# Astragalus Polysaccharides (PG2): Enhancing Macrophage M1 Polarization, Dendritic Cell Maturation, and T Cell-Mediated Immunity

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Moderator: 陳明豐主任 義大醫療財團法人義大癌治療醫院

# Outline

- PG2 AND LAC Cells Migration and Invasion
- PG2 AND Cisplatin
  PG2 AND Tumor-Related Inflammation
- PG2 AND Immune Checkpoint Inhibitors

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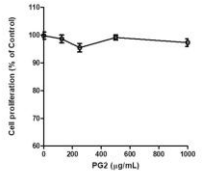
# *Astragalus* Polysaccharide (PG2) Suppresses Macrophage Migration Inhibitory Factor and Aggressiveness of Lung Adenocarcinoma Cells

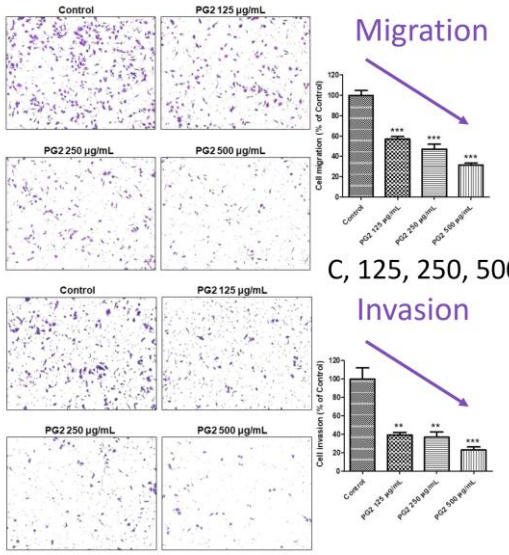
Chien-Huang Liao, Chen-Yin Yong, Gi-Ming Lai, Jyh-Ming Chow, Chieh-Fang Cheng, Chia-Lang Fang, Pei-Chun Lin, Chia-Lun Chang, Yu-Mei Zheng, Shuang-En Chuang, Jacqueline Whang-Peng, and Chih-Jung Yao

PG2 Attenuated migration and invasion abilities of A549 cells.

Viability



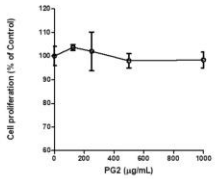

1000 mM



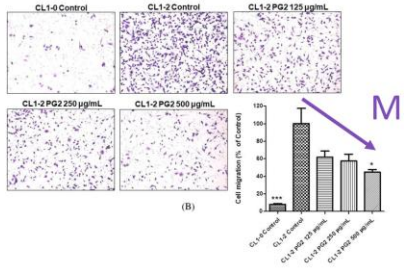

C, 125, 250, 500 mM

PG2 Attenuated migration and invasion abilities of CL1-2 cells.

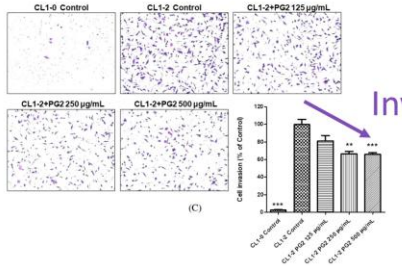
Viability




1000 mM




C, C, 125, 250, 500 mM



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No Access

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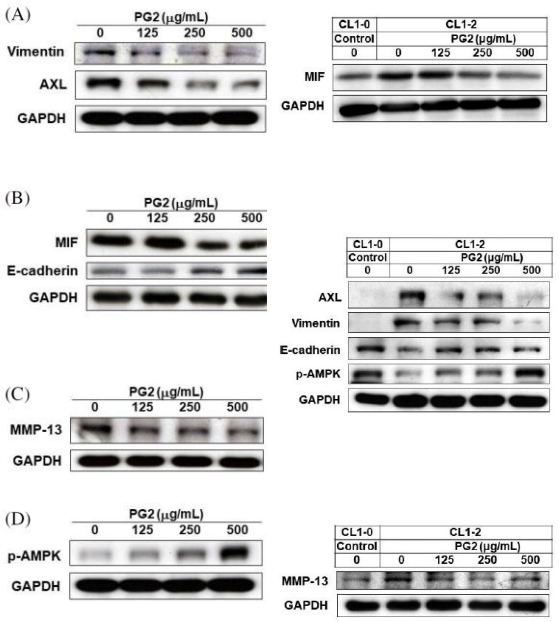
# PG2 Suppresses MIF Accompanied by Inhibition of EMT Related Protein Expression in A549 and CL1-2 Cells

| Protein | Function | Effects of PG2 |
|---|---|---|
| Vimentin | EMT | ↓ |
| AXL | Cell Proliferation, Survival, Migration, Invasion, Immune escape, Drug-resistance | ↓ |
| MIF | Macrophage migration inhibitory factor<br>Cell proliferation, Tumorigenesis, Metastasis | ↓ |
| E-cadherin | MET | ↑ |
| MMP13 | ECM remodeling, Cancer Progression, Metastasis | ↓ |
| P-AMPK | Tumor Suppressor | ↑ |



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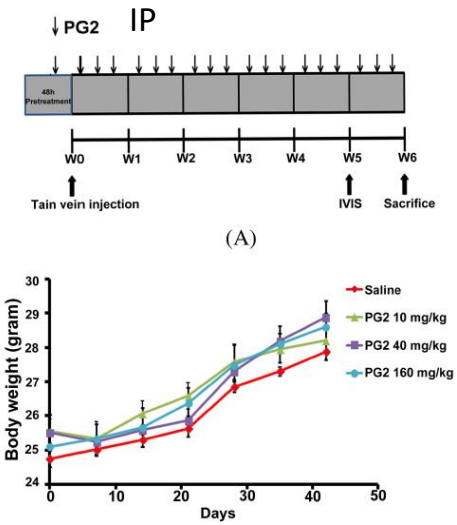
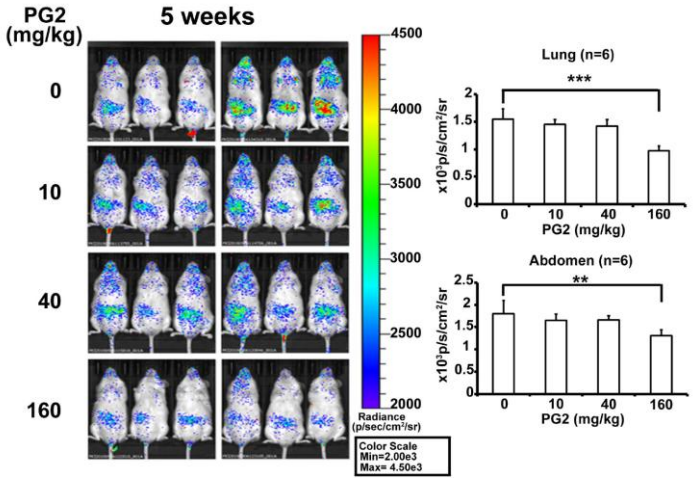
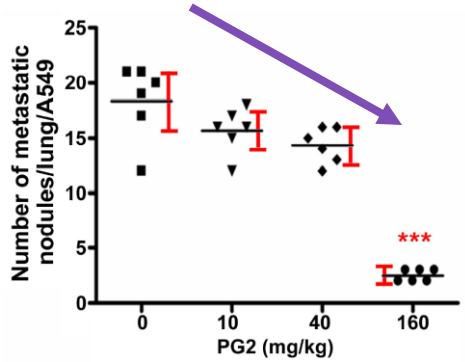
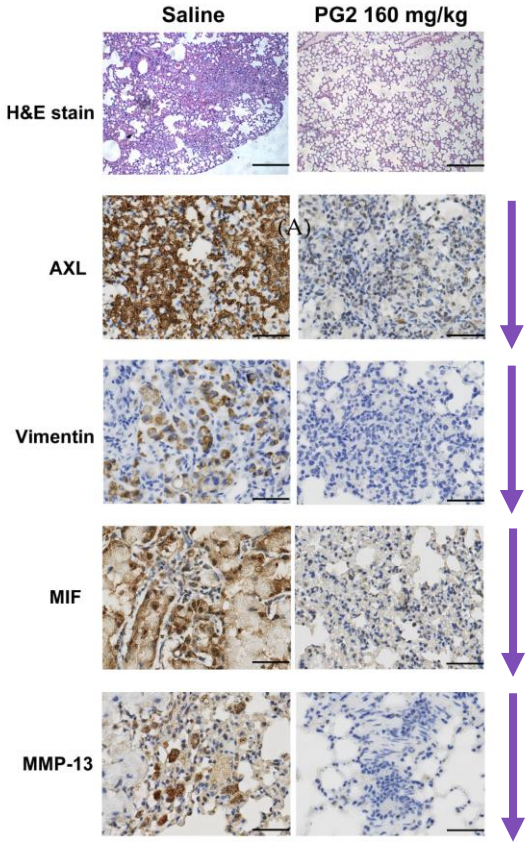
# PG2 Suppresses Lung Cancer Metastasis in A Mouse Xenograft Model



# Summary - Part 1

- **PG2 attenuated migration and invasion of LAC Cells *in vivo* and *in vitro.***

- **PG2 Suppresses MIF (Macrophage Migration Inhibitory Factor) Accompanied by Inhibition of EMT Related Protein Expression in A549 and CL1-2 Cells**

# Outline

- PG2 Attenuates the Migration and Invasion of LAC Cells in Vivo & in Vitro
- PG2 AND Cisplatin
  PG2 AND Tumor-Related Inflammation
- PG2 AND Immune Checkpoint Inhibitors

