乳癌病人癌因性疲憊症治療經驗分享

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高雄醫學大學附設醫院

11:00-11:50 2022/08/27

幫助病患改善癌因性疲憊

- 92% 台灣癌症患者罹癌期間有疲憊問題，1/4 癌症病患有中重度疲憊
  - ✓ 癌因性疲憊症之ICD-10 code：R53.0
- 癌症病患應在初診和回診時，接受規律性疲憊評估
  - ✓ 住院患者為每日評估，門診患者則每次回診時評估
- 癌症病患依疲憊嚴重程度給予相對應的治療，治療後再評估疲憊程度
  - ✓ 輕度：非藥物治療，VAS≧4中重度：加上藥物治療
- 台灣癌因性疲憊症臨床指引建議：中度以上癌因性疲憊症之具適應症藥物為黃耆多醣注射劑(PG2)。
- 合併使用黃耆多醣注射劑(PG2)，可改善癌症患者之疲憊症，使癌症療程能順利完成。

什麼是 CANER RELATED FATIGUE ?

癌因性疲憊的定義：NCCN, ICD-10

美國國家綜合癌症網絡[1] (National Comprehensive Cancer Network, NCCN)

與癌症或癌症治療相關而且和近期活動量不成比例的疲累感，
具有持續、令人感到不適、而主觀的特性，且足以影響正常生活

國際疾病分類第 10 版 (ICD-10)[2]

符合 A–D 四大要件

A. 症狀	B. 影響生活	C. 引起原因	D. 排除
最近一個月至少有**連續兩週**期間，每天或幾乎每天出現**至少六項 A1–A11 的症狀** (A1 為必需)。	疲累不堪的感覺會**干擾**到職場工作、家務處理、或人際互動。	病歷、身體檢查、或生化檢查有記錄顯示疲憊症狀為**癌症或癌症治療所引起**。	疲憊**不是由精神共病**（如重度憂鬱、身體化疾患、心身症、或譫妄）所引起。

1. NCCN. NCCN Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue, Version 2.2020.
2. Yeh ET et al. BMC Cancer 2011; 11:387.

癌因性疲憊的定義: ICD-10

A

最近**一個月至少有連續兩週**期間，每天或幾乎每天出現**至少六項 A1-A11 的症狀**（A1 為必需）

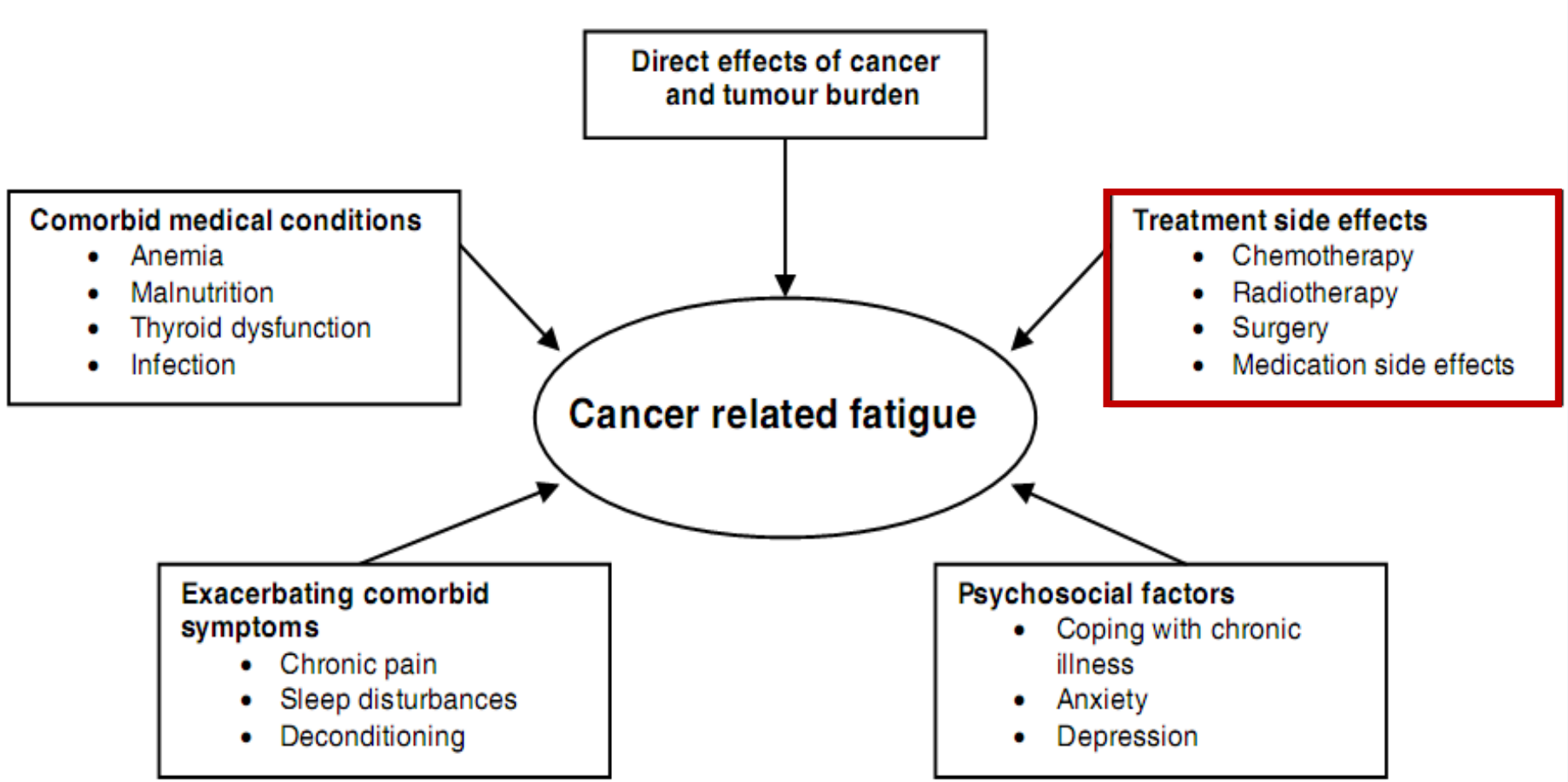
ICD-10 Code:
R53.0

國際疾病分類第10版 (ICD-10)[1]

A1 感到明顯的疲累、缺少活力、或需要增加休息，且與近期活動程度不成比例
A2 感到**全身**虛弱、沉重
A3 感到很**難集中精神**或注意力
A4 感到平常習慣做的事都變得**乏味**而不想去做
A5 感到**難以入睡**、睡得不安穩、早起有困難、或是睡得太多
A6 感到**睡覺起來還是覺得疲累**，精神沒有恢復
A7 感到做什麼事情都必須經過一番掙扎，**勉強**自己去做
A8 因為疲累而感到**悲傷**、失意、或煩躁
A9 因為疲累不堪而事情做一半就**做不下去**了
A10 感到**記性變差**
A11 只要做了**費力的事**就會**持續感到病懨懨、不舒服**

Yeh ET et al. BMC Cancer 2011; 11:387.

癌因性疲憊症



British Journal of Cancer (2004) 91, 822–828

Fatigue in Different Adjuvant Chemotherapy Regimens Had the same pattern Over Time

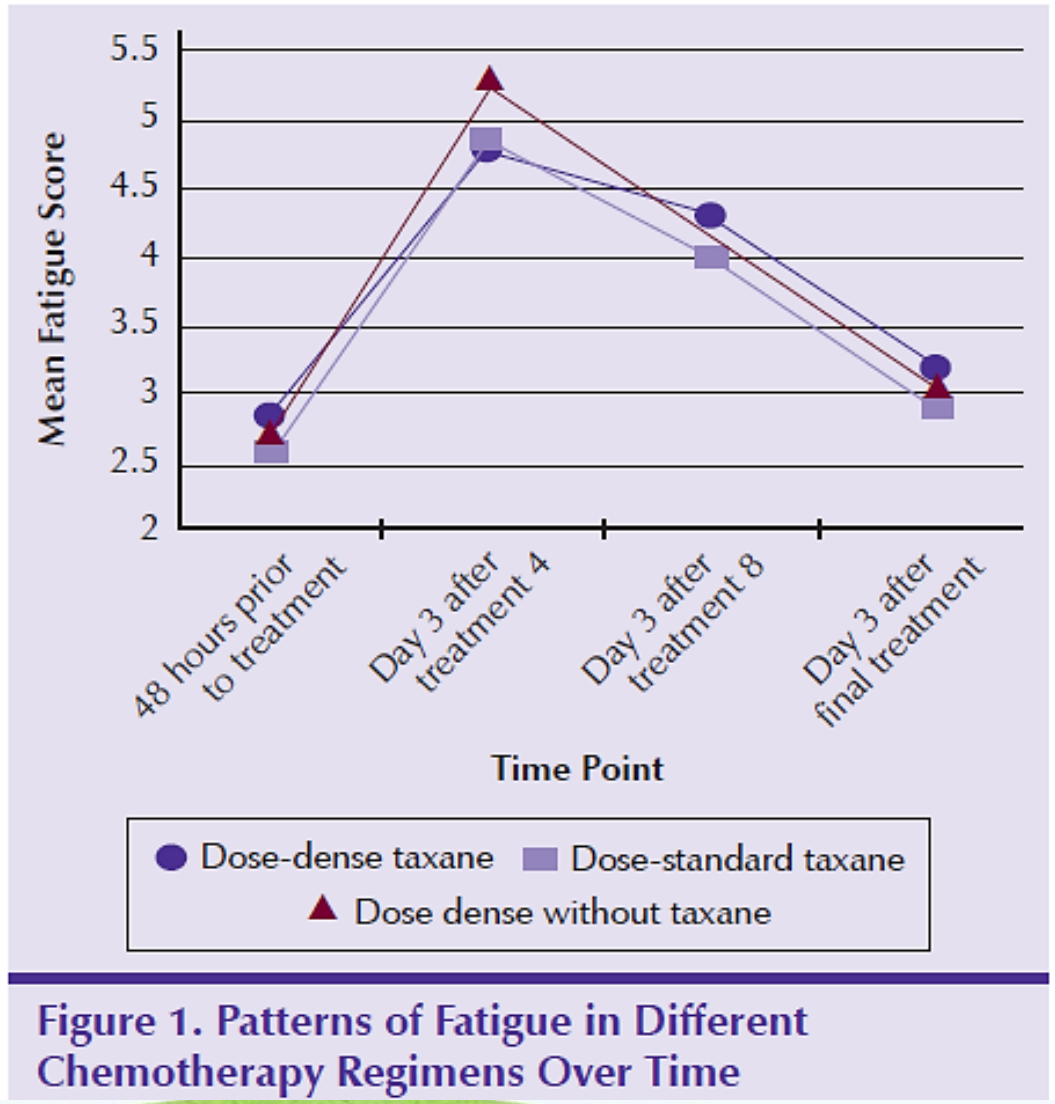


Figure 1. Patterns of Fatigue in Different Chemotherapy Regimens Over Time

- Participants rated their fatigue **highest at treatment 4**.
- Fatigue levels for all regimens **did not return to baseline levels by the 30-day measurement**.

