



2026 World Conference on Lung Cancer

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

PAI-1 Promotes Survival of Chemotherapy-Induced Drug-Tolerant Persister Cells and Predicts Poor Prognosis in NSCLC

Takatsune Hosoya¹, Takeshi Masuda², Kiyofumi Shimoji², Kakuhiro Yamaguchi², Shinjiro Sakamoto²,
Yasushi Horimasu², Taku Nakashima¹, Hironobu Hamada³, Hiroshi Iwamoto¹

¹Department of Molecular and Internal Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University

²Department of Respiratory Medicine, Hiroshima University Hospital

³Department of Physical Analysis and Therapeutic Sciences, Hiroshima University

Introduction- Background

- Cytotoxic chemotherapy remains widely used in NSCLC, particularly as later-line therapy and as treatment in patients with interstitial lung disease.
- However, its antitumor efficacy is often limited by the emergence of chemoresistance, resulting in rarely durable responses.
- Therefore, overcoming chemotherapy resistance is essential to improve treatment outcomes.

Introduction- Background

- **Drug-tolerant persister cells (DTPs)** that survive early treatment contribute to treatment resistance.

Mikubo M, et al. J Thorac Oncol. 2021;16:1798-1809.

- Our group has shown that **plasminogen activator inhibitor-1 (PAI-1)** promotes DTP survival in NSCLC treated with anti-PD-1 antibodies and EGFR tyrosine kinase inhibitors.

Tokumo K, et al. Cancers (Basel) 2023;15.

Sumii M, et al. Mol Cancer Ther 2025;25:435-447.

- However, its role in DTP survival during cytotoxic chemotherapy remains unclear.

Introduction- Aim

- This study aimed to investigate the role of PAI-1 in DTP survival following cytotoxic chemotherapy and its potential as a therapeutic target to overcome treatment resistance.

Methods- Clinical Investigation

- We retrospectively analyzed 80 patients with advanced NSCLC who received first-line cytotoxic chemotherapy between April 2008 and March 2021.
- **Serum PAI-1 levels before first-line chemotherapy** were measured, and their associations with treatment response and survival outcomes were evaluated.

Methods- Experimental Investigation

- In vitro, A549 NSCLC cells surviving 6 days of treatment with pemetrexed (PEM), paclitaxel (PTX), or docetaxel (DOC) were defined as **DTPs**.
- **PAI-1 expression** was assessed by qRT-PCR on day 6 and by ELISA on day 7 following a switch to serum-free medium on day 6.
- The effect of the **PAI-1 inhibitor TM5614** on DTP proliferation was evaluated. The effect of TM5614 on **early apoptosis** was evaluated using an Annexin V assay.