*nutrients*

MDPI

*Article*

# *Astragalus polysaccharides* (PG2) Enhances the M1 Polarization of Macrophages, Functional Maturation of Dendritic Cells, and T Cell-Mediated Anticancer Immune Responses in Patients with Lung Cancer

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nutrients

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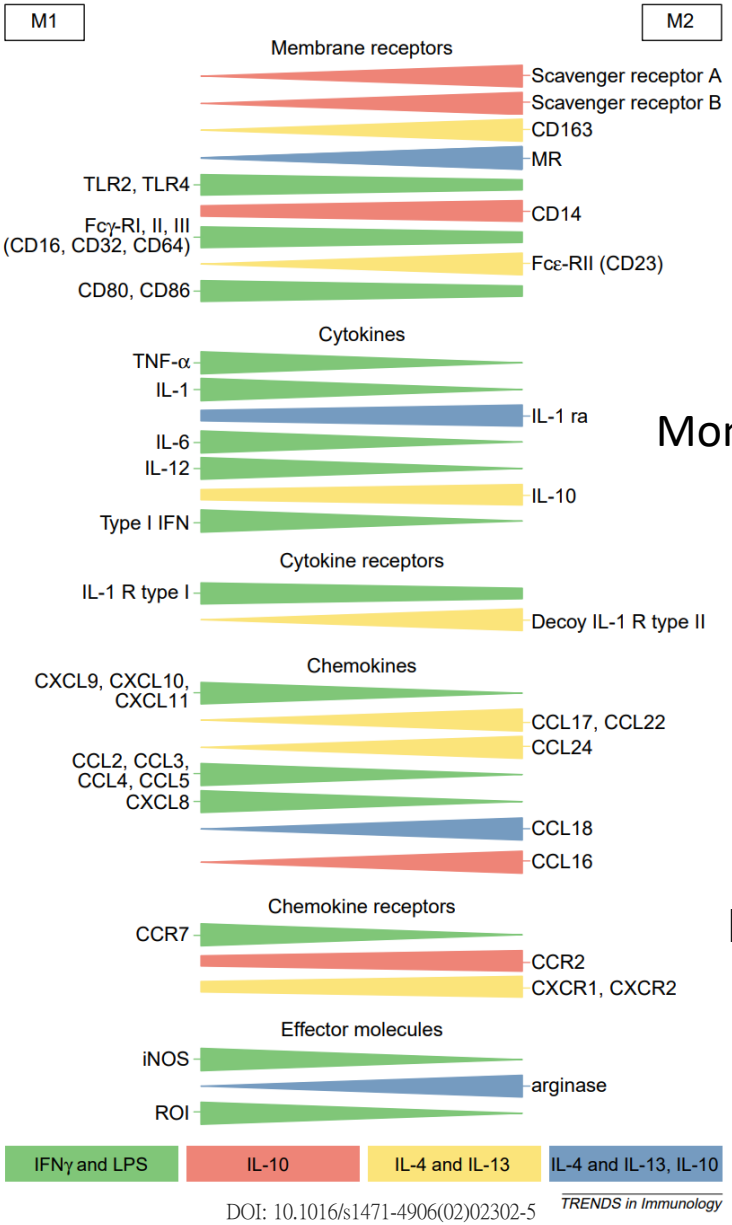



DOI: 10.1016/s1471-4906(02)02302-5 TRENDS in Immunology

## M1: Anti-tumorigenic

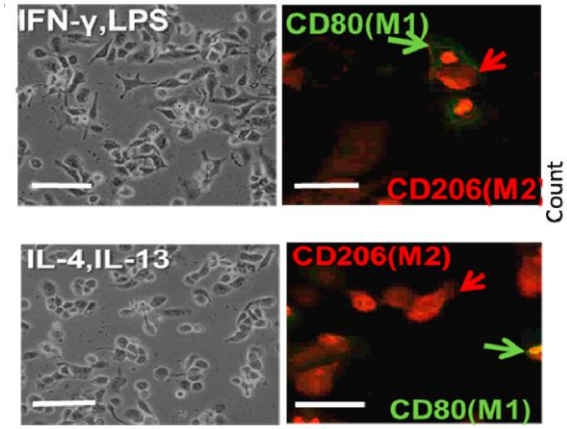
## M2: Pro-tumorigenic

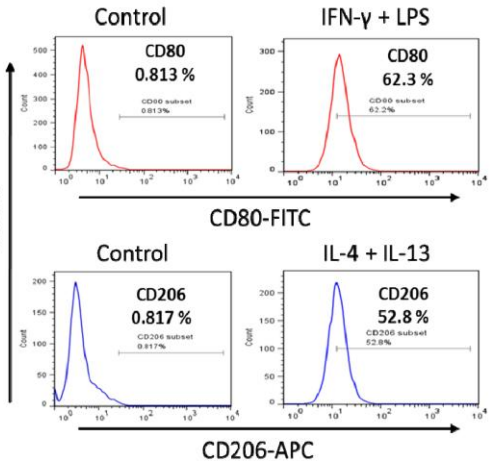

**Antimicrobial properties**
- ↑ Glycolysis
- Blocked TCA cycle
- ↓ OXPHOS activity
- ↑ Production of inflammatory intermediates
- ↑ Antimicrobial responses
  - ↑ NADPH oxidase activity
  - Use of arginine to generate NO
  - ↑ Antigen presentation
  - ↑ Production of itaconate

**Tissue repair properties**
- ↑ Mitochondrial respiration
- Intact TCA cycle
- ↑ Fatty acid utilization
- ↑ Production of anti-inflammatory cytokines
- ↑ Tissue remodelling responses
  - ↓ Production of inflammatory lipids
  - Promotion of angiogenesis
  - ECM remodelling

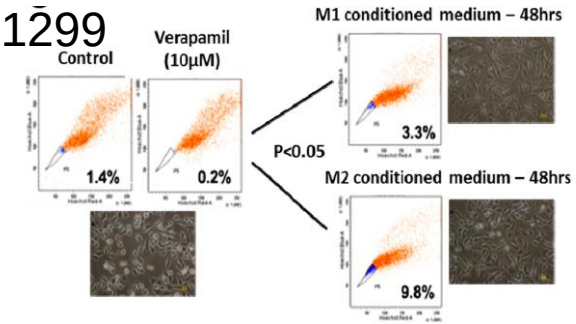
https://doi.org/10.1038/s41577-019-0124-9

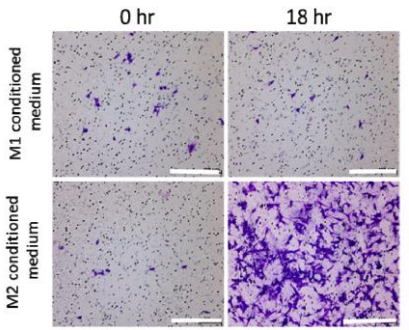
## Monocyte-Derived Macrophages




## H1299



nutrients

MDPI

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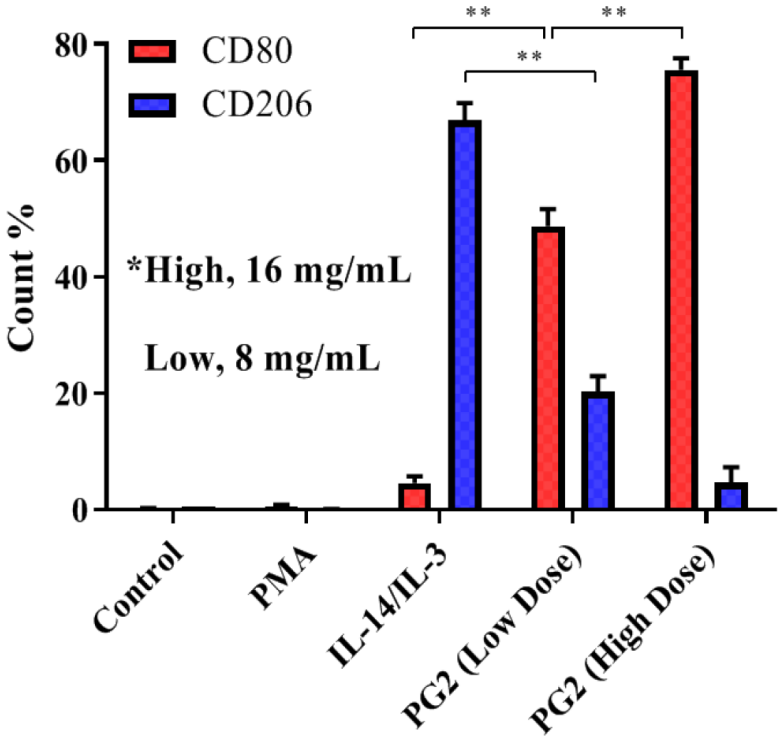
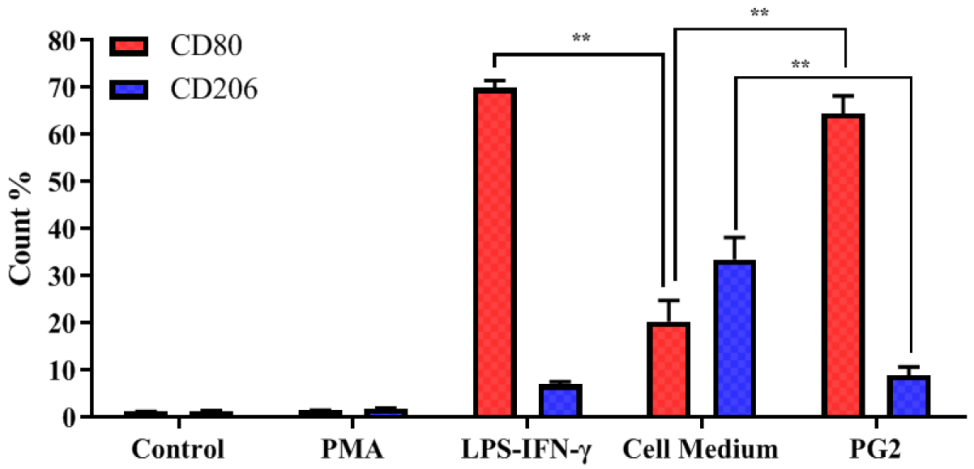
PG2 enhances M1 polarization and down-regulates IL-4/IL-13-induced M2 polarization.