Oncology Nursing Forum 2009; 36 (5): [7]
563-569

Fatigue is common at adjuvant chemotherapy for Breast Cancer

	Epirubicin, cyclophosphamide, and paclitaxel plus gemcitabine (n=1565)			Epirubicin, cyclophosphamide, and paclitaxel (n=1567)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	397 (25%)	323 (21%)	204 (13%)	364 (23%)	212 (14%)	200 (13%)
Myalgia and arthralgia	1140 (73%)	200 (13%)	7 (<1%)	1147 (73%)	175 (11%)	11 (1%)
Fatigue	1254 (80%)	198 (13%)	9 (1%)	1287 (82%)	140 (9%)	12 (1%)
Infection	578 (37%)	194 (12%)	8 (1%)	601 (38%)	131 (8%)	10 (1%)
Vomiting	786 (50%)	134 (9%)	9 (1%)	736 (47%)	101 (6%)	7 (1%)
Nausea	1271 (81%)	132 (8%)	0	1255 (80%)	102 (7%)	0

Table 3. Frequency of Patient-Reported Adverse Events During Chemotherapy

	No. of Patients (%)										
	EC-D (n = 994)					DC (n = 1,006)					
Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	*P*
Nausea	103 (10)	465 (47)	340 (34)	71 (7)	7 (1)	255 (25)	552 (55)	182 (18)	11 (1)	4 (0)	< .001
Fatigue	8 (1)	255 (26)	427 (43)	249 (25)	48 (5)	33 (3)	290 (29)	436 (43)	225 (22)	20 (2)	< .001
Peripheral edema	387 (39)	464 (47)	110 (11)	25 (3)	—	334 (33)	463 (46)	181 (18)	26 (3)	—	< .001

J Clin Oncol. 2017 Aug 10;35(23):2639-2646
Lancet Oncol. 2017 Jun;18(6):755-769.

隨著癌症多種合併治療的進行，可預測患者發生重度疲憊的風險更高

整合分析12,327位乳癌存活者，1/4病患在癌症治療後有重度疲憊

Table 3. Risk factors of severe fatigue in breast cancer survivors

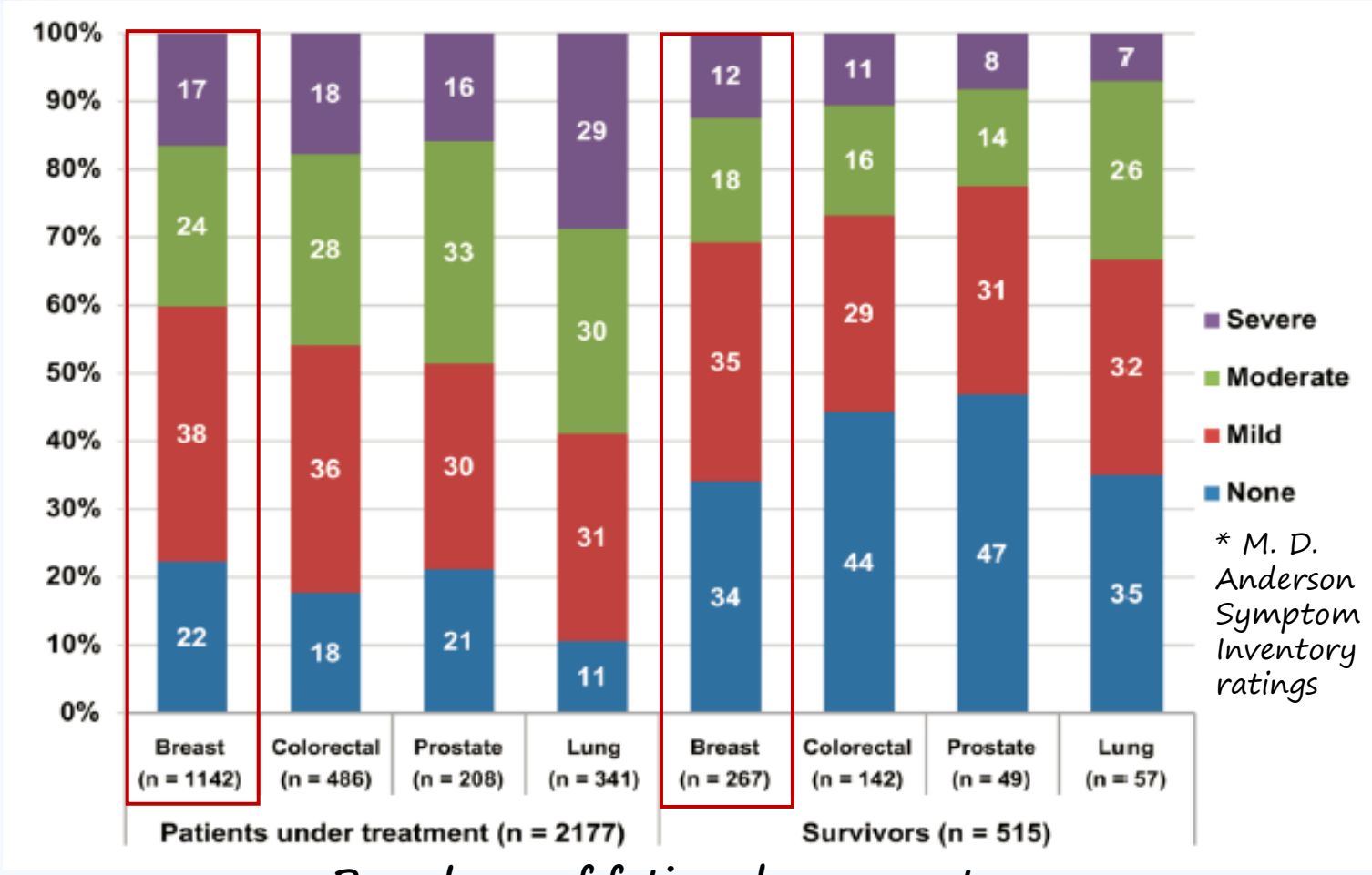
Variables	References	Number of studies	Sample size (*N*)	Risk ratio (CI)
Treatment combinations				
SU	[26, 38, 42, 45, 47, 56, 57]	6	3028	0.83 (0.70 to 0.98)*
SU + CT	[32, 38, 42, 47, 55–57]	7	3379	1.33 (0.97 to 1.82)
SU + RT	[26, 32, 38, 45–48, 50, 55–57]	11	4164	0.87 (0.78 to 0.96)*
SU + HT	[38, 42, 45–47]	4	981	0.83 (0.57 to 1.20)
SU + CT + RT	[26, 32, 38, 45–48, 55–57]	10	3882	1.18 (1.05 to 1.33)*
SU + CT + HT	[38, 42, 45–47]	4	981	0.99 (0.66 to 1.49)
SU + RT + HT	[26, 38, 45–48]	6	1264	0.89 (0.74 to 1.07)
SU + CT + RT + HT	[26, 38, 45–48]	6	1264	1.38 (1.15 to 1.66)*

*$P < 0.05$.

SU, surgery; CT, chemotherapy; RT, radiotherapy; HT, hormone therapy; SMD, standardized mean difference; SD, standard deviation.

Abrahams HJ et al. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. Ann Oncol. 2016 Jun;27(6):965-74.

High prevalence of moderate/severe fatigue in both actively treated cancer patients & survivors



Prevalence of fatigue by cancer type

Wang et al. Prevalence and characteristics of moderate-to-severe fatigue: a multicenter study in cancer patients and survivors. Cancer. 2014; 120(3): 425–432.

癌因性疲憊症之臨床治療指引

MANAGEMENT OF CANCER-RELATED FATIGUE

– A GUIDELINE FOR TAIWAN –

2017年 11月 第一版

台灣癌症安寧緩和醫學會 台灣腫瘤護理學會

癌因性疲憊評估與治療

以VAS或BFI-T評估疲憊

<4分 輕度疲憊

非藥物治療

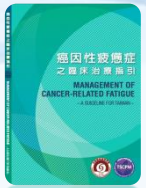
運動、營養飲食、認知行為治療、睡眠衛生等

≥4分 中重度疲憊

加上藥物治療

- 癌因性疲憊適應症處方用藥
  PG2 Injection
- 其他用藥
  類固醇、中樞神經 興奮劑

癌因性疲憊症之藥物治療



黃耆多醣注射劑有初步臨床試驗顯示可改善中重度癌因性疲憊症。 (Level IA, Grade A)	**蔘類**在臨床試驗顯示可以改善癌因性疲憊，但因中藥在使用上會因原料製備等影響，建議使用前應諮詢醫療團隊。 (Level IB, Grade B)
Methylphenidate 臨床研究顯示使用於疲憊程度或病情較嚴重的病人較具效果； 但在用藥前應審慎考量劑量、用藥時間、濫用風險、及病人個人疾病等臨床情形， 充分評估相關風險與效益。 (Level IA, Grade A)	**Methylprednisolone、dexamethasone**等類固醇藥物有臨床證據顯示可以改善癌症病人的疲憊和生活品質，但長期使用有安全風險， 故建議只用於癌症末期、合併疲憊與厭食症、或有腦部或骨骼轉移而疼痛的癌症病人。 (Level IB, Grade B)

癌因性疲憊治療適應症之處方用藥
PG2® Injection

- 成份：黃耆多醣 (Polysaccharides of *Astragalus membranaceus*)
  萃取物 500 mg ，不含任何賦形劑。
  分子量約20,000~60,000 Da