Results- Clinical Investigation

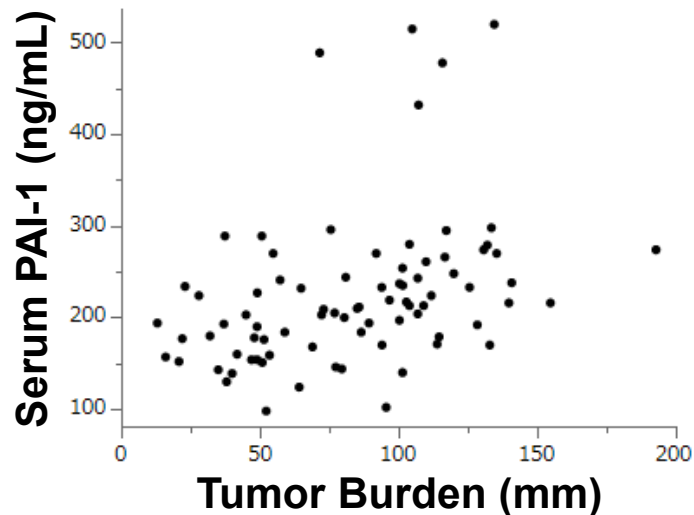
Patient characteristics

Patient characteristics	Patients, No. (%) (n = 80)
Age, years median (range)	69 (49-91)
Sex Male/Female	68 (85.0)/ 12 (15.0)
ECOG PS 0/1/2	45 (56.25)/ 26 (32.5)/ 9 (11.3)
Smoking status Non-smokers/former or current smokers	7 (8.75)/ 73 (91.25)
Histological diagnosis Adenocarcinoma/squamous cell carcinoma/others	58 (72.5)/ 17 (21.3)/ 5 (6.2)
Platinum doublet +/-	66 (82.5)/ 14 (17.5)
Interstitial lung disease +/-	33 (41.3)/ 47 (58.7)
Serum PAI-1 (ng/mL) median (range)	221.5 (98-520)

Results- Clinical Investigation

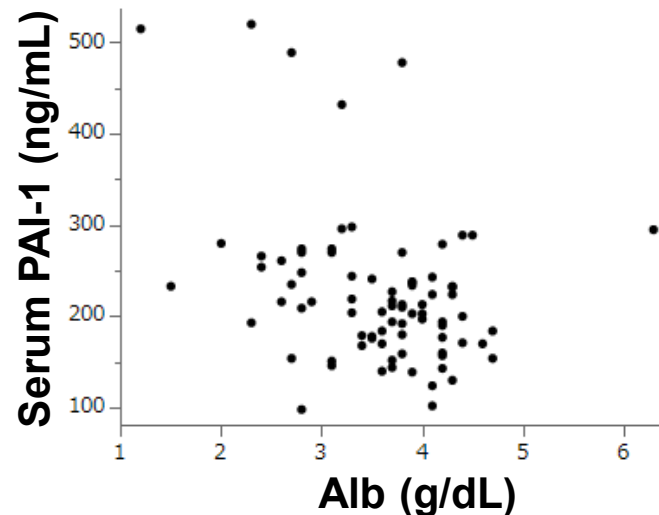
Association of Serum PAI-1 Levels with Tumor Burden and systemic inflammatory status

(A) Tumor Burden



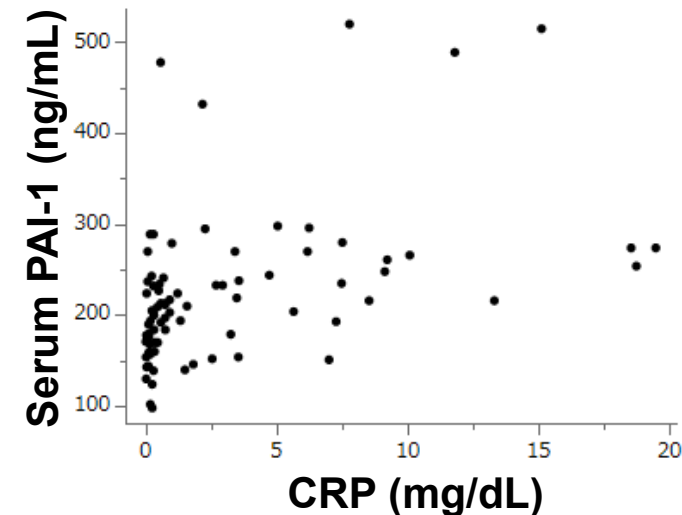
$$\sigma=0.37$$
$$p=0.0007$$

(B) Alb



$$\sigma=-0.35$$
$$p=0.0017$$

(C) CRP



$$\sigma=0.44$$
$$p<0.0001$$

Serum PAI-1 levels were significantly associated with tumor burden and systemic inflammatory status.