The enhancement of M1 macrophage polarization by PG2 is akin to the effect of LPS/IFN-stimulation of MDMs.



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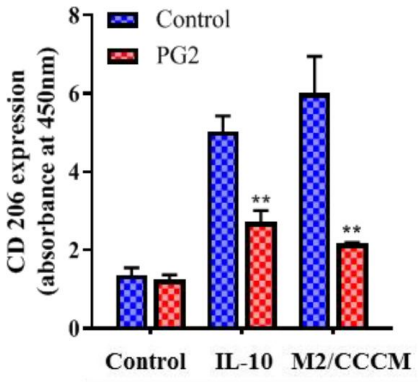
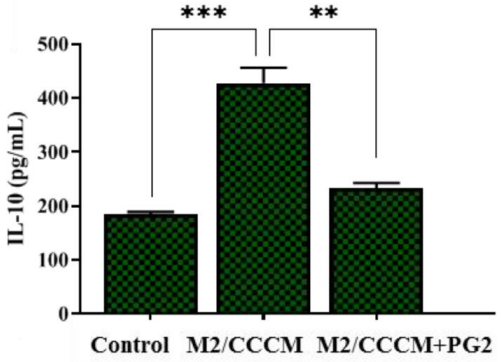
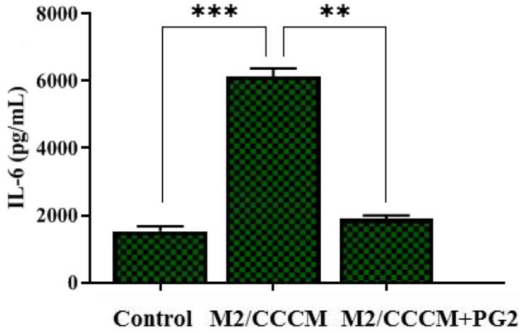
PG2 inhibits IL-10-enhanced M2 macrophage proliferation, and negatively modulates the secretion of tumor-promoting anti-inflammatory cytokines.



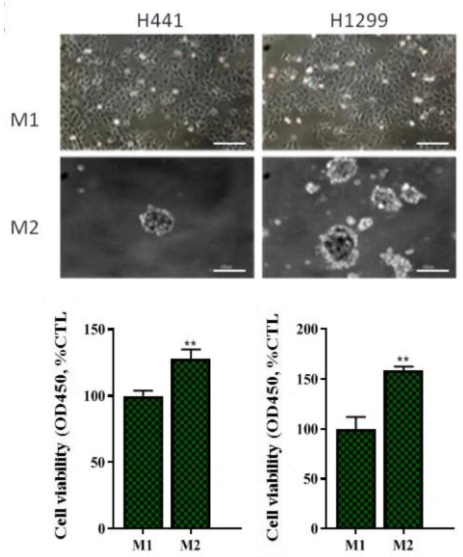

IL-10



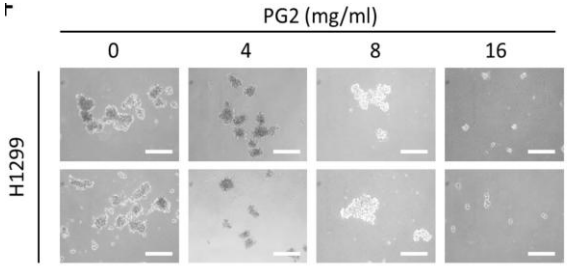

IL-6

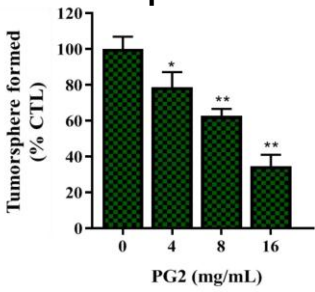



PG2 inhibited the viability of tumorspheres grown from M2/H1299 co-culture in a dose-dependent manner.




Tumorspheres



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Article
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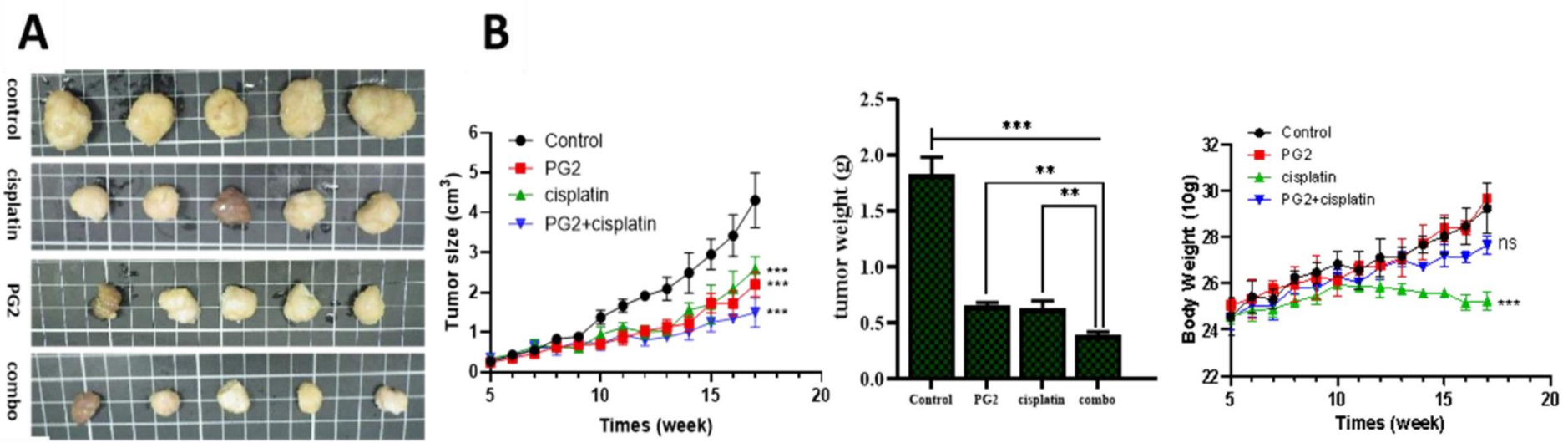
# Inhibited tumor growth & suppressed cisplatin-associated weight-loss




(A) Photo images show the anticancer effect of cisplatin and/or PG2 in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

(B) Graphical representation of the effect of cisplatin and/or PG2 on the tumor size, tumor weight, and body weight in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

*ns, not significant; **p < 0.01, ***p < 0.001;*

(17 weeks, and/or cisplatin in syngeneic LLC1 tumor-bearing C57BL/6 mice)

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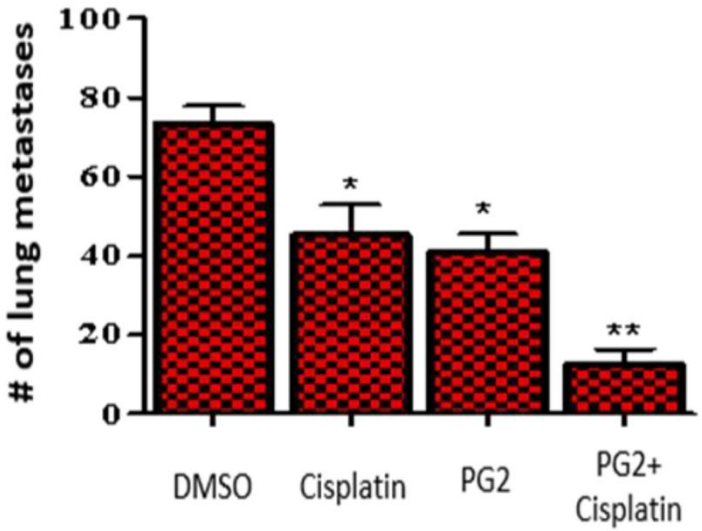
# Suppression of tumor growth and metastasis