- 適應症：**治療癌症療程中所導致的中、重度疲憊症**

- 機轉：增強免疫功能及刺激骨髓造血功能

- 用法及用量：
  - 成人每次劑量 500 mg，
    以 2.5 - 3.5 小時點滴靜脈滴注。
  - 每週2 - 4次，使用2 - 4週。

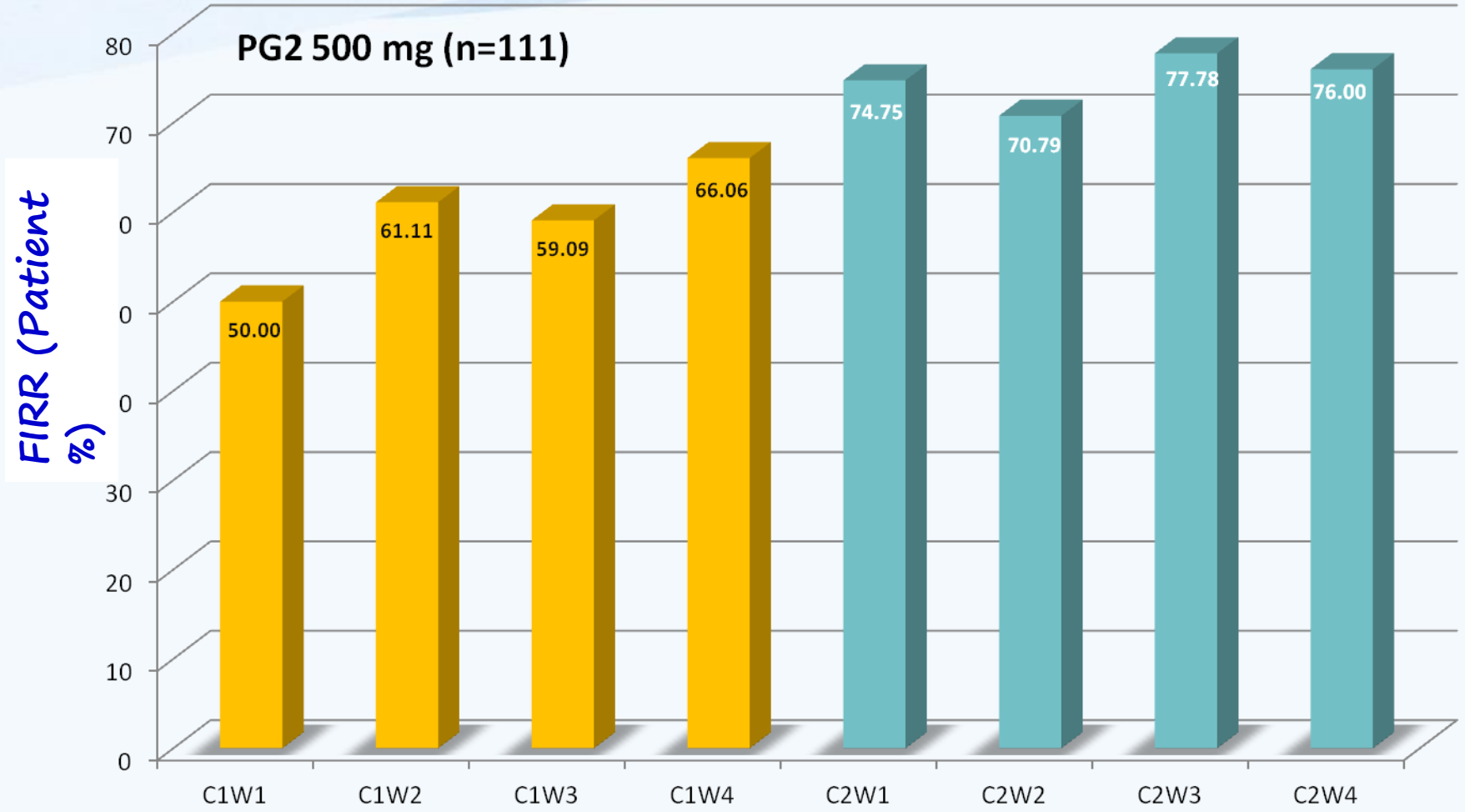
食品藥物管理署(TFDA)核准之第一個植物性處方用藥：**西藥藥證 衛部藥製字第058837號**

PG2 Phase IV Trial

Center	馬偕，雙和，基隆長庚情人湖院區，三總，彰基，奇美柳營，中醫大，林口長庚，高雄長庚
Trial Objective	To evaluate the **efficacy and safety** of different doses of PG2 for relieving fatigue among advanced cancer patients who are under standard palliative care (SPC).
Blinding/ Randomization	Double-blinded/Randomized
Population	Advanced progressive cancer patients with moderate to severe fatigue (**BFI Fatigue score ≥ 4**) under palliative care.
Treatment Regimens	Two parallel arms: (1:1 ratio) 1. PG2 500 mg by IV infusion for 3 days per week 2. PG2 250 mg by IV infusion for 3 days per week
Study Period	8 weeks
Primary Endpoint	Fatigue Improvement Response Rate (FIRR)
Sample Size	Enrolled Patient No.: 323 Evaluable Patient No.: 214

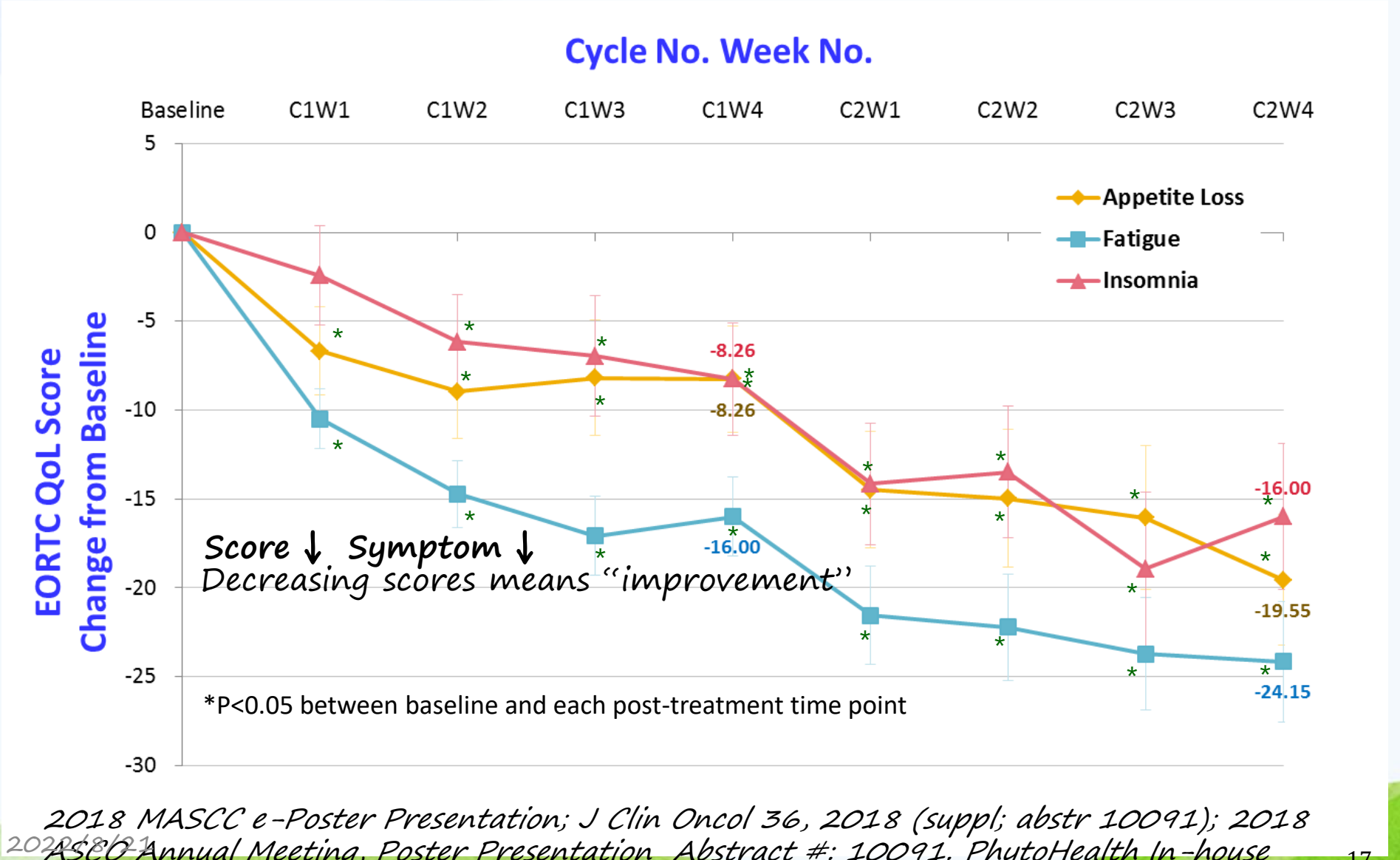
FIRR by Week during the Whole Study Period

Cut-off Point of FIR: 10 %



J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091. PhytoHealth In-house Data

Global Health Status: domains with significant improvement



2018 MASCC e-Poster Presentation; J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091. PhytoHealth In-house Data

cancers

MDPI

Article

Karnofsky Performance Status as A Predictive Factor for Cancer-Related Fatigue Treatment with Astragalus Polysaccharides (PG2) Injection—A Double Blind, Multi-Center, Randomized Phase IV Study

Cheng-Hsu Wang [1], Cheng-Yao Lin [2], Jen-Shi Chen [3,4], Ching-Liang Ho [5], Kun-Ming Rau [6,7,8], Jo-Ting Tsai [9,10], Cheng-Shyong Chang [11], Su-Peng Yeh [12], Chieh-Fang Cheng [13] and Yuen-Liang Lai [14,15,*]

Received: 22 October 2018; Accepted: 15 January 2019; Published: 22 January 2019

check for updates

Cancers **2019**, *11*, 128; doi:10.3390/cancers11020128 www.mdpi.com/journal/cancers