Results- Clinical Investigation

Univariate and Multivariable Cox Regression Analysis

(A) Progression-Free Survival; (1st line chemotherapy)

		Univariate analysis		
Factors		HR	95% CI	p-value
Age	≥75 years	1.29	0.77-2.14	0.34
Sex	Male	1.41	0.67-2.97	0.37
ECOG PS	≥2	2.10	0.89-4.96	0.09
Histology	Sq	0.95	0.37-2.47	0.12
Platinum doublet	No	1.16	0.59-2.30	0.67
ILD	Yes	1.14	0.68-1.89	0.62
Tumor burden*	≥85.58 (mm)	1.69	1.01-2.80	<0.05
Alb*	<3.7 (g/dL)	1.26	0.77-2.07	0.35
CRP*	≥0.75 (mg/dL)	1.13	0.69-1.85	0.63
PAI-1*	≥211.5 (ng/mL)	1.56	0.94-2.60	0.09

*Each factor was dichotomized at the median.

In univariate analysis, high serum PAI-1 levels were associated with a trend toward shorter PFS.

Results- Clinical Investigation

Univariate and Multivariable Cox Regression Analysis

(B) Overall Survival

		Univariate analysis			Multivariate analysis		
Factors		HR	95% CI	p-value	HR	95% CI	p-value
Age	≥75 years	1.23	0.73-2.10	0.92	0.68	0.37-1.25	0.22
Sex	Male	1.39	0.67-2.93	0.39	0.99	0.41-2.40	0.98
ECOG PS	≥2	2.53	0.99-6.45	0.05	1.21	0.44-3.31	0.72
Histology	Sq	0.59	0.14-2.45	0.47			
Platinum doublet	No	1.42	0.74-2.75	0.29	3.01	1.30-6.98	<0.05
ILD	Yes	1.66	1.00-2.74	<0.05	1.82	1.04-3.16	<0.05
Tumor burden*	≥85.58 (mm)	2.38	1.41-4.03	<0.01			
Alb*	<3.7 (g/dL)	2.10	1.25-3.50	<0.01			
CRP*	≥0.75 (mg/dL)	1.88	1.14-3.12	<0.05			
PAI-1*	≥211.5 (ng/mL)	2.69	1.59-4.55	<0.01	3.54	1.89-6.63	<0.0001

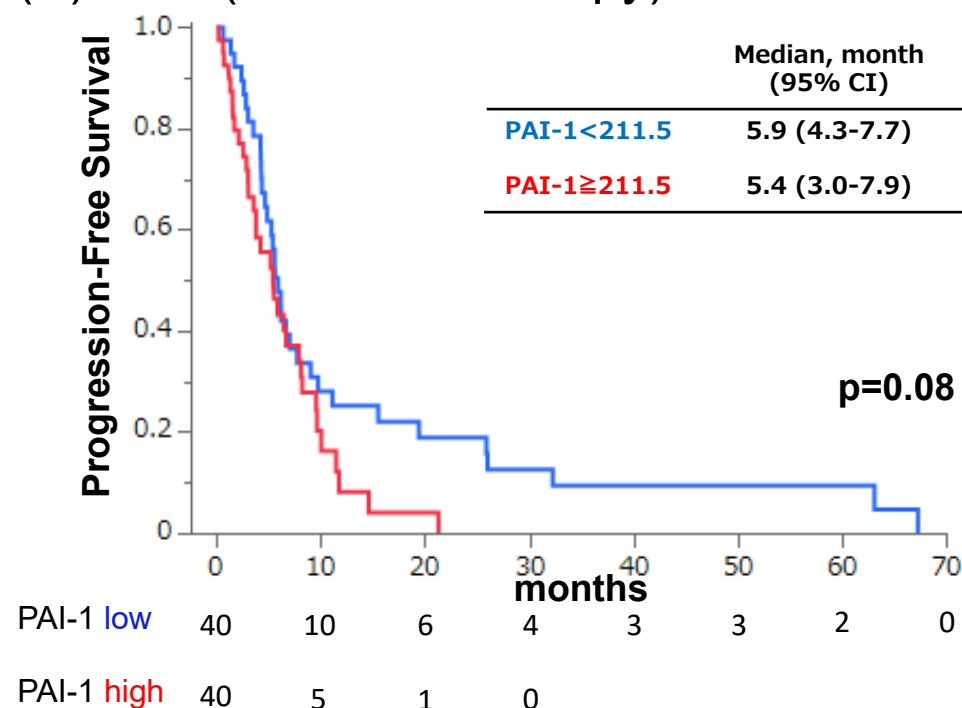
*Each factor was dichotomized at the median.