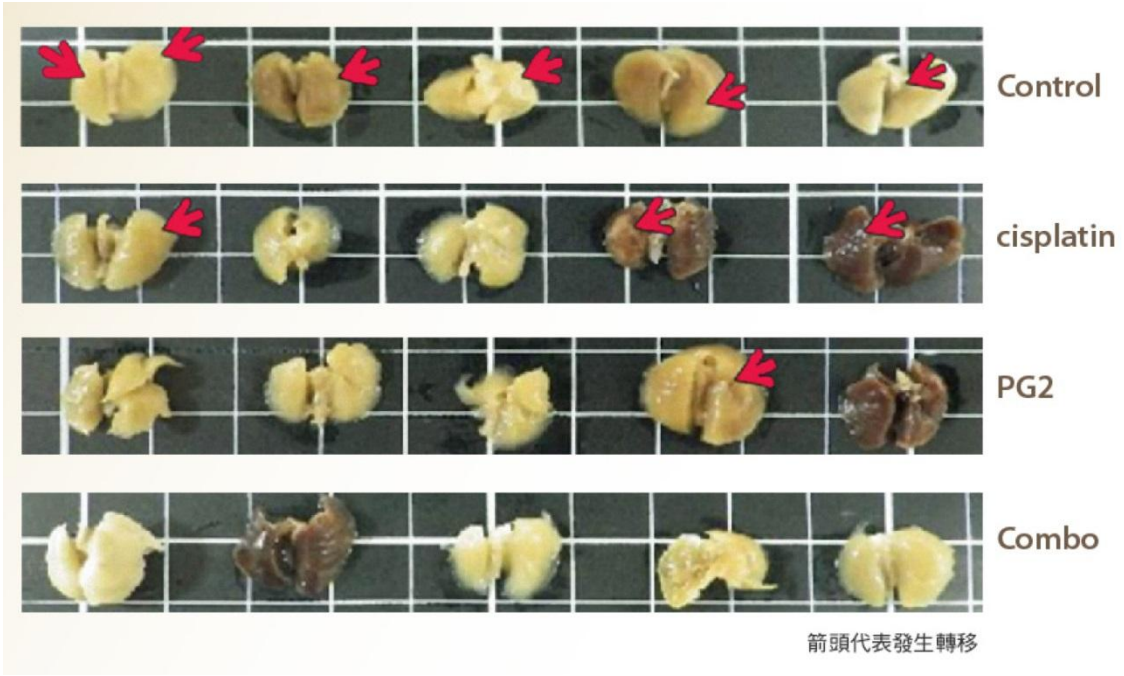




Photo images show the effect of cisplatin and/or PG2 on metastasis in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

*ns, not significant; *p < 0.05, **p < 0.01; DMSO, dimethyl sulfoxide*

(17 weeks, and/or cisplatin in syngeneic LLC1 tumor-bearing C57BL/6 mice)

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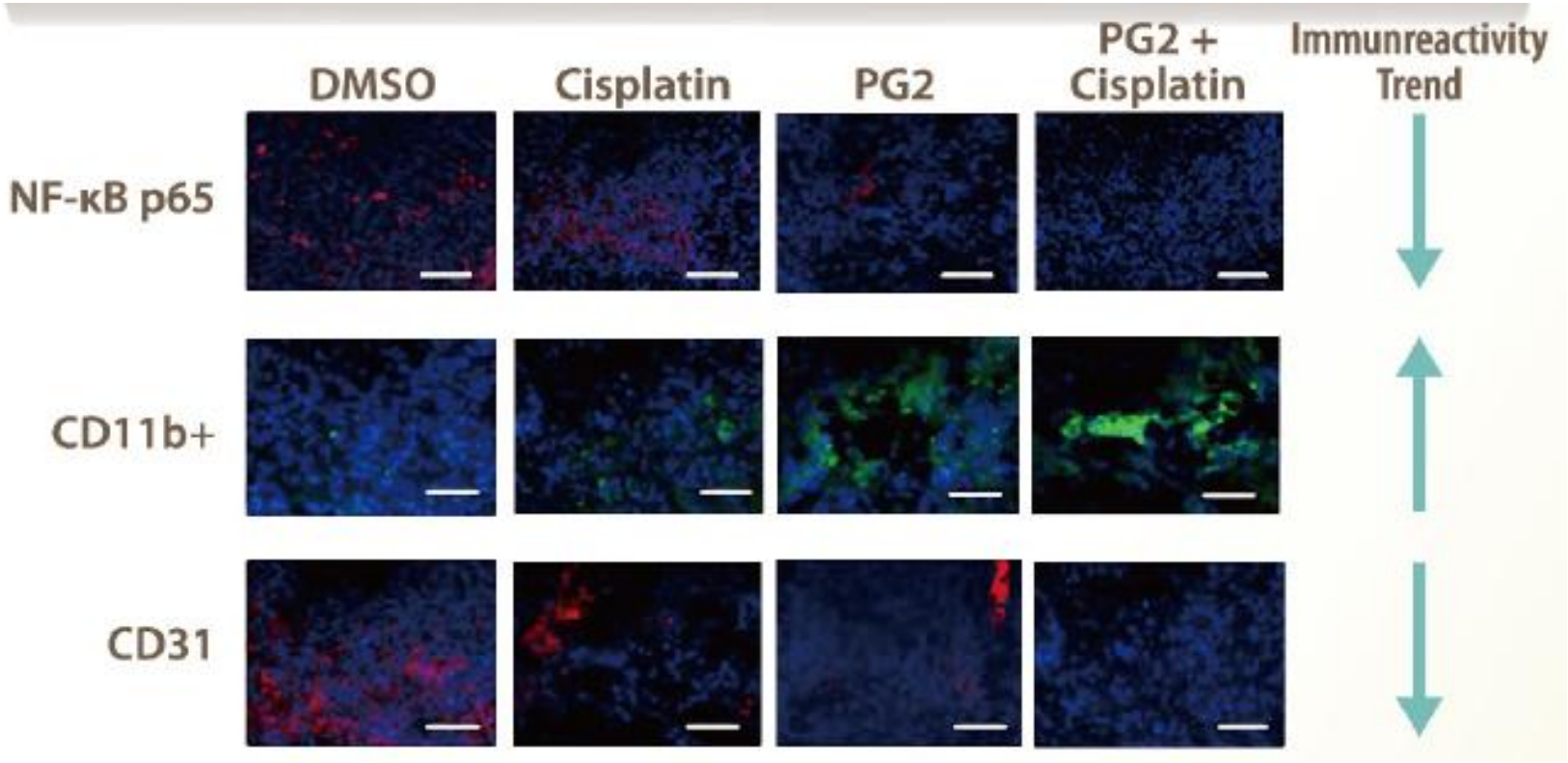
# Regulating Tumor Micro-environment

**Combining cisplatin with PG2 significantly inhibited NF-κB and CD31 expression in the tissue specimen**



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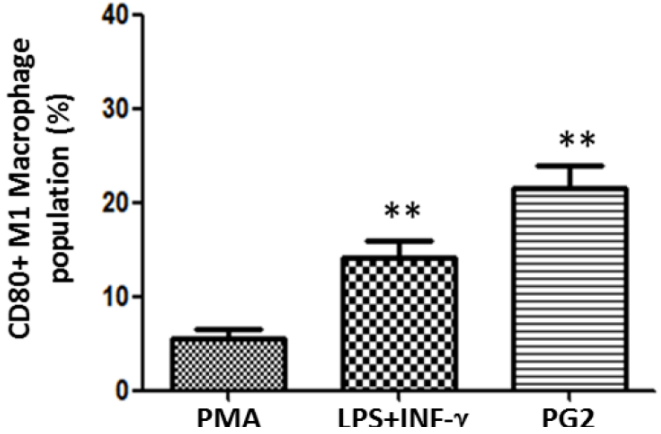
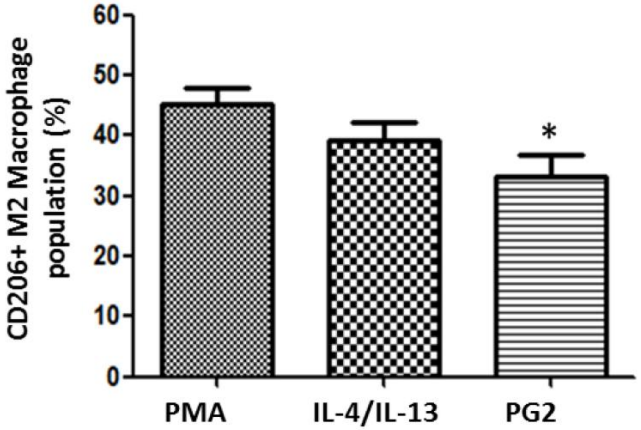
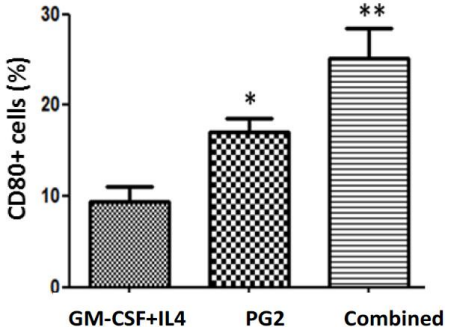
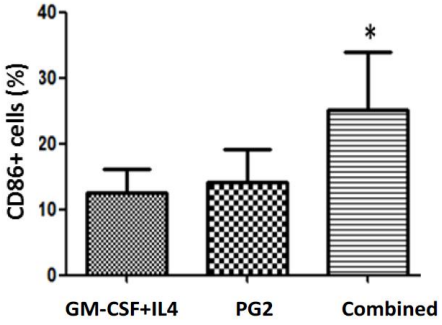
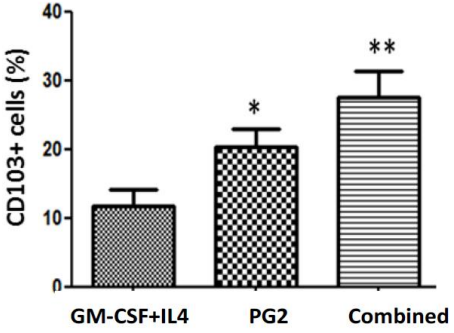
# PG2 Facilitates T cell Activation, M1 Differentiation to DCs, and Maturation of DCs to mDCs of PBMCs from NSCLC Patients.



