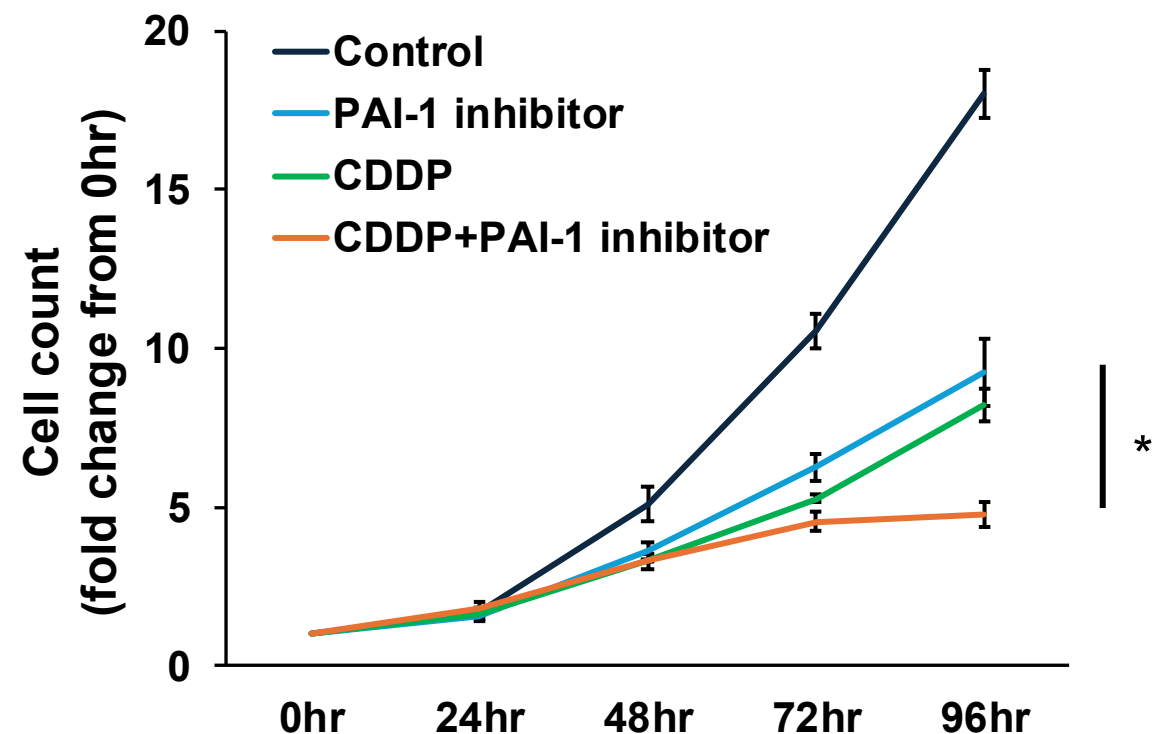
RESULTS

Figure4. Cell growth after Cisplatin and PAI-1 inhibitor treatment

(A) SBC-3



(B) SBC-5



Combined treatment with cisplatin and the PAI-1 inhibitor TM5614 reduced the number of surviving cells.

RESULTS

Summary of Result 2

- *In vitro*, surviving human SCLC cells after 72hr of cisplatin exposure exhibited **increased PAI-1 expression**.
- In the same experimental setting, combined treatment with cisplatin and **the PAI-1 inhibitor TM5614 reduced the number of surviving cells**.

DISCUSSION

Our analysis of pretreatment plasma PAI-1 levels in patients with ES-SCLC suggests that **PAI-1 is associated with tumor progression and resistance to chemotherapy.**

PAI-1 is likely to promote tumor progression and chemoresistance by acting on cancer cells and the tumor microenvironment.⁴⁻⁶

4) T. Masuda, et al. *Biomed J.* 2025;49:100911.

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6) M. Sumii, et al. *Mol Cancer Ther.* 2026 ;25:435-447.

DISCUSSION

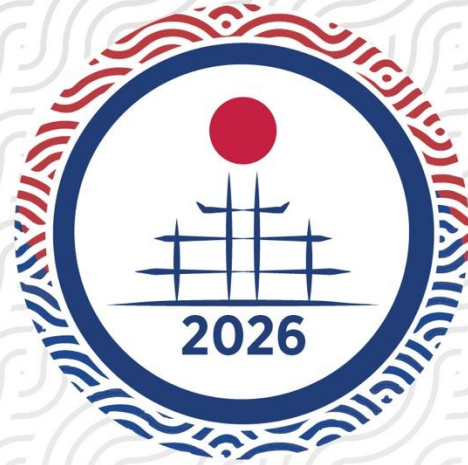
Our *in vitro* findings further demonstrated that PAI-1 contributes to the survival of SCLC cells following chemotherapy.

Moreover, the combination of chemotherapy and the PAI-1 inhibitor TM5614 markedly enhanced the antitumor effect, suggesting that this combination may represent a promising therapeutic strategy for overcoming chemoresistance.

Our next step is to evaluate the efficacy of TM5614 *in vivo* and to generate preclinical evidence supporting its clinical translation.

CONCLUSION

- **PAI-1** contributes to tumor progression and chemoresistance in SCLC.
- **PAI-1 inhibitor (TM5614)** represents a promising strategy to overcome chemoresistance and warrants further clinical investigation.



Thank You.