In multivariate analysis, high serum PAI-1 levels were an independent predictor of shorter OS.

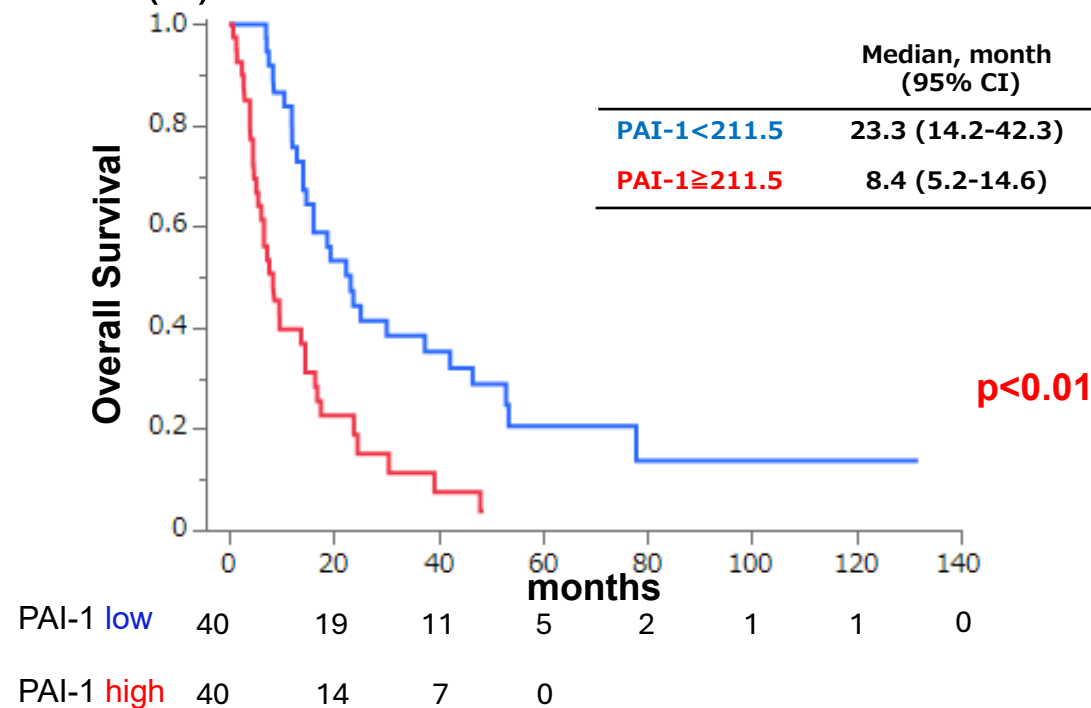
Results- Clinical Investigation

Association of Serum PAI-1 Levels with Prognosis

(A) PFS (1st chemotherapy)



(B) OS



The high serum PAI-1 group had significantly shorter OS than the low serum PAI-1 group by the log-rank test.