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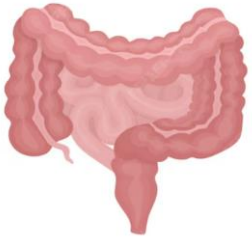
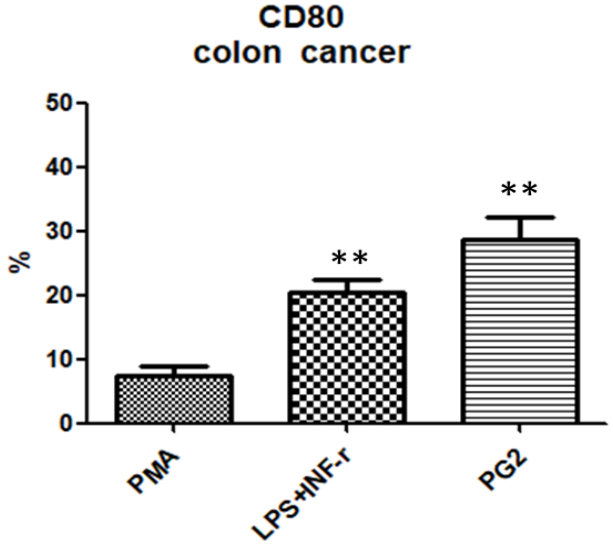
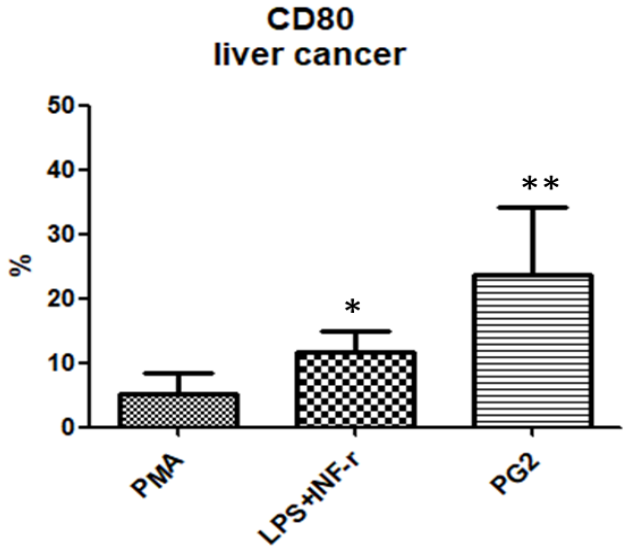
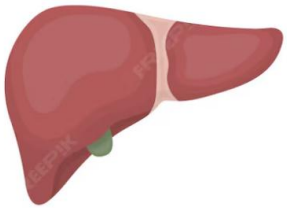
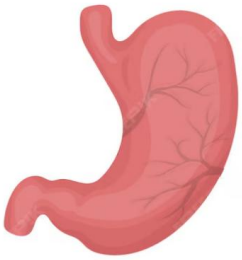
# PG2 modulated the population of CD80+ M1 macrophages derived from PBMCs of different type of cancer patients

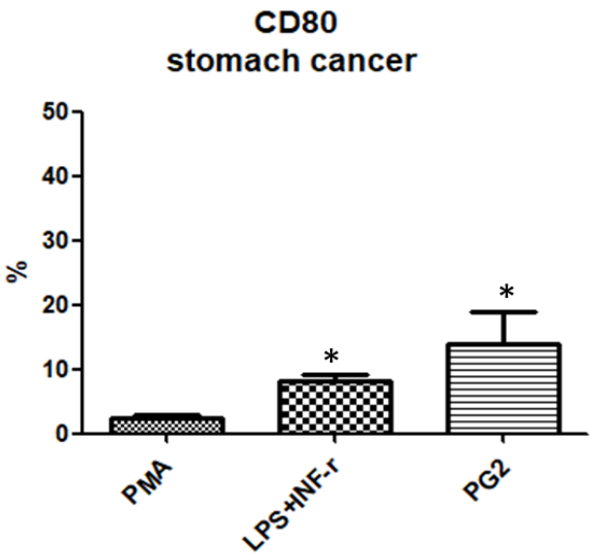


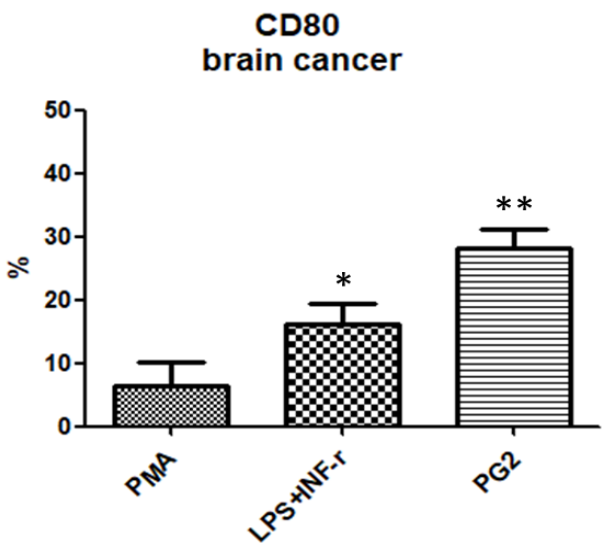







# Summary - Part 2

- **A therapeutically-relevant role for PG2 in modulating the M1/M2**
  - ✓ The treatment with PG2 elicited significant depletion of the tumor-associated M2 population.
  - ✓ Associated with cell migration and tumorspheres grown
  - ✓ Applicable on PBMCs from patients
- **Additionally/Synergistically enhanced the anticancer effect of chemotherapeutic agent, cisplatin**
  - ✓ Inhibited tumor growth and metastasis *in vivo*
  - ✓ In the presence of PG2, cisplatin-associated dyscrasia and weight-loss was markedly suppressed

# Outline

- PG2 Attenuates the Migration and Invasion of LAC Cells in Vivo & in Vitro
- PG2 Enhances Anti-tumor Effects of Cisplatin by Modulating Anti-cancer Immune Responses
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- PG2 AND Immune Checkpoint Inhibitors

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*International Journal of Medical Sciences*

2020; 17(7): 939-945. doi: 10.7150/ijms.42978

Research Paper

# The extracts of *Astragalus membranaceus* overcome tumor immune tolerance by inhibition of tumor programmed cell death protein ligand-1 expression

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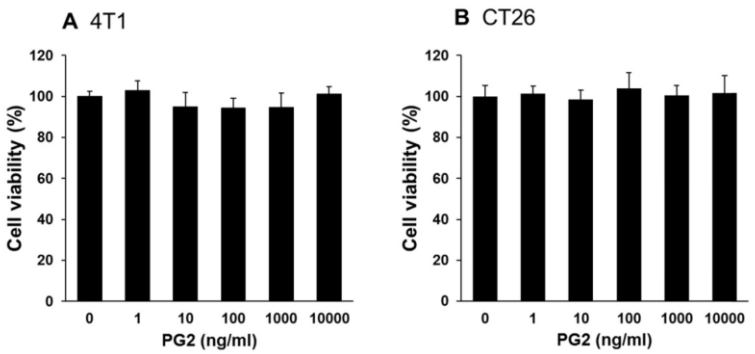
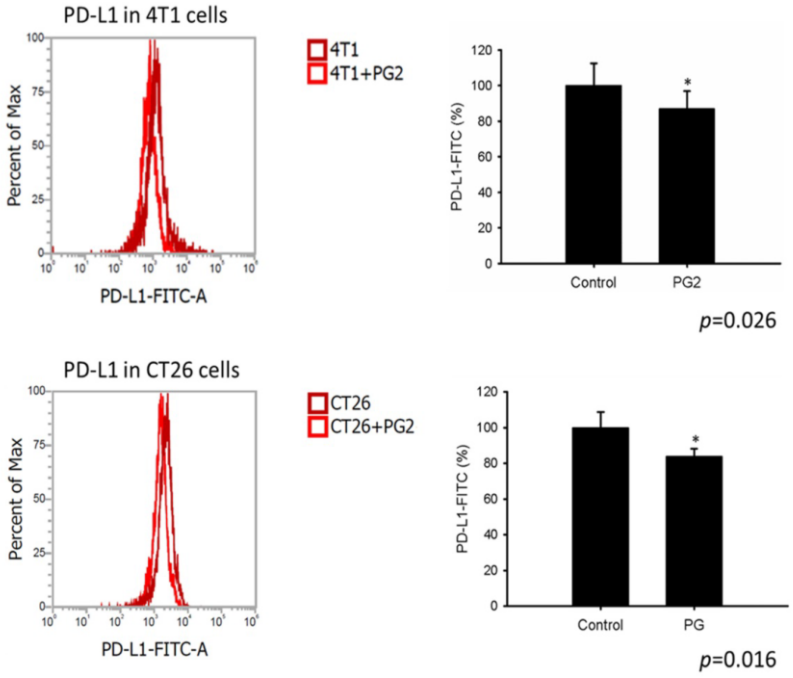



**PG2 reduced PD-L1 protein expression on the surface of 4T1 and CT26 cells after treatment with PG2 (10 μg/ml) for 24 h.**