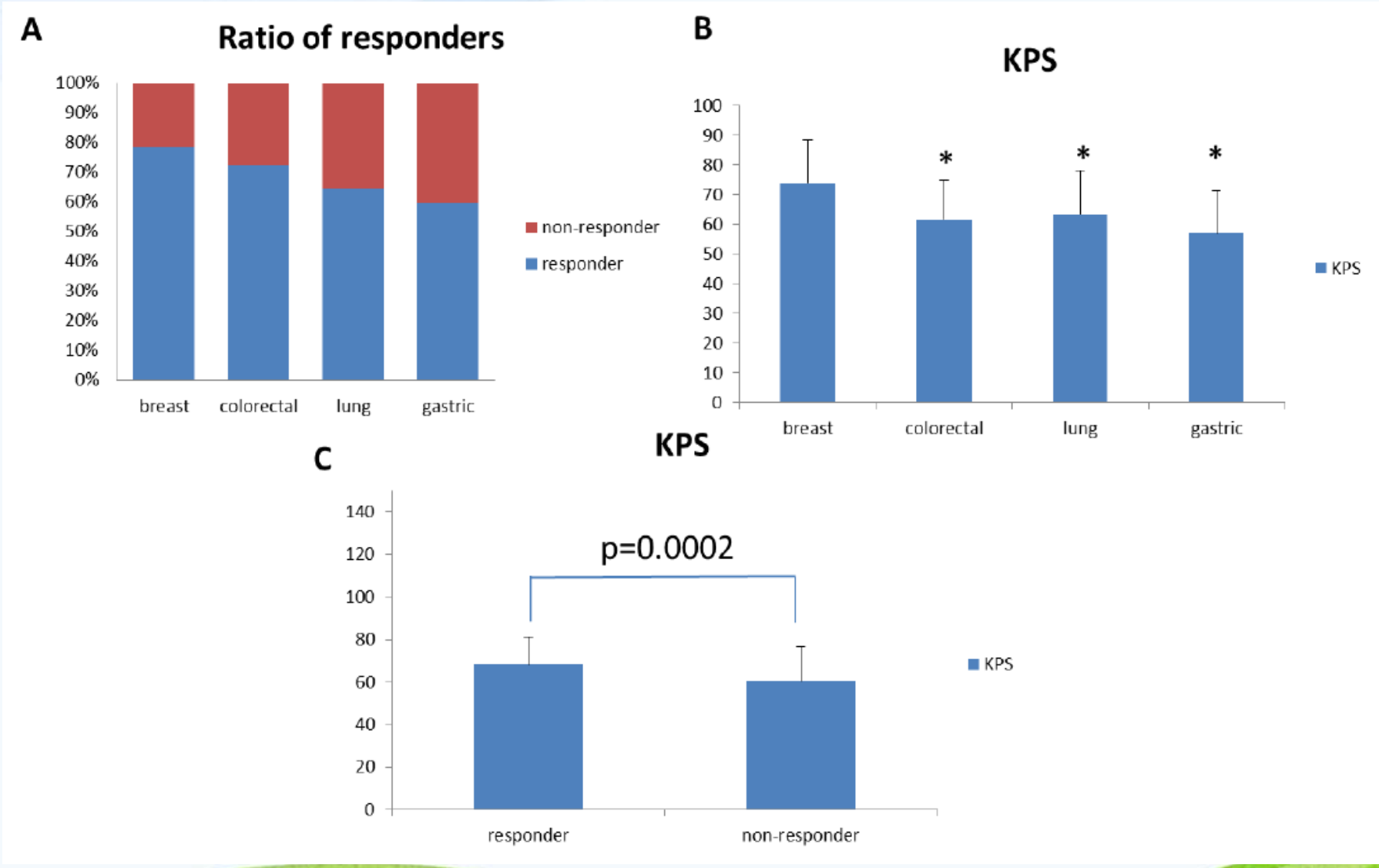
Cancers . 2019 Jan 22;11(2):128-140.

KPS vs. ECOG

ECOG		Karnofsky	
Normal activity fully ambulatory (無症狀)	0	100	Normal, no complaints(沒有任何抱怨，確定沒有疾病)
Symptoms, but nearly fully ambulatory (有症狀，但對生活無影響)	1	90	Able to carry on normal activities, Minor signs or symptoms of disease (可以正常活動，有一些疾病症狀)
		80	Normal activity with effort (可以稍微正常活動，已經有一些疾病的症狀)
Some bed time, but needs to be in bed less than 50% of normal daytime (躺在床上的時間<50%)	2	70	Cares for self. Unable to carry on normal activity or to do active work (需要自己照顧，無法從事正常活動)
		60	Requires occasional assistance, but able to care for most of his needs (有時需要別人幫助，能照顧患者大部分的需要)
Needs to be in bed more than 50% of normal daytime (躺在床上的時間>50%)	3	50	Requires considerable assistance, and frequent medical care (需要考慮別人幫助，經常給予醫療照顧)
		40	Disabled. Requires special care and assistance (傷殘，需要特別照顧及幫助)
Unable to get out of bed (長期臥床)	4	30	Severely disabled. Hospitalization indicated though death not imminent (嚴重傷殘，尚未有死亡的危險)
		20	Very sick. Hospitalization Necessary. Active supportive Treatment necessary (痛情嚴重，尚未有死亡的危險)
		10	Moribund (病況緊急，很快有死亡的危險)
Dead	5	0	Dead

012可化療

Responders vs. KPS



Cancers. 2019 Jan 22;11(2): 128-140.

Multivariate analysis for responders and non-responders to PG2

Table 3. Multivariate analysis for responders and non-responders to Astragalus Polysaccharides (PG2) injection.

All Subjects					
	Cut-off Points = 10%			Multivariate Analysis	
Variable/Status	Responder (N = 140)	Non-Responder (N = 74)	Univariate Analysis p-value *	Odds Ratio (95% CI)	p-value **
Age (years)					
n	140	74	0.3085 [W]	1.007 (0.978, 1.036)	0.6518
Mean (SD)	62.06 (11.28)	63.39 (10.66)			
Median (min, max)	62 (28, 91)	65 (22, 81)			
95% CI	(60.17, 63.94)	(60.92, 65.86)			
Gender					
Male	75 (53.57%)	46 (62.16%)	0.2279 [C]	0.774 (0.387, 1.546)	0.4677
Female	65 (46.43%)	28 (37.84%)			
Body mass index (BMI) (kg/m^2)					
<19	39 (28.26%)	27 (36.99%)	0.1935 [C]	0.724 (0.364, 1.440)	0.3570
≥19	99 (71.74%)	46 (63.01%)			
number of missing	2	1			
Body weight loss in previous 6 months					
<5%	63 (45.65%)	30 (40.54%)	0.4746 [C]	0.998 (0.512, 1.944)	0.9944
≥5%	75 (54.35%)	44 (59.46%)			
NA	2	0			
Baseline KPS score					
30–50	22 (15.71%)	31 (41.89%)	<0.0001 [C]	0.253 (0.126, 0.504)	<0.0001
60–90	118 (84.29%)	43 (58.11%)			
Baseline BFI score					
4–6	72 (51.43%)	41 (55.41%)	0.5794 [C]	0.885 (0.475, 1.647)	0.6998
7–10	68 (48.57%)	33 (44.59%)			
Cancer Type: three categories					
Lung cancer	22 (15.71%)	12 (16.22%)	0.2876 [C]		
Breast cancer	22 (15.71%)	6 (8.11%)		1.297 (0.343, 4.905)	0.7020
other	96 (68.57%)	56 (75.68%)		0.957 (0.414, 2.208)	0.9173
Albumin (g/dL)					
<3.0	20 (14.29%)	11 (14.86%)	0.9088 [C]	1.272 (0.518, 3.124)	0.5997
≥3.0	120 (85.71%)	63 (85.14%)			
Hemoglobin (g/dL)					
<10	48 (34.29%)	30 (40.54%)	0.3659 [C]	0.767 (0.405, 1.452)	0.4148
≥10	92 (65.71%)	44 (59.46%)			
Peripheral blood TLC (/μL)					
<700	46 (32.86%)	18 (24.32%)	0.1947 [C]	1.709 (0.846, 3.452)	0.1353
≥700	94 (67.14%)	56 (75.68%)			

* The Wilcoxon rank-sum test [W] was used to compare the difference between responders and non-responders for continuous variables; the Chi-squared test [C] was used to compare the difference between responders and non-responders for categorical variables. ** A logistic regression model was used to compare the differences between responders and non-responders.

Cancers. 2019 Jan 22;11(2): 128-140.

Multivariate analysis for responders and non-responders to PG2

- Patients with **higher KPS** responded **better to PG2**.
- Identified **KPS as a promising predictive factor** for the therapeutic efficacy of PG2.

	Cut-off Points = 10%			Multivariate Analysis	
Variable/Status	Responder (N = 140)	Non-Responder (N = 74)	Univariate Analysis p-value *	Odds Ratio (95% CI)	p-value **
Baseline KPS score					
30–50	22 (15.71%)	31 (41.89%)	<0.0001 [C]	0.253 (0.126, 0.504)	<0.0001
60–90	118 (84.29%)	43 (58.11%)			

Single Patient

Baseline KPS score	Responder %
30-50 (N=53)	22 (42%)
60-90 (N=161)	118 (73%)

Cancers. 2019 Jan 22;11(2): 12

Summary of PG2® Phase IV Study

- **Fatigue improvement**

✓ PG2® treatment showed efficacy in relieving fatigue as early as the first week of treatment.

✓ Clinically meaningful fatigue improvement (≥ 10%) was observed in more than 65% of subjects receiving PG2® after the cycle 1 treatment when compared to baseline.

✓ Patients with higher KPS showed better chance to respond to PG2 treatment in BFI-T score.

J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091.
Cancers. 2019 Jan 22;11(2): 128-140.

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

Oluwaseun Adebayo Bamodu [1,2,†], Kuang-Tai Kuo [3,4,†], Chun-Hua Wang [5,6], Wen-Chien Huang [7,8], Alexander T.H. Wu [9], Jo-Ting Tsai [10,11], Kang-Yun Lee [12], Chi-Tai Yeh [1,2,13,*] and Liang-Shun Wang [3,4,*]

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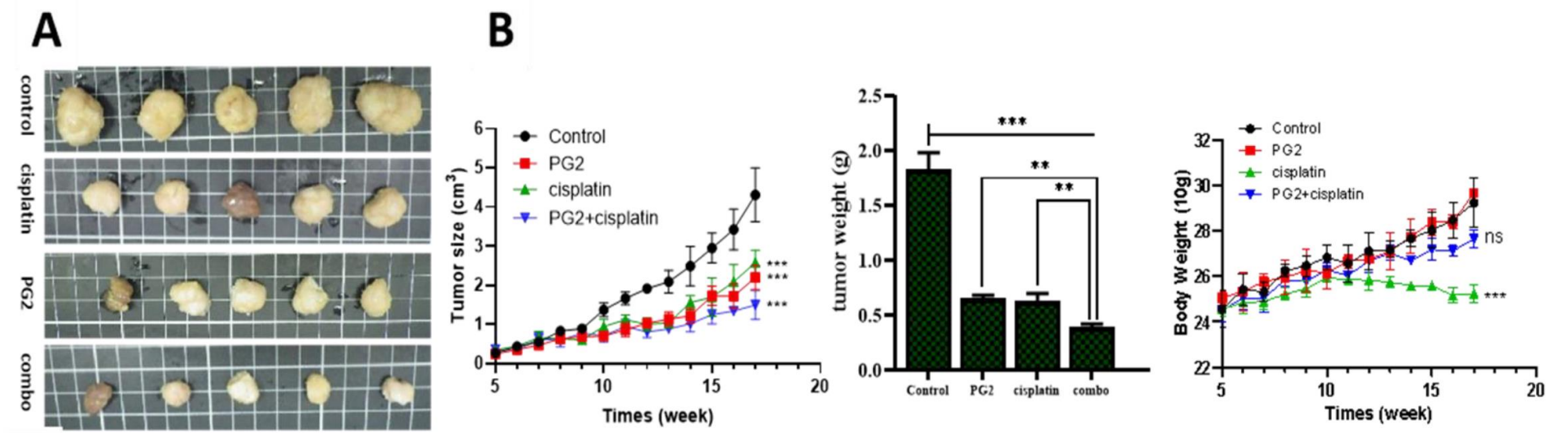
4 Division of Thoracic Surgery, Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taipei City 110, Taiwan

Nutrients_2019(11)2264-2283.