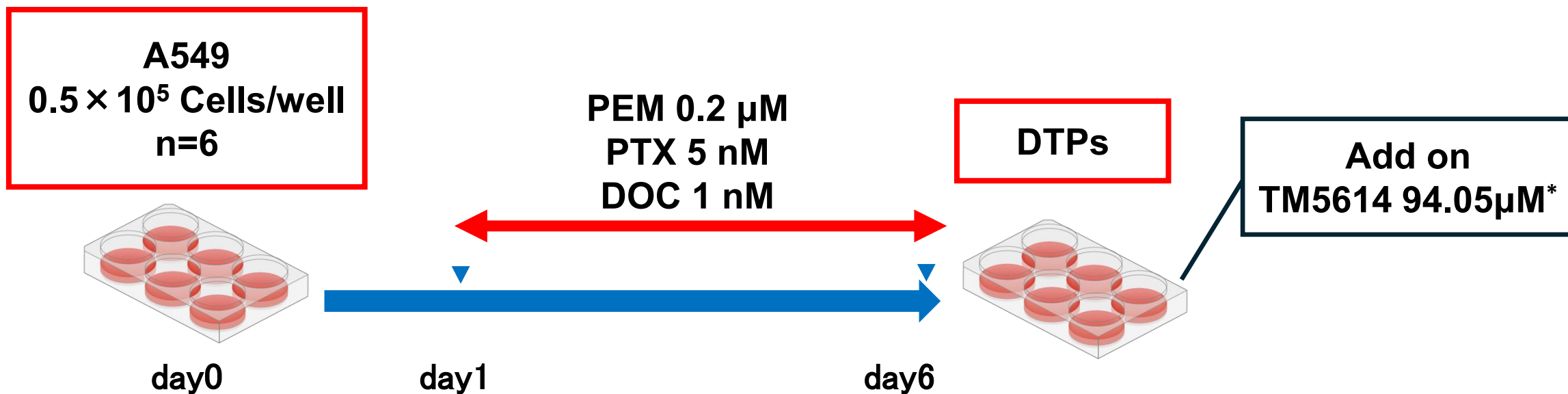
Results- Clinical Investigation

Summary

- Overall survival was significantly shorter in the high PAI-1 group than in the low PAI-1 group.
- In multivariate Cox regression analysis, **high serum PAI-1 levels remained an independent predictor of poor overall survival.**

Results- Experimental Investigation

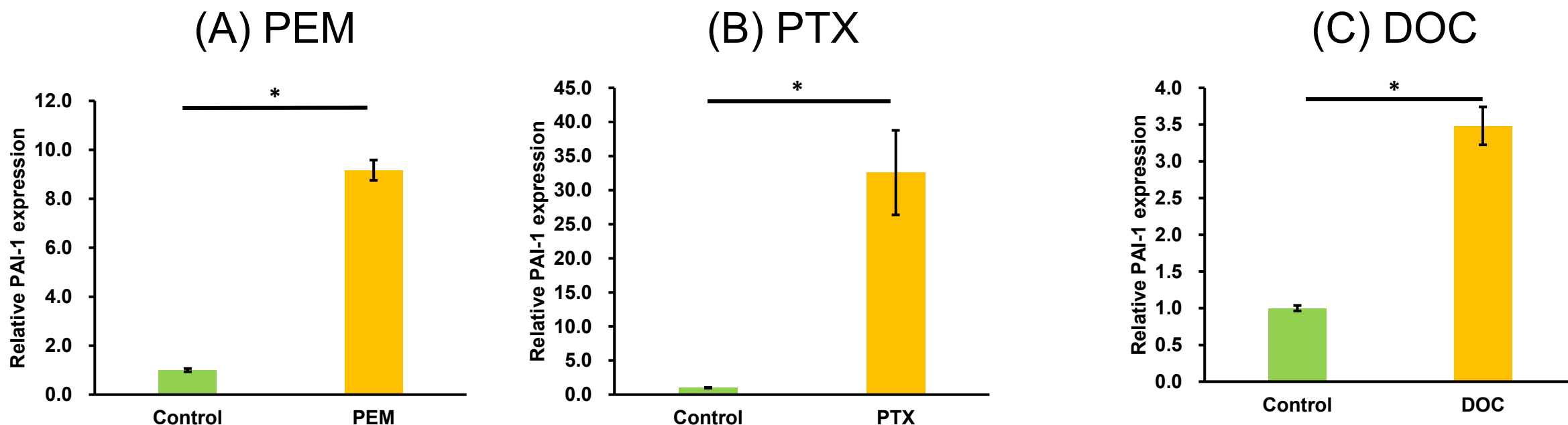
Experimental scheme



* TM5614 at 94.05 μ M corresponds to a human dose of 180 mg/day for 7 days.