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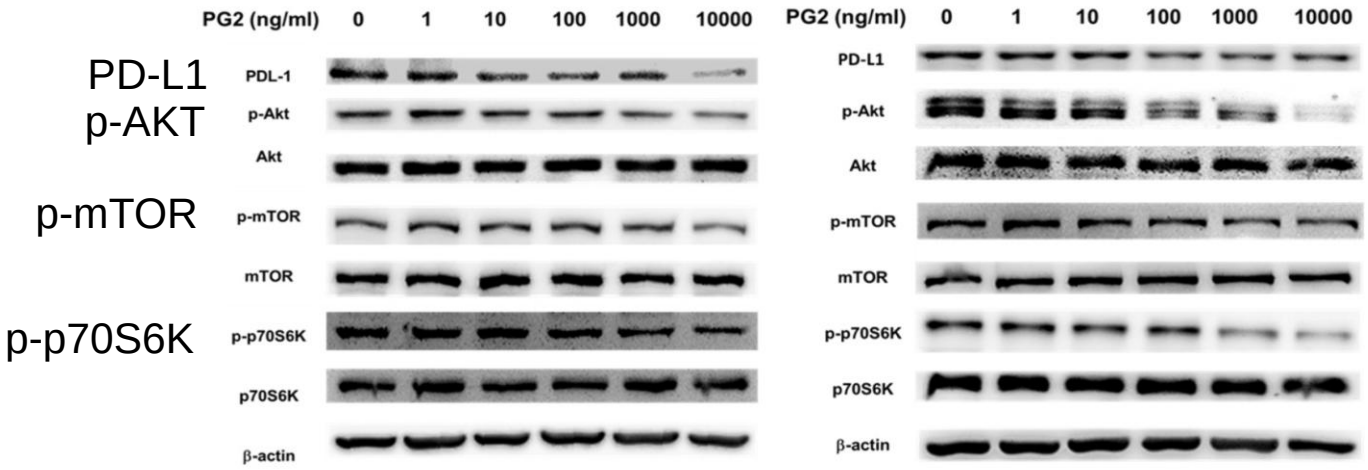
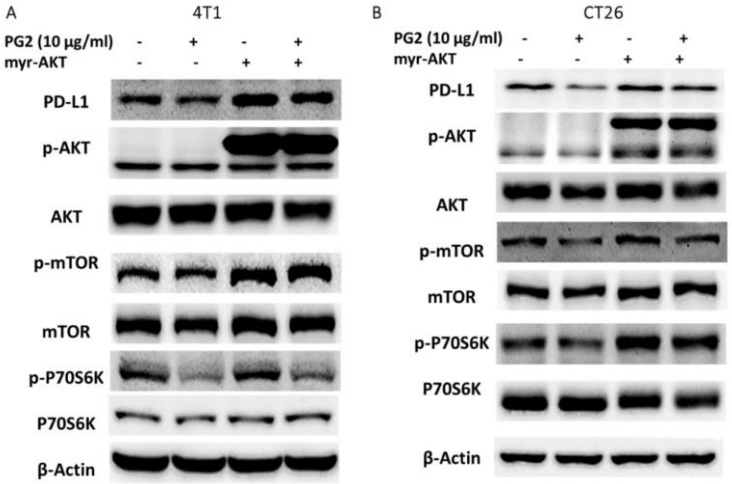
The extracts of *Astragalus membranaceus* overcome tumor immune tolerance by inhibition of tumor programmed cell death protein ligand-1 expression

# PG2 reduced PD-L1 expression and AKT/mTOR/p70S6K signaling pathways in a dose-dependent manner.




# PG2 reduced PD-L1 expression via downregulation AKT signaling pathway

Overexpression



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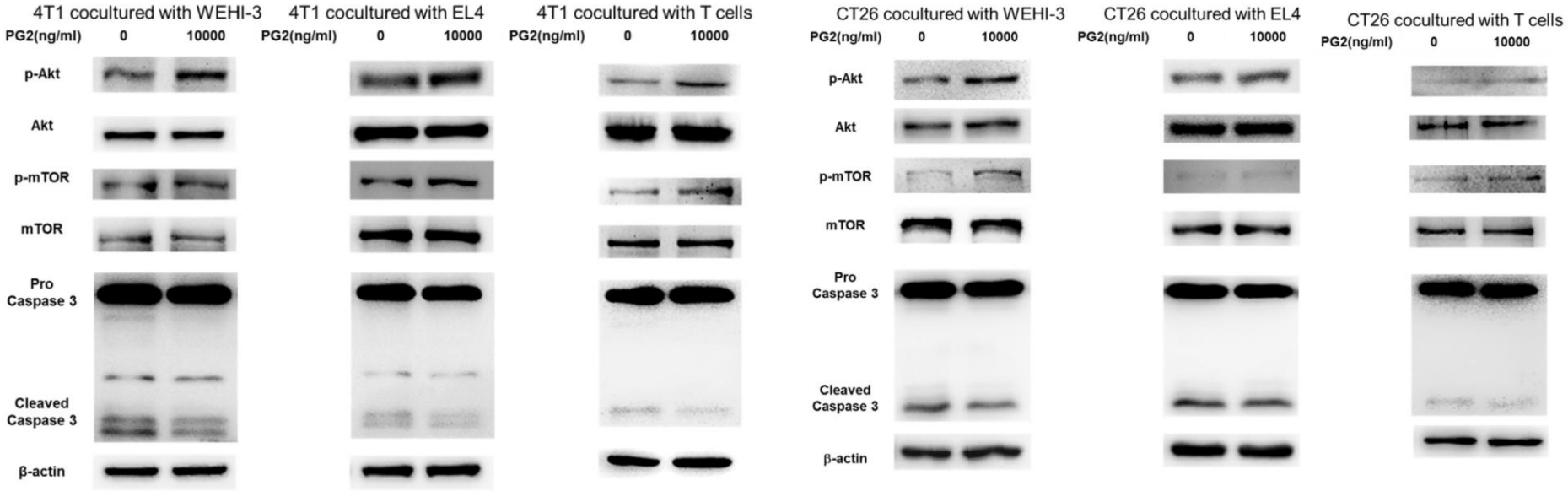
The extracts of *Astragalus membranaceus* overcome tumor immune tolerance by inhibition of tumor programmed cell death protein ligand-1 expression

# PG2 enhances AKT/mTOR signaling and reduce apoptosis in immune cells.

WEHI-3 leukemia, Murine EL4 lymphoblast cells, primary murine T lymphocyte cells



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# Astragalus Polysaccharide Injection (PG2) Normalizes the Neutrophil-to-Lymphocyte Ratio in Patients with Advanced Lung Cancer Receiving Immunotherapy

**Shih Ming Tsao, PhD, MD[1], Tz Chin Wu, PhD, MD[1], JiZhen Chen, Msc[2], Feichi Chang, BS[1], and Thomos Tsao, PhD, MD[1]**

**Abstract**

**Objectives:** The neutrophil-to-lymphocyte ratio (NLR) is a prognostic marker in patients with cancer receiving immunotherapy. Recent studies have shown that a high NLR was associated with a poor response and decreased survival. However, there is no intervention to reverse abnormally high NLR and improve clinical outcomes. Astragalus polysaccharide injection (PG2) is an immunomodulatory therapy for cancer-related fatigue. This study aimed to examine whether PG2 might normalize the NLR and affect the overall survival of patients with lung cancer treated with immunotherapy. **Materials and Methods:** We retrospectively examined the medical records of patients with lung cancer treated with immune checkpoint inhibitors (ICIs) between October 1, 2015 and November 30, 2019. All patients received ICI combination chemotherapies, and some similarly received PG2 (Control vs PG2). The NLR was assessed before treatment and 6 weeks after ICI initiation, and the survival data was collected at least 4 years after treatment initiation for the first enrolled patient. **Results:** Fifty-three patients were included. Six weeks after ICI initiation, 91.3% of the patients in the PG2 group exhibited a predefined "Decrease or no change" in the NLR, which was 28% higher than that in the Control group (63.3%) ($P = .028$). The NLR significantly decreased by 31.60% from baseline in the PG2 group ($P = .012$), whereas it increased by 5.80% in the Control group ($P = .572$). Six weeks after ICI treatment initiation, both groups had a median NLR of 3.73, and the overall survival was also similar (PG2 vs Control, 26.1 months vs 25.4 months, respectively); however, the PG2 group had a higher median baseline NLR than the Control group (PG2 vs Control, 4.51 vs 2.81, respectively). **Conclusion:** This study demonstrated that PG2 could normalize the NLR in patients with lung cancer receiving ICI combination treatments.