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 tumore 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)

Nutrients 2019(11)2264-2283.

Suppression of tumor growth and metastasis

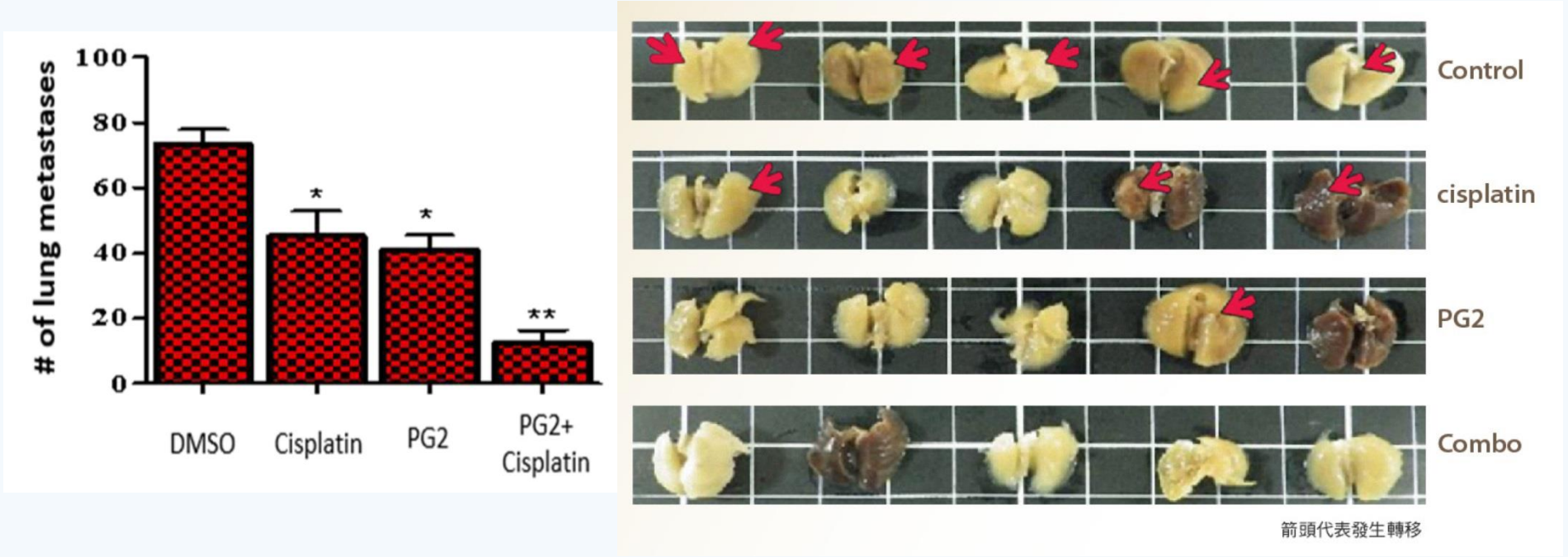


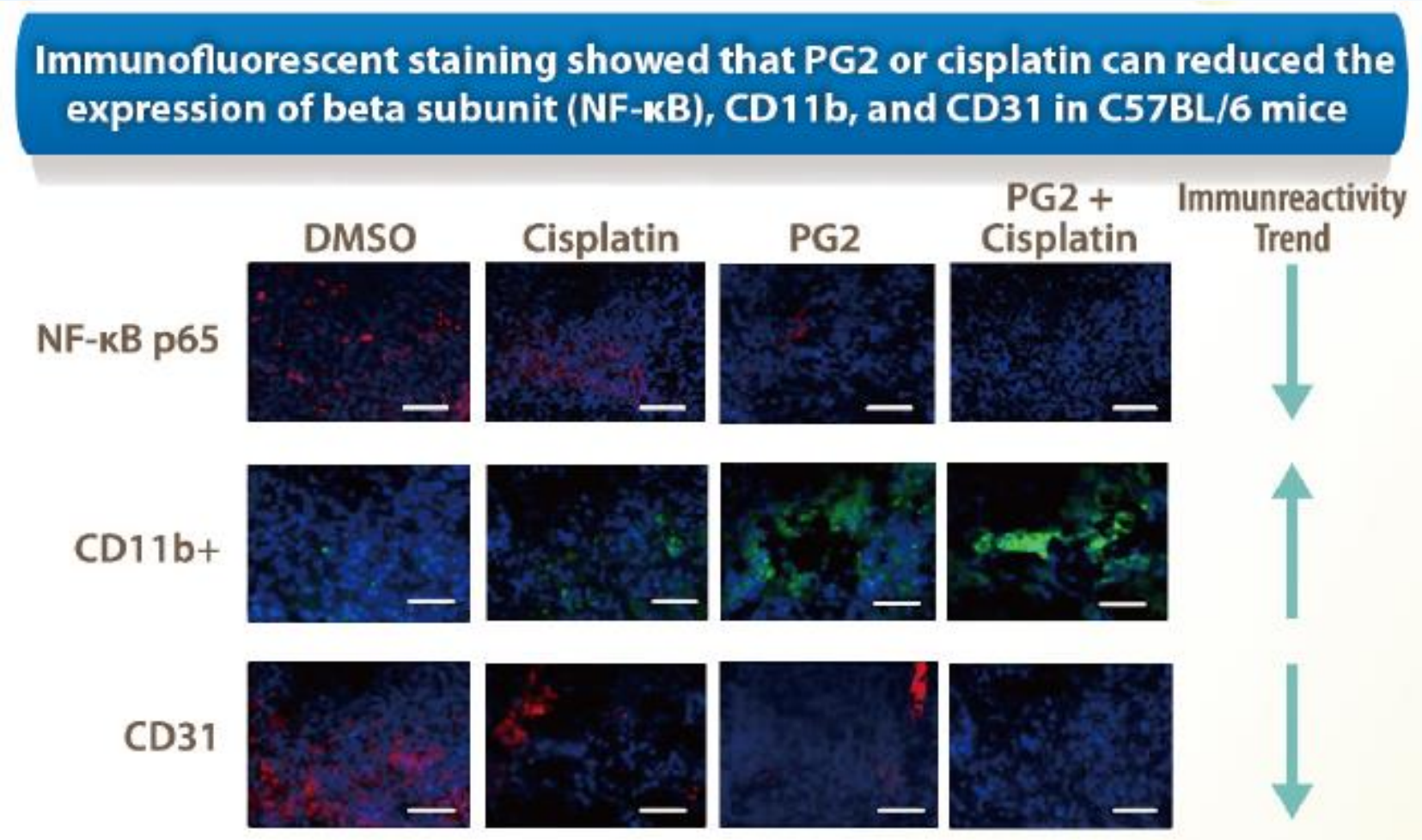
Photo images show the effect of cisplatin and/or PG2 on metastasis in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

*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)

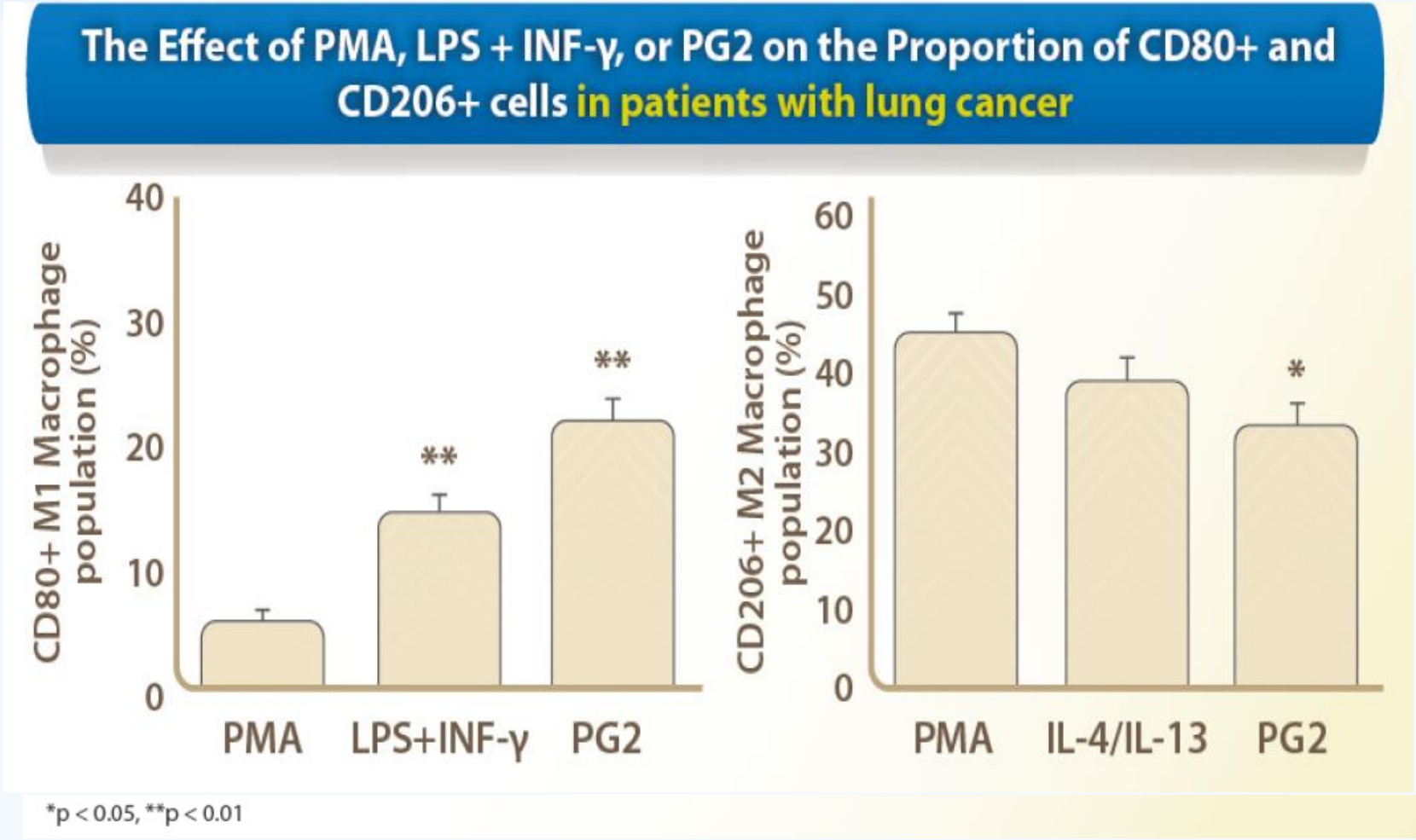
Nutrients 2019(11)2264-2283.

Regulating tumor micro-environment & suppressing oncogenicity



Nutrients_2019(11)2264-2283.