Results- Experimental Investigation

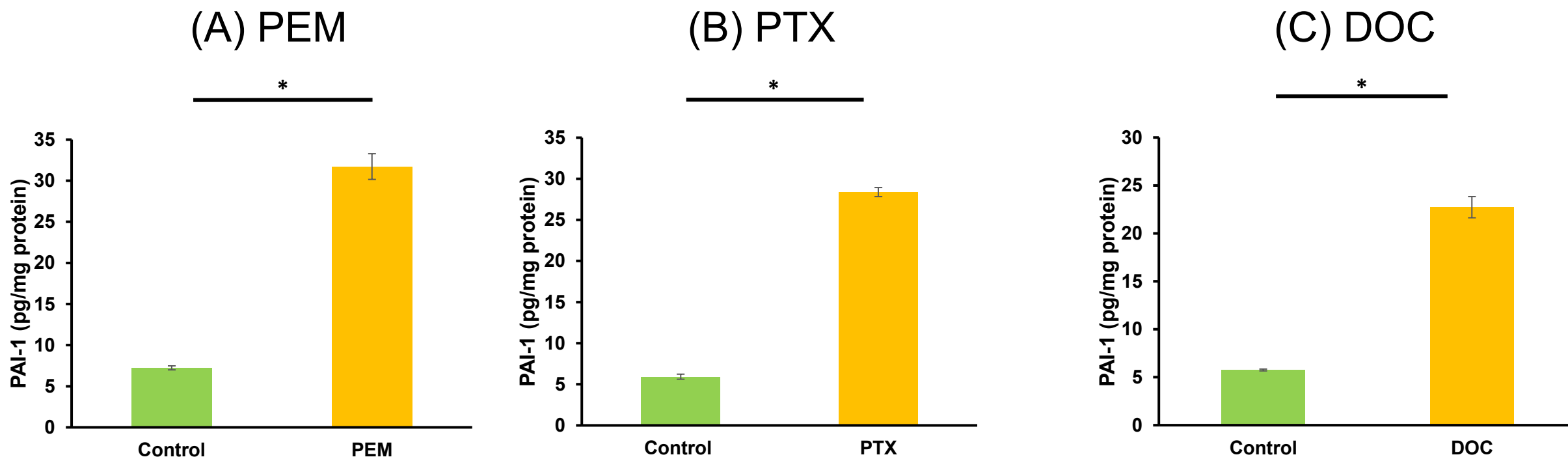
PAI-1 mRNA expression at day6 (qRT-PCR)



Across all three cytotoxic chemotherapeutic agents, DTPs exhibited significantly higher PAI-1 mRNA expression than their corresponding controls.