Submitted August 31, 2020; revised December 24, 2020; accepted January 26, 2021

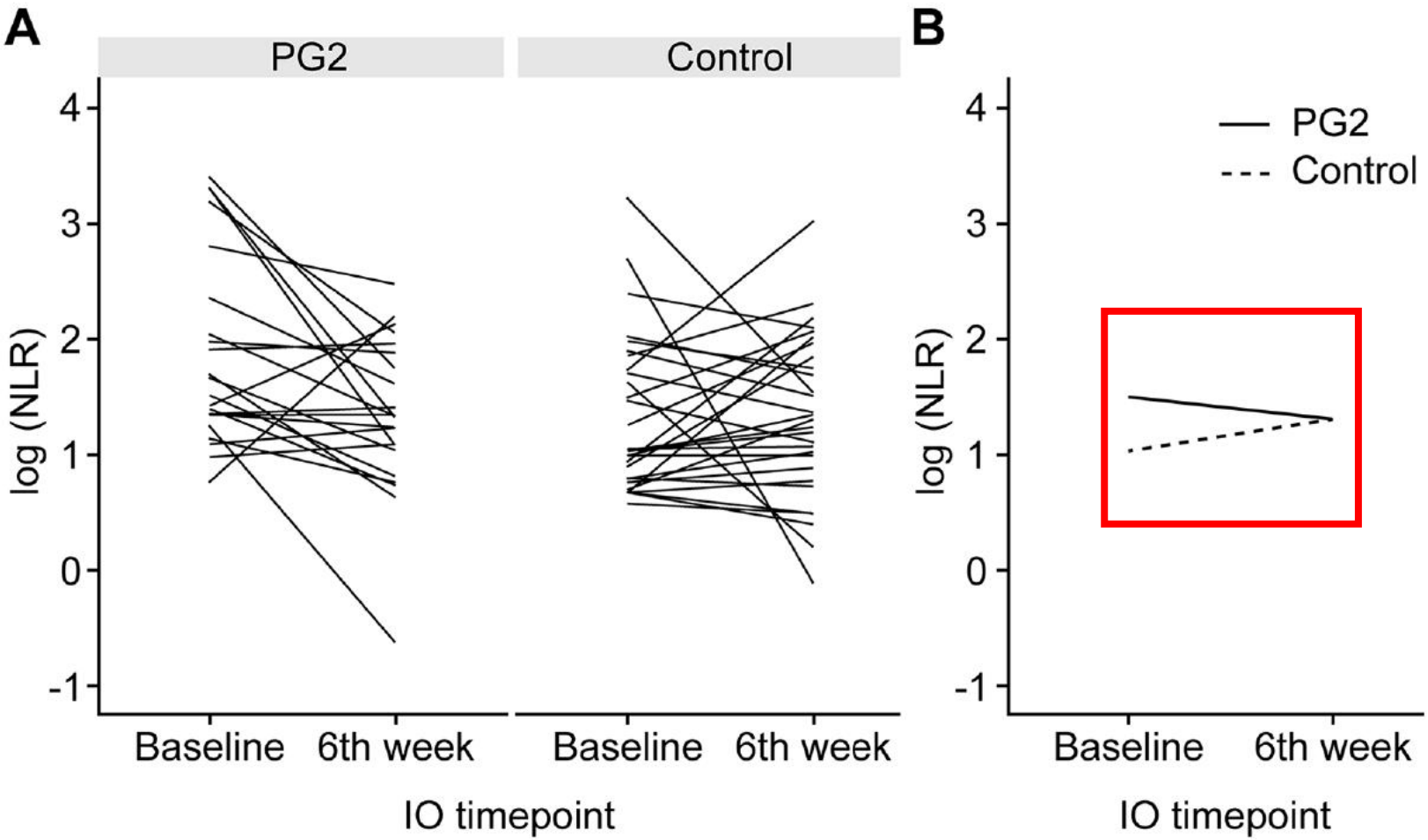
# PG2: Lung Cancer Patients with IO Therapy

**High NLR** was associated with a **poor response and decreased survival** → Examine whether PG2 might **normalize the NLR** and affect the overall survival of patients with lung cancer treated with immunotherapy.

| | |
|---|---|
| **Site** | Chung Shan Medical University Hospital |
| **Collection Period** | 2015/10~2019/11 |
| **IO Therapy** | ICI +/- chemo |
| **Groups** | 1) **PG2 group**: PG2 combined with IO Therapy<br>2) **Control group**: IO Therapy alone |
| **Study Timepoints** | Baseline：within 3 days prior to initiation of IO<br>$6^{th}$ week： 6±2 weeks after baseline |
| **Primary Endpoint** | NLR change (**all patients, baseline NLR ≥5 and <5**)<br>• **Decrease or no change**: The NLR decreased or increased <25% from baseline.<br>• **Increase**: The NLR increased ≥ 25% from baseline. |

*Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.*

| | PG2 (N = 23) 23 | Control (N = 30) 30 | *P* value* |
|---|---|---|---|
| Age at immunotherapy (y) | | | |
| Median (range) | 66 (44-81) | 61.5 (48-89) | .148 |
| Sex (N, %) | | | .747 |
| Male | 18 (78.3%) | 22 (73.3%) | |
| Female | 5 (21.7%) | 8 (26.7%) | |
| Smoking status (N, %) | | | .387 |
| Never-smoker | 9 (39.1%) | 8 (26.7%) | |
| Current or ex-smoker | 14 (60.9%) | 22 (73.3%) | |
| ECOG performance status (N, %) | | | .431 |
| 1 | 14 (60.9%) | 22 (73.3%) | |
| 2 | 8 (34.8%) | 8 (26.7%) | |
| 3 | 1 (4.4%) | 0 (0.00%) | |
| Histology (N, %) | | | .352 |
| Adenocarcinoma | 13 (56.5%) | 19 (63.3%) | |
| Squamous cell | 5 (21.7%) | 9 (30.0%) | |
| Others (Small cell, LELC) | 5 (21.7%) | 2 (6.7%) | |
| Stage (N, %) | | | .845 |
| II | 0 (0.0%) | 1 (3.3%) | |
| III | 4 (17.4%) | 7 (23.3%) | |
| IV | 19 (82.6%) | 22 (73.3%) | |
| Previous lines of systemic treatment (N, %) | | | .769 |
| 1 | 9 (39.1%) | 10 (33.3%) | |
| ≥2 | 14 (60.9%) | 20 (66.7%) | |
| PD-L1 positivity (N, %) | | | .751 |
| <1, Negative | 7 (30.4%) | 7 (23.3%) | |
| 1-49% | 5 (21.7%) | 4 (13.3%) | |
| ≥50% | 4 (17.4%) | 7 (23.3%) | |
| Unknown | 7 (30.4%) | 12 (40.0%) | |
| Metastasis | | | |
| Liver | 4 (17.4%) | 2 (6.7%) | |
| Brain | 11 (47.8%) | 5 (16.7%) | |
| Bone | 15 (65.2%) | 12 (40.0%) | |
| Other: lymph node, adrenal gland, pleura | 9 (39.1%) | 19 (63.3%) | |




Change in the NLR before and 6 weeks after ICI initiation among all patients.
(A) Each line represents the data for an individual patient.
(B) The **median** of the 2 groups.

Abbrev. ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio.

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# Distribution of the change in the NLR 6 weeks after ICI initiation

**Patients with lung cancer who received combination therapy with PG2 and ICIs had a stable or decreased NLR 6 weeks after treatment initiation**

**PG2 組維持NLR穩定的人數比例顯著高於Control 組**

| Population | Classification | PG2 | | Control | | p value‡ |
|---|---|---|---|---|---|---|
| | | N | (%) | N | (%) | |
| All Patients N = 53 | Decrease or no change* | 21 | (91.3%) | 19 | (63.3%) | 0.028 |
| | Increase† | 2 | (8.7%) | 11 | (36.7%) | |
| Baseline NLR ≥5 N = 21 | Decrease or no change* | 11 | (100%) | 8 | (80.0%) | 0.214 |
| | Increase† | 0 | (0%) | 2 | (20.0%) | |
| Baseline NLR <5 N = 32 | Decrease or no change* | 10 | (83.3%) | 12 | (60.0%) | 0.139 |
| | Increase† | 2 | (16.7%) | 8 | (**40.0%**) | |

Abbreviations: ICI: immune checkpoint inhibitors; NLR, neutrophil to lymphocyte ratio

*Decrease or no change: The NLR decreased or increased <25% from baseline.

†Increase: The NLR increased 25% from baseline.

‡Chi-square test or Fisher Exact test

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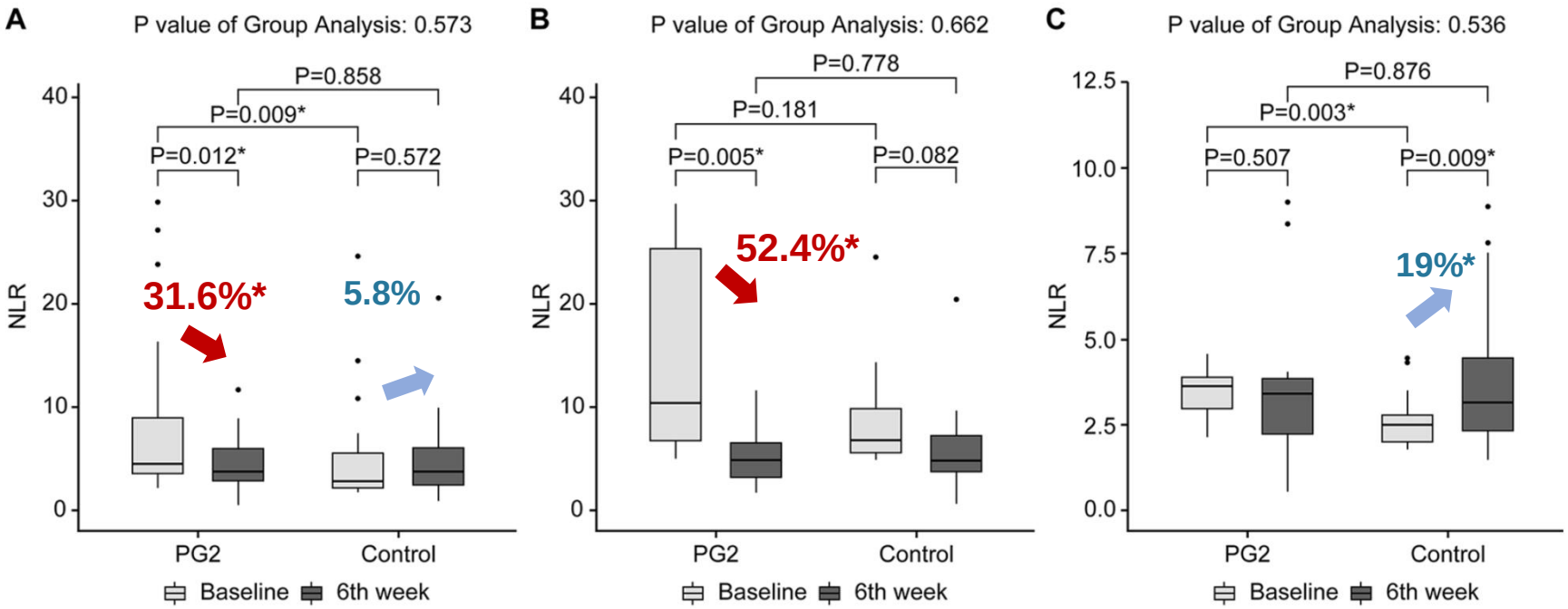
# NLR at baseline and 6 after ICI initiation




**(A) All patients. (B) Patients with a baseline NLR ≥ 5. (C) Patients with a baseline NLR <5.**

(Mann–Whitney tests: *P < .05.)