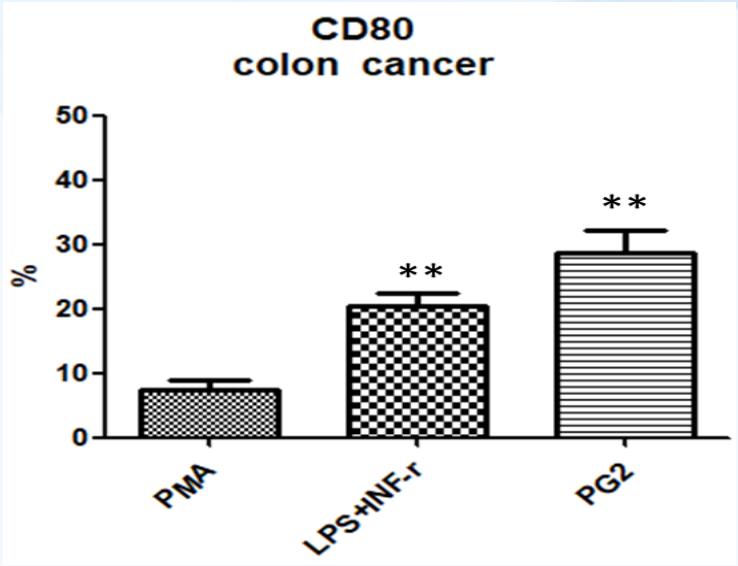
U.S. Patent. Patent No.: US 10,478,468 B2. Method for enhancing effect of immunotherapy for cancer



Nutrients_2019(11)2264-2283.

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

A



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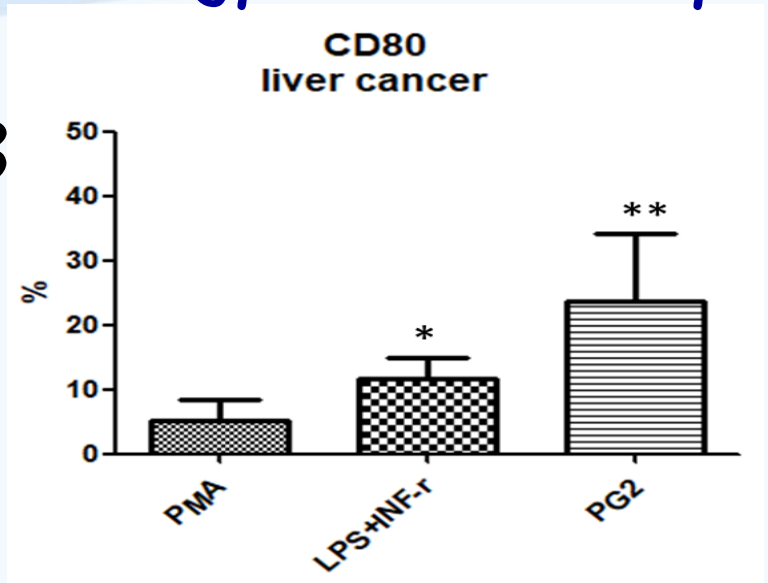

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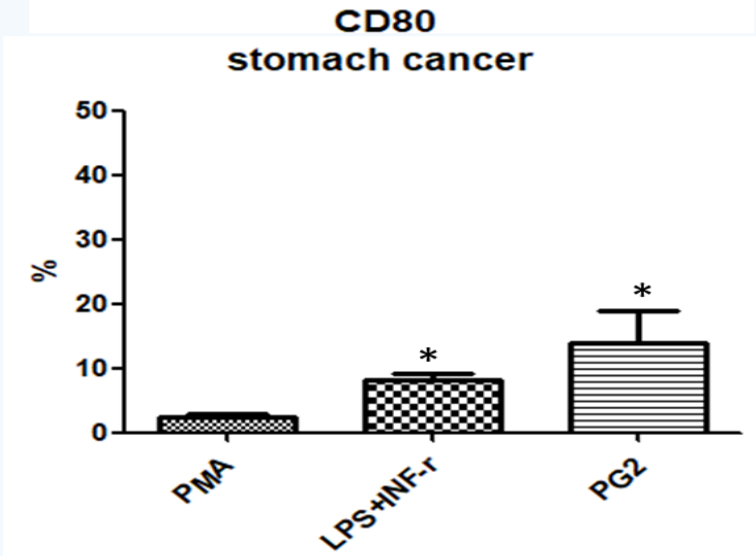

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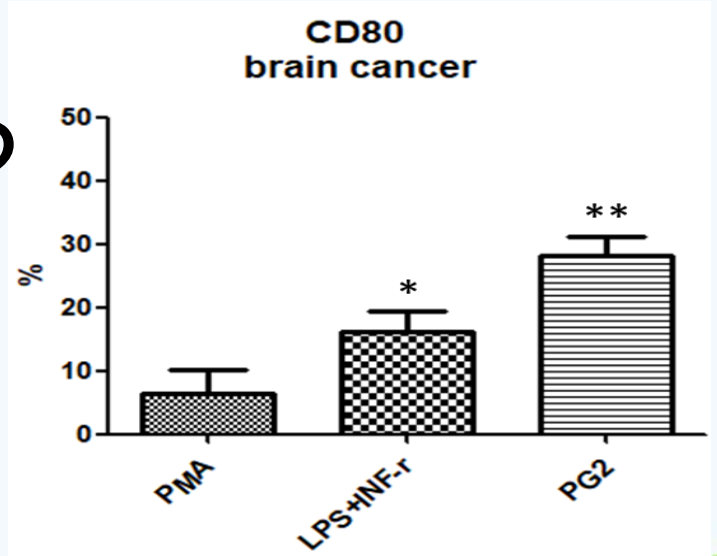

U.S. Patent. Patent No.: US 10,478,468 B2. Method for enhancing effect of immunotherapy for cancer

Nutrients_2019(11)2264-2283.

IVYSPRING INTERNATIONAL PUBLISHER

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

Hsu-Liang Chang[1], Yi-Hsuan Kuo[2], Li-Hsien Wu[2], Chih-Min Chang[2,3], Kai-Jen Cheng[2,4], Yu-Chang Tyan[5], Che-Hsin Lee[2,6,7,8,9]✉

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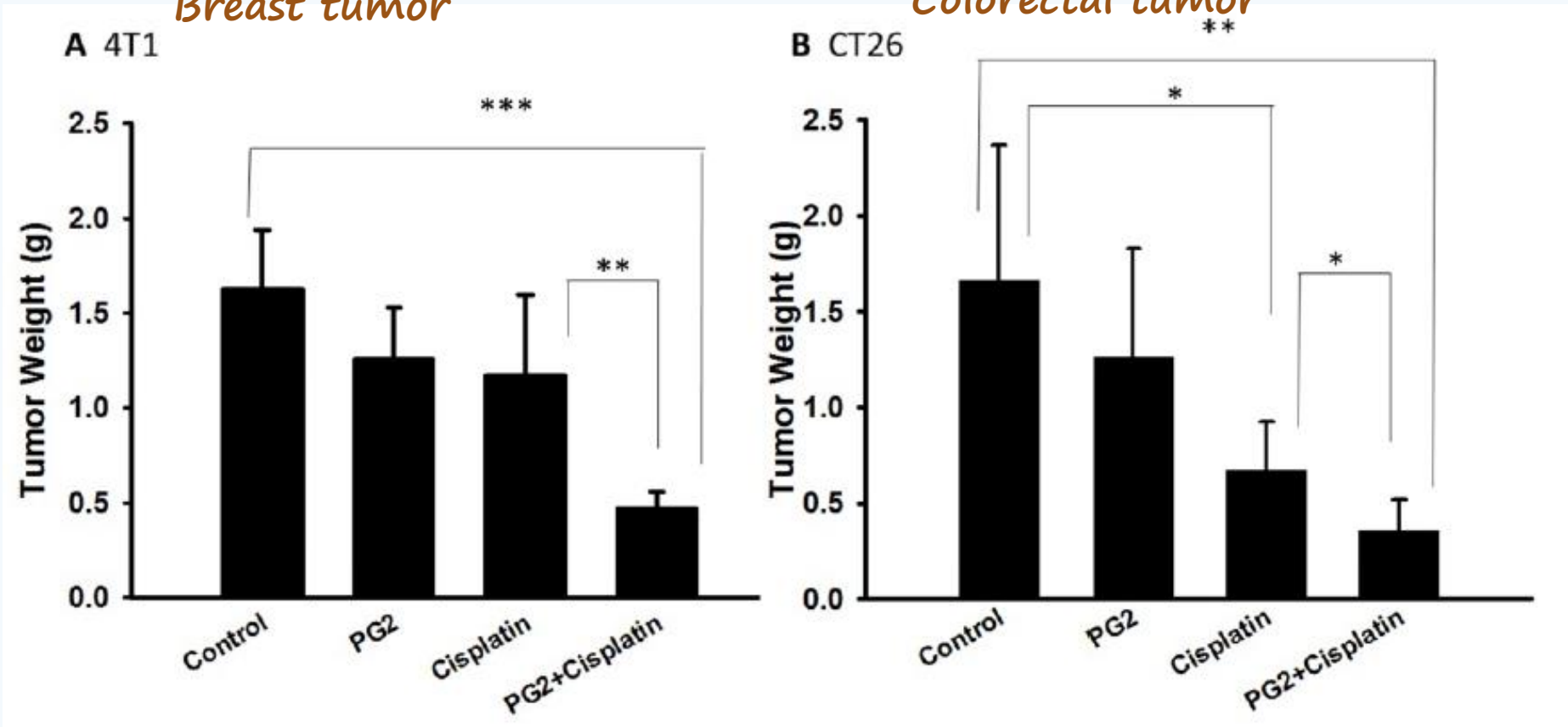
Int. J. Med. Sci. 2020; 17(7): 939-945.

The murine breast tumor and colorectal tumor were significantly reduced growth after Cisplatin/PG2 therapy

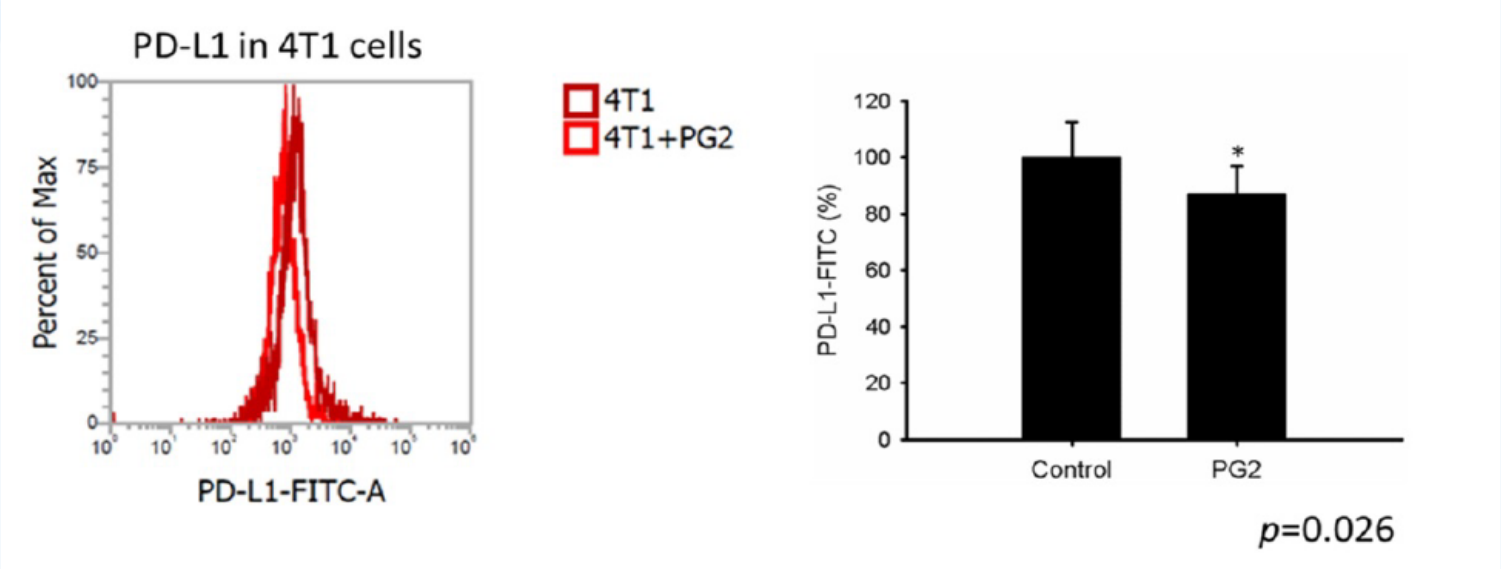
Breast tumor

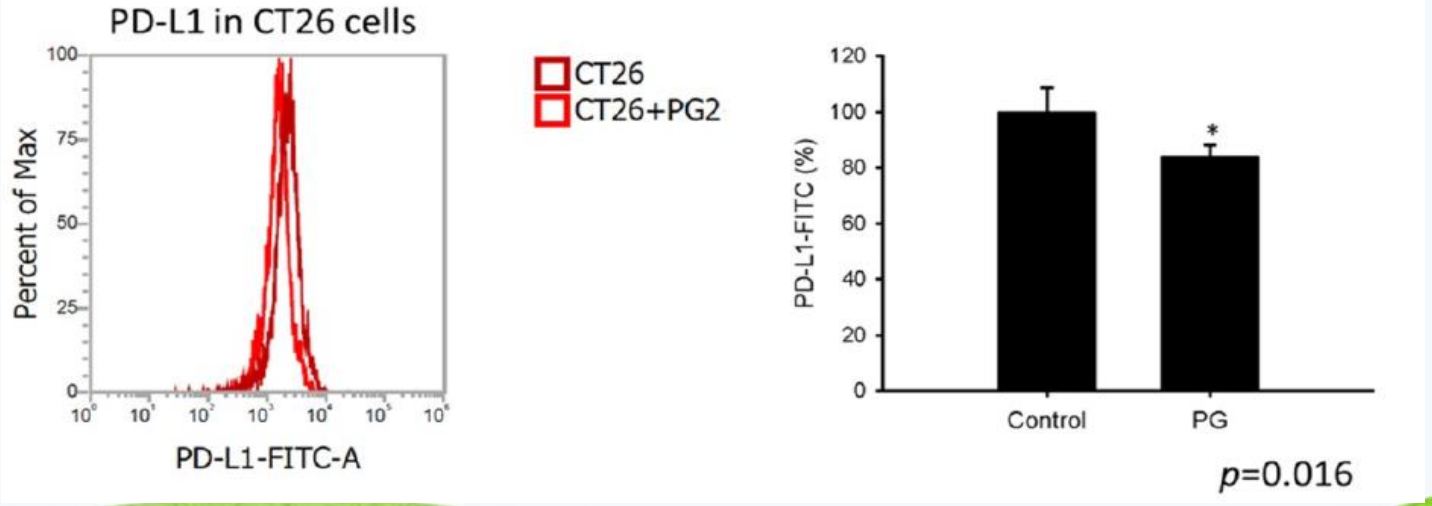
Colorectal tumor



Int. J. Med. Sci. 2020; 17(7): 939-945.

PG2 enhanced the chemotherapy by stimulating host immunity by reducing the expression of tumor surface PD-L1 expression





Int. J. Med. Sci. 2020; 17(7): 939-945.

PG2®: beyond Cancer-related Fatigue Treatment

- **A therapeutically-relevant role for PG2 in modulating the M1/M2**
  - ✓ The treatment with PG2 elicited significant depletion of the tumor-associated M2 population.
- **Synergistically enhanced the anticancer effect of chemotherapeutic agent, cisplatin**
  - ✓ Inhibited tumor growth and metastasis.
  - ✓ In the presence of PG2, cisplatin-associated dyscrasia and weight-loss was markedly suppressed.

Cancers 2019, 11, 128;
doi:10.3390/cancers11020128

「懷特血寶凍晶注射劑 」健保 RWE 研究計畫
Interim Analysis Result of PG2 RWE Study

Data Collection Period: Mar/01/2021 to Apr/15/2022

Please be aware that some information provided by CRCs have not been verified. Only data confirmed by investigators, verified by monitors and retrieved into database can be used as final data.

Study Introduction

- **研究目的：**以**病歷回溯方式**，收集使用懷特血寶凍晶注射劑 (PG2 Lyo. Injection) 健保給付病患之治療紀錄，以了解並探討懷特血寶凍晶注射劑之**臨床使用、病人之疲憊症改善及使用滿意度**。
- **研究設計：**
  - 預計收案人數: 200; 執行醫院: 7;
  - 預計收案期間: Mar 01, 2021~Aug 31, 2023;
  - 納入條件: 健保給付申請通過使用懷特血寶凍晶注射劑之病患
  - **Primary Endpoint: Fatigue Improvement** by VAS Fatigue Scale (疲憊量尺)
  - **Secondary Endpoint: Fatigue Treatment Satisfaction**
    - Clinical Global Impression-Improvement (CGI-I) by Patients
    - Patient's Expectation to Continue CRF Treatment
    - Overall Clinical Evaluation by Physicians

Subject Disposition

Population (N)	Subject Enrolled	Baseline	4-Dose	6-Dose
All	48 (100.00%)	48 (100.00%)	48 (100.00%)	36 (100.00%)
01 VGHTC	15 (31.25%)	15 (31.25%)	15 (31.25%)	11 (30.56%)
02 KMUH	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
03 EDAH	11 (22.92%)	11 (22.92%)	11 (22.92%)	7 (19.44%)
04 CGMH-TP	6 (12.50%)	6 (12.50%)	6 (12.50%)	6 (16.67%)
05 TSGH	10 (20.83%)	10 (20.83%)	10 (20.83%)	8 (22.22%)
06 CMUH	3 (6.25%)	3 (6.25%)	3 (6.25%)	2 (5.56%)

A total of 48 evaluable breast cancer (stage IV) patients:

- 36 subjects had completed all 6 doses of PG2 Lyo. Injection
- 12 subjects had completed up to 4 doses and less than 6 doses of PG2 Lyo. Injection at the time of analysis.

Demographic Information

Characteristics	Results
Gender	
N	48
Missing Data	0
Male	0 (0%)
Female	48 (100%)
Age	
N	48
Missing Data	0
Mean(SD)	60.95 (9.46)
Range	43.12~80.39
Weight (kg)	
N	48
Missing Data	0
Mean(SD)	59.67 (11.55)
Range	38.8~89.7
Height (cm)	
N	48
Missing Data	0
Mean(SD)	156.58 (5.34)
Range	143~168.5
BMI	
N	48
Missing Data	0
Mean(SD)	24.27 (3.96)
Range	15.94~33.01

Disease Characteristics

Characteristics	Results
Histological type	
N	48
Missing Data	0
Ductal	**36 (75.00%)**
Lobular	0 (0.00%)
Mixed	2 (4.17%)
Other	3 (6.25%)
Unknown	7 (14.58%)
Locally Advanced or Distant Metastasis	
N	48
Missing Data	0
Locally Advanced	0 (0.00%)
Distant Metastasis	48 (100.00%)
Bone	**28 (58.33%)**
Liver	**23 (47.92%)**
Lymph nodes (Regional LN)	**19 (39.58%)**
Lymph nodes (Distant LN)	**16 (33.33%)**
Lungs	**26 (54.17%)**
Brain	8 (16.67%)
Skin	2 (4.17%)
Other	2 (4.17%)
Menopausal Status	
N	48
Missing Data	0
Premenopausal	2 (4.17%)
Premenopausal with ovary function suppression	3 (6.25%)
Postmenopausal	**43 (89.58%)**
NA	48
Molecular Type	
N	48
Missing Data	0
Lumina A	3 (6.25%)
Lumina B	**23 (47.92%)**
Her-2 enriched	4 (8.33%)
Triple-negative	**12 (25.00%)**
Unknown	6 (12.50%)

- Most were **postmenopausal** women **(90%)**.
- The major histologic type of breast cancer was **ductal carcinomas (75%)**.
- Patients with stage IV breast cancers that had spread mainly to **lymph nodes (73%), bone (58%), Lung (54%)**

Previous and Current Cancer Therapy

No. Cancer Therapies/type	Previous	4-Doses	6-Doses	Treatment period
N	48	48	36	36
0	0 (0.00%)	0 (0.00%)	1 (2.78%)	0 (0.00%)
1	20 (41.67%)	20 (41.67%)	13 (36.11%)	11 (30.56%)
Chemotherapy	14 (29.17%)	15 (31.25%)	10 (27.78%)	9 (25.00%)
Targeted Therapy	5 (10.42%)	5 (10.42%)	3 (8.33%)	2 (5.56%)
Hormone Therapy	1 (2.08%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
2	25 (52.08%)	25 (52.08%)	21 (58.33%)	21 (58.33%)
Chemotherapy + Surgery	0 (0.00%)	1 (2.08%)	1 (2.78%)	1 (2.78%)
Chemotherapy + Targeted Therapy	13 (27.08%)	12 (25.00%)	10 (27.78%)	11 (30.56%)
Chemotherapy + CCRT	0 (0.00%)	2 (4.17%)	2 (5.56%)	1 (2.78%)
Chemotherapy + Hormone Therapy	5 (10.42%)	3 (6.25%)	4 (11.11%)	4 (11.11%)
Chemotherapy + Immunotherapy	1 (2.08%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Targeted Therapy + Hormone Therapy	5 (10.42%)	6 (12.5%)	4 (11.11%)	4 (11.11%)
Hormone Therapy + Others	1 (2.08%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
3	3 (6.25%)	3 (6.25%)	1 (2.78%)	2 (5.56%)
Chemotherapy +Targeted Therapy + Surgery	1 (2.08%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chemotherapy + Targeted Therapy + CCRT	1 (2.08%)	0 (0.00%)	0 (0.00%)	1 (2.78%)
Chemotherapy + Targeted Therapy + Hormone Therapy	1 (2.08%)	3 (6.25%)	1 (2.78%)	1 (2.78%)
4 and above	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.78%)
Chemotherapy + Targeted Therapy + CCRT + Hormone Therapy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.78%)

Previous and Current Cancer Therapy

75% of patients received PG2 Injection treatment under chemotherapy or chemo-combination therapy.

PG2 Administration

6 Doses of PG2 Treatment Duration Range		
N	36	%
Missing data		
Duration ≦1Mo	0	0.00%
1 Mo<duration ≦2 Mos	8	22.22%
2 Mos<duration ≦3 Mos	10	27.78%
3 Mos<duration ≦4 Mos	12	33.33%
4 Mos<duration ≦5 Mos	0	0.00%
5 Mos<duration ≦6 Mos	3	8.33%
6 Mos<duration ≦7 Mos	2	5.56%
7 Mos<duration ≦8 Mos	1	2.78%

- Nearly **50%** of patients received 6 doses of PG2 Lyo. Injection administration **less than 3 months.**

PG2 Administration	4-Dose		6-Dose	
N	48		36	
1 Vial of PG2	40	83.33%	28	77.78%
Before Cancer Treatment	22	45.83%	13	36.11%
After Cancer Treatment	10	20.83%	10	27.78%
Before or After Cancer Treatment	6	12.50%	5	13.89%
NA (No cancer treatment)	2	4.17%	0	0.00%
2 Vials of PG2	7	14.58%	8	22.22%
Before Cancer Treatment	0	0.00%	1	2.78%
After cancer treatment	0	0.00%	1	2.78%
Before AND after cancer treatment	7	14.58%	6	16.67%
4 Vials of PG2	1	2.08%	-	-
After Cancer Treatment	1	2.08%	-	-

- Most patients (78-83%) received one dose of PG2 Lyo. Injection during cancer treatment.
- Of these patients, 46% of patients administrated PG2 Lyo. Injection before cancer treatment.

II. Primary & Secondary Endpoint

Primary Endpoint

- Fatigue Improvement
  by VAS Fatigue Scale (疲憊量尺)

Secondary Endpoint

- Fatigue Treatment Satisfaction
  - Clinical Global Impression-Improvement (CGI-I) by Patients
  - Patient's Expectation to Continue CRF Treatment
  - Overall Clinical Evaluation by Physicians
- ECOG

VAS Fatigue Score by Visits

VAS Fatigue Score of the WORST Level during **Past 24 hours**

visit	N	Missing Data	Mean	SD	Median	Min	Max	95% CI			Paired t-test from base line
Baseline	48	0	6.54	1.49	7.00	3.00	9.00	6.12	~	6.96	
4-Doses	48	0	4.21	1.44	4.00	0.00	7.00	3.80	~	4.62	1.64E-14
6-Doses	36	0	3.33	1.33	3.00	1.00	7.00	2.90	~	3.77	1.08E-09

*Paired t-test between 4-Doses and 6-Doses is 0.005971463

VAS Fatigue Score of the WORST Level after the **Last Anti-cancer Treatment (or within 4 weeks until now)**

visit	N	Missing Data	Mean	SD	Median	Min	Max	95% CI			Paired t-test from base line
Baseline	44	0	6.93	1.25	7.00	5.00	10.00	6.56	~	7.30	
4-Doses	48	0	4.38	1.54	4.00	2.00	9.00	3.94	~	4.81	1.97E-11
6-Doses	36	0	3.56	1.34	3.00	1.00	8.00	3.12	~	3.99	1.64E-12

*Paired t-test between 4-Doses and 6-Doses is 0.000827413

Patients received 6 doses of PG2 Lyo. Injection had significantly low fatigue scores (VAS score 3.33~3.56; <4 of treatment goal).

VAS Fatigue Score Change from Baseline

The WORST Level during **Past 24 hours**

visit	N	Missing Data	Mean	SD	Median	Min	Max	95% CI
4-Doses	48	0	-2.33	1.48	-2.00	-6.00	1.00	-2.75 ~ -1.92
	48	0	-34.96%	21.63%	-35.42%	-100.00%	16.67%	-41.08% ~ -28.84%
6-Doses	36	0	-3.06	2.23	-3.00	-7.00	3.00	-3.78 ~ -2.33
	36	0	-42.76%	34.00%	-50.00%	-83.33%	75.00%	-53.86% ~ -31.65%

*paired t-test between score change of 4-Doses and 6-Doses is 0.005971463
**paired t-test between score change percentage of 4-Doses and 6-Doses is 0.148840705

The WORST Level after the **Last Anti-cancer Treatment (or within 4 weeks until now)**

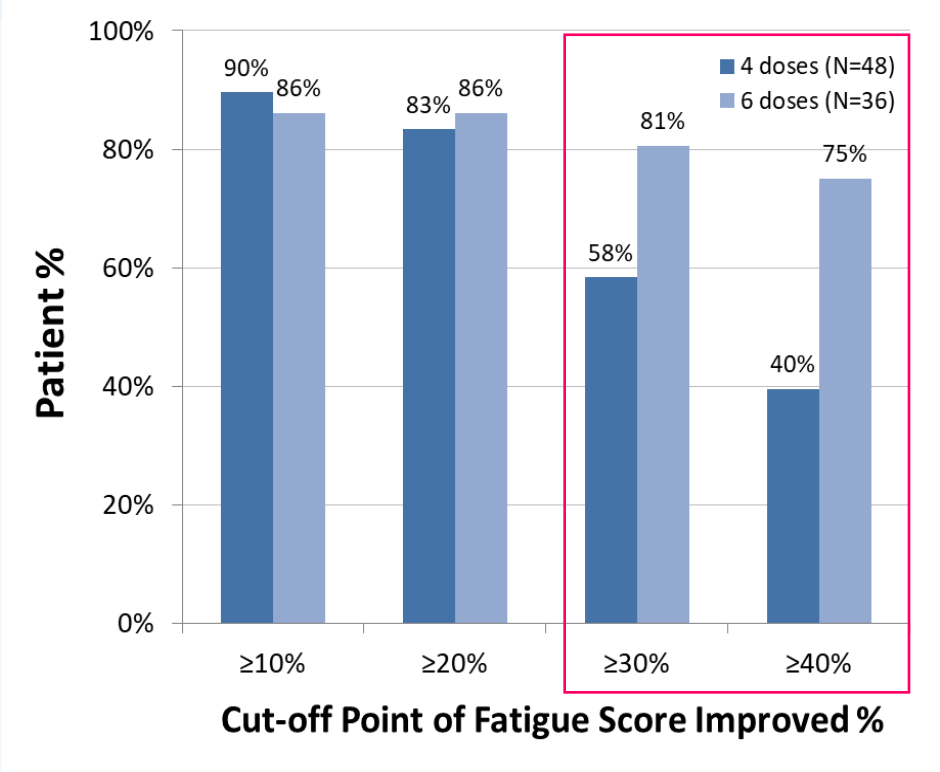
visit	N	Missing Data	Mean	SD	Median	Min	Max	95% CI
4-Doses	44	4	-2.52	1.86	-3.00	-8.00	2.00	-3.07 ~ -1.97
	44	4	-34.84%	23.55%	-37.50%	-80.00%	40.00%	-41.80% ~ -27.88%
6-Doses	33	3	-3.45	1.79	-3.00	-7.00	1.00	-4.06 ~ -2.84
	33	3	-48.43%	21.89%	-55.56%	-83.33%	14.29%	-55.90% ~ -40.96%

*paired t-test between score change of 4-Doses and 6-Doses is 0.000190575
**paired t-test between score change percentage of 4-Doses and 6-Doses is 0.000128219

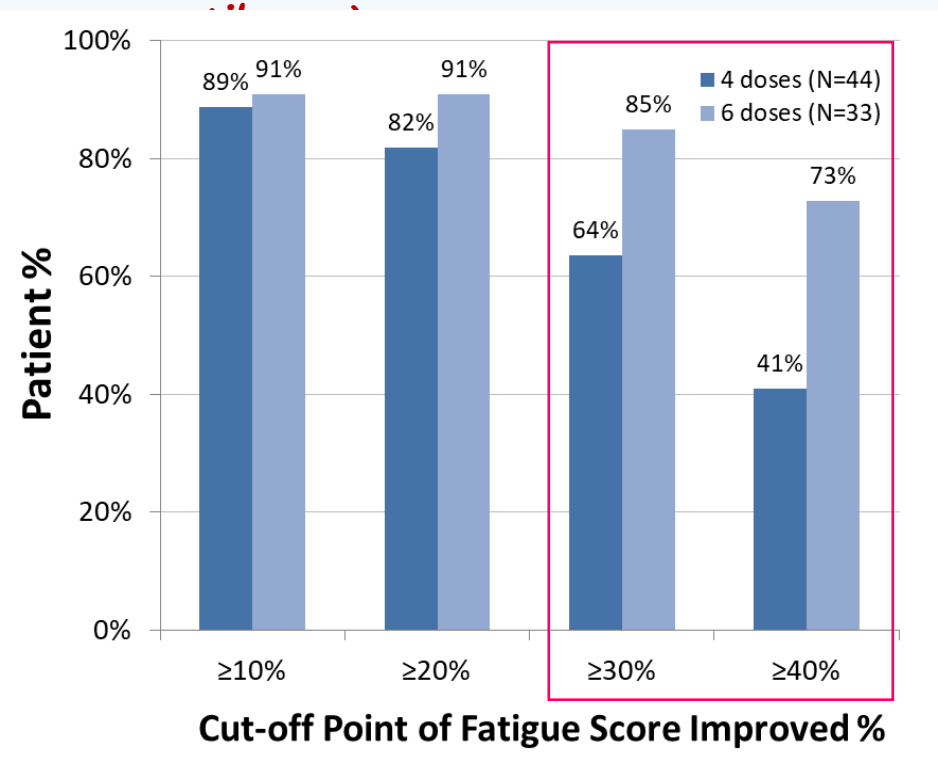
The mean decreases in fatigue score from baseline were **3.06 ~ 3.45 (42.76 ~ 48.43%)** after 6 doses of PG2 Lyo. Injection treatment.

Fatigue Improvement Response Rate (by Score Change%)

The WORST Level during **Past 24 hours**