Results- Experimental Investigation

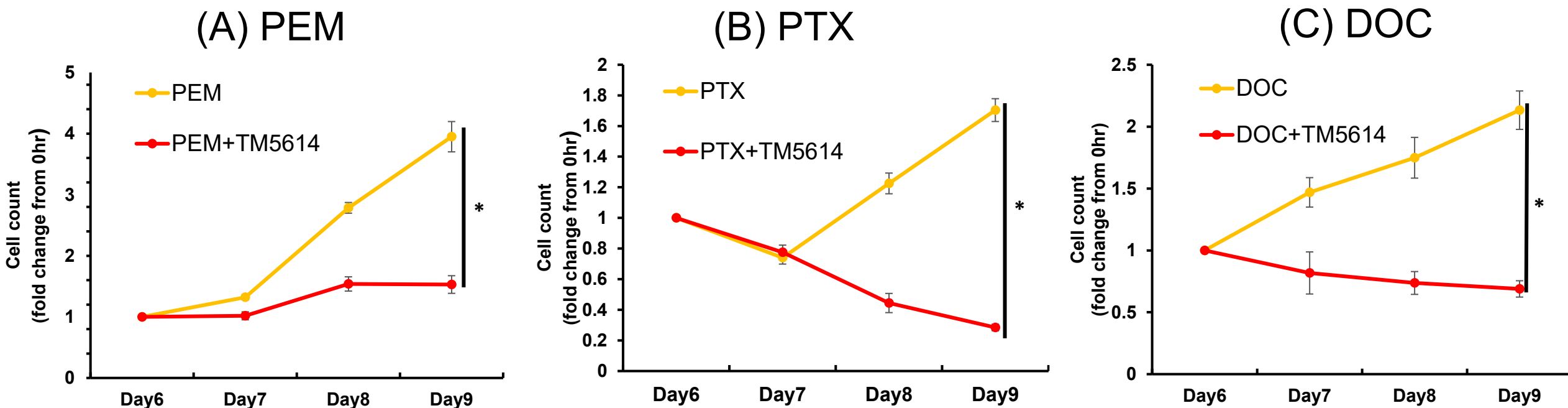
PAI-1 protein expression at day7 (ELSIA)



Across all three cytotoxic chemotherapeutic agents, DTPs exhibited significantly higher PAI-1 secreted protein levels than their corresponding controls.

Results- Experimental Investigation

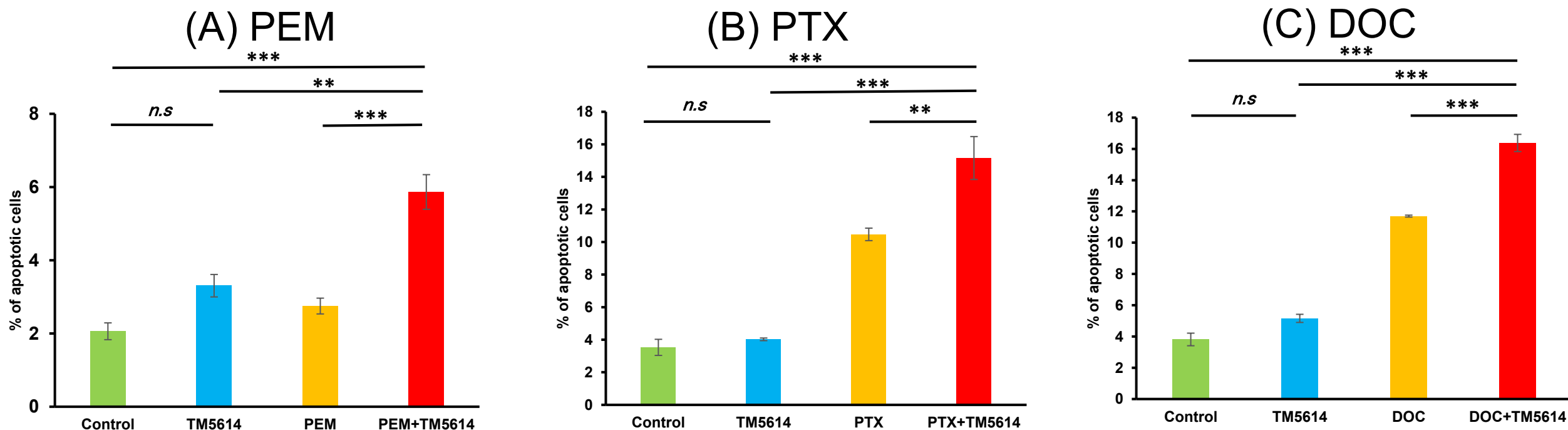
Cell growth after chemotherapy and PAI-1 inhibitor treatment



Across all three cytotoxic chemotherapeutic agents, combination treatment with TM5614 significantly reduced DTP cell numbers compared with continued treatment with PEM, PTX, or DOC alone.