**(A) The NLR value of the PG2 group at the 6th week was significantly decreased from baseline (-1.92, p = 0.012), while that of control group was slightly increased from baseline (0.13, 5.8%).**

**(B) In the subgroup of baseline NLR≧5, the NLR values had a statistically significant decrease in the PG2 group (-4.8, p=0.005), but had no significant change in the control group after 6 weeks of ICIs treatment.**

(C) The NLR values had slightly increased in the PG2 group (P=0.507) , but notably increased by 19% after 6 weeks of treatment in the control group (0.52, p=0.009).

Abbrev. ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio.

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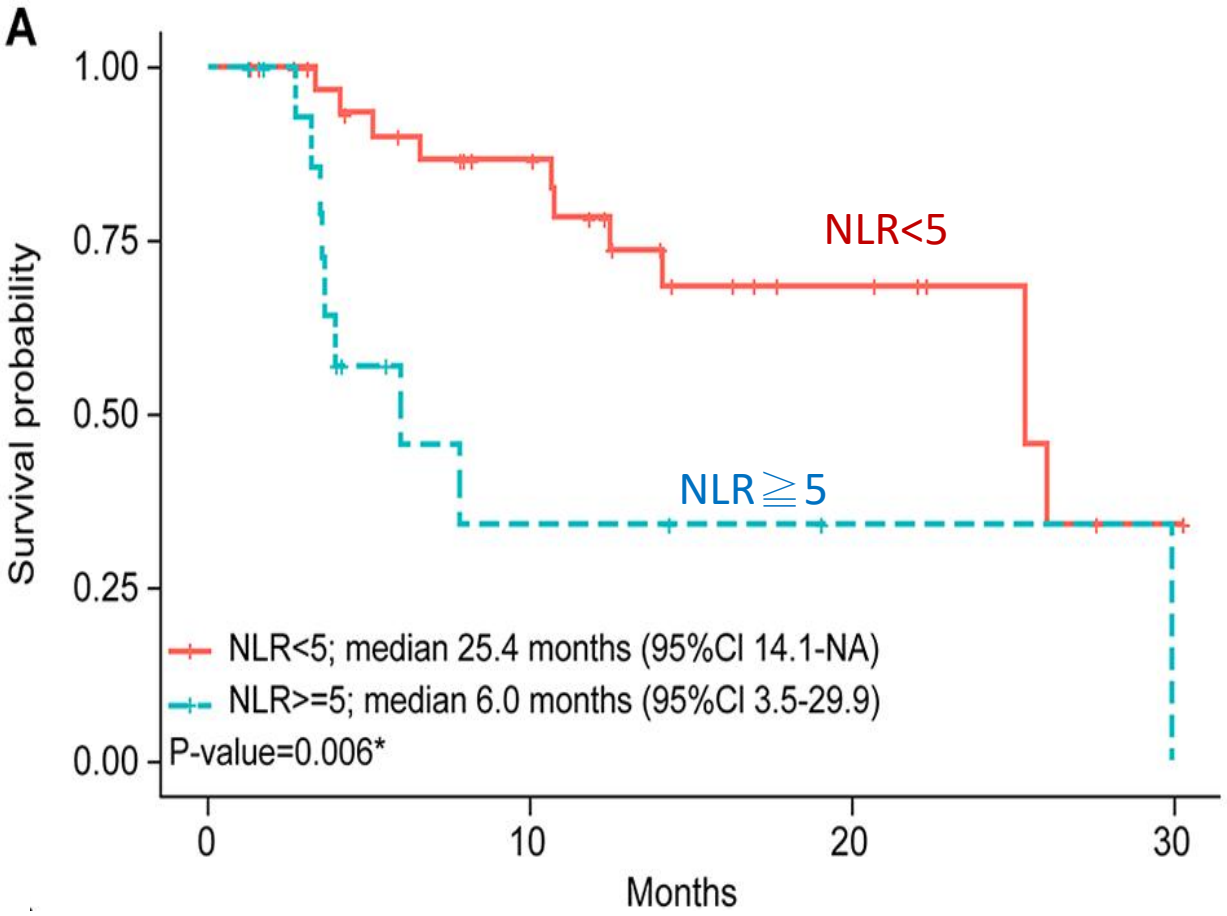
# Overall survival：Patients with a baseline NLR ≥5 vs. <5.




Patients with a high NLR (≥ 5) at 6 weeks had a significantly shorter OS than those with a low NLR (<5) (*p=0.009)*.

**As PG2 stabilizes or decreases the NLR, might promote the antitumor immune effect created by immunotherapy?**

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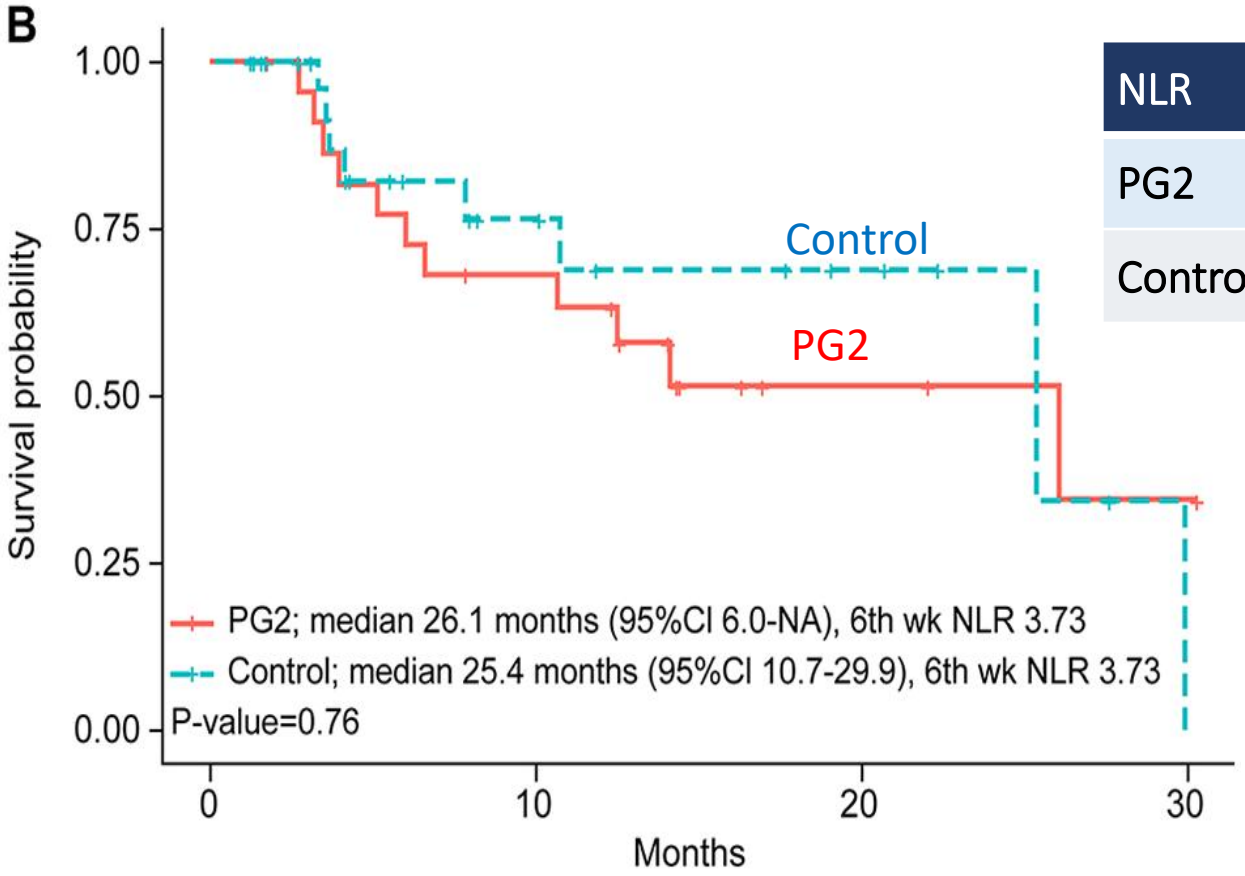
# Overall survival：Patients in PG2 vs. Control group




| NLR | Baseline | 6-wk | OS |
|---|---|---|---|
| PG2 | 4.51 ➡ | 3.73 | 26.1 M |
| Control | 2.81 ➡ | 3.73 | 25.4 M |

- **There were no statistically significant differences between two group (p=0.76).**

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# Summary - Part 3

- **PG2 reduced PD-L1 expression of cancer cells**
  - ✓ Downregulation AKT signaling pathway of cancer cells
  - ✓ Enhances AKT/mTOR signaling and reduce apoptosis in immune cells

- **PG2 might normalize the NLR of patient receiving ICIs**
  - ✓ Especially the group with NLR>5 before treatment
  - ✓ Unknown correlation with overall survival

# Conclusion

- PG2 Attenuates the Migration and Invasion of LAC Cells in Vivo & in Vitro
- PG2 Enhances Anti-tumor Effects of Cisplatin by Modulating Anti-cancer Immune Responses
  - modulating the M1/M2 and related DC differentiation
- PG2 Downregulates PD-L1 Expression and NLR (Neutrophil-to-Lymphocyte Ratio) of Patients with ICI Therapy

# Thank You!