Results- Experimental Investigation

Annexin V assay after chemotherapy and PAI-1 inhibitor treatment



Across all three cytotoxic chemotherapeutic agents, the proportion of apoptotic cells was significantly higher with TM5614 combination treatment than with PEM, PTX, or DOC alone.

Results- Clinical Investigation

Summary

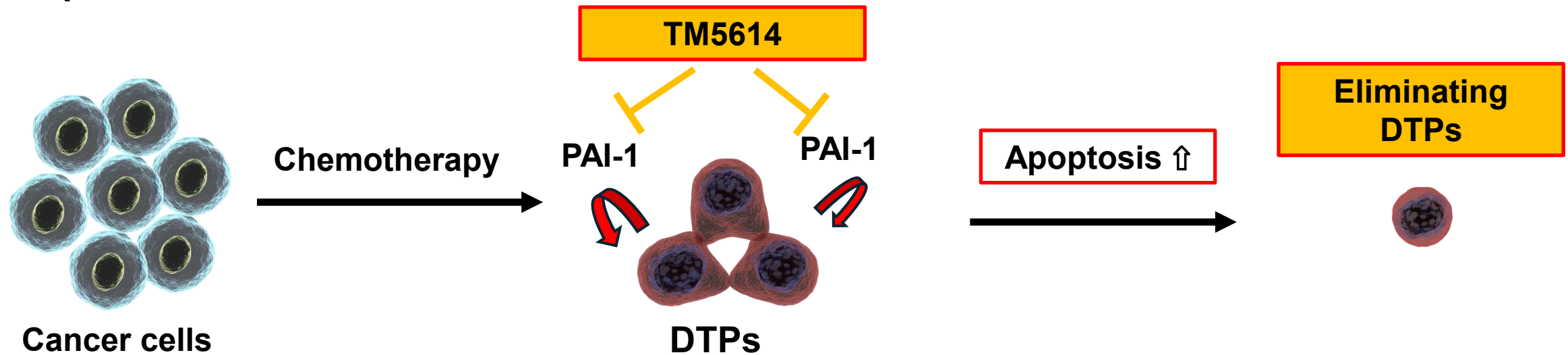
- **DTPs** following PEM, PTX, or DOC treatment exhibited significantly **increased PAI-1 mRNA and protein expression** compared with control cells.
- **Combination treatment with TM5614 and PEM or PTX, DOC significantly reduced cell survival** compared with continued treatment with PEM or PTX, or DOC alone.
- Combination treatment further **enhanced apoptosis** induced by PEM, PTX or DOC alone.

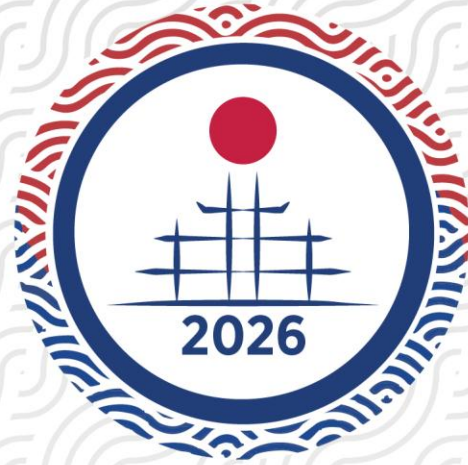
Discussion and conclusion

- High serum PAI-1 levels were associated with tumor progression in patients with advanced NSCLC and were an independent prognostic factor for poor survival following cytotoxic chemotherapy.
- In vitro, PAI-1 contributed to the survival of DTPs following chemotherapy, potentially through suppression of apoptosis.
- These findings suggest that PAI-1 contributes to tumor progression and chemoresistance and that targeting PAI-1 may represent a promising therapeutic strategy to overcome chemoresistance in NSCLC.

Discussion and conclusion

Graphical abstract





Thank You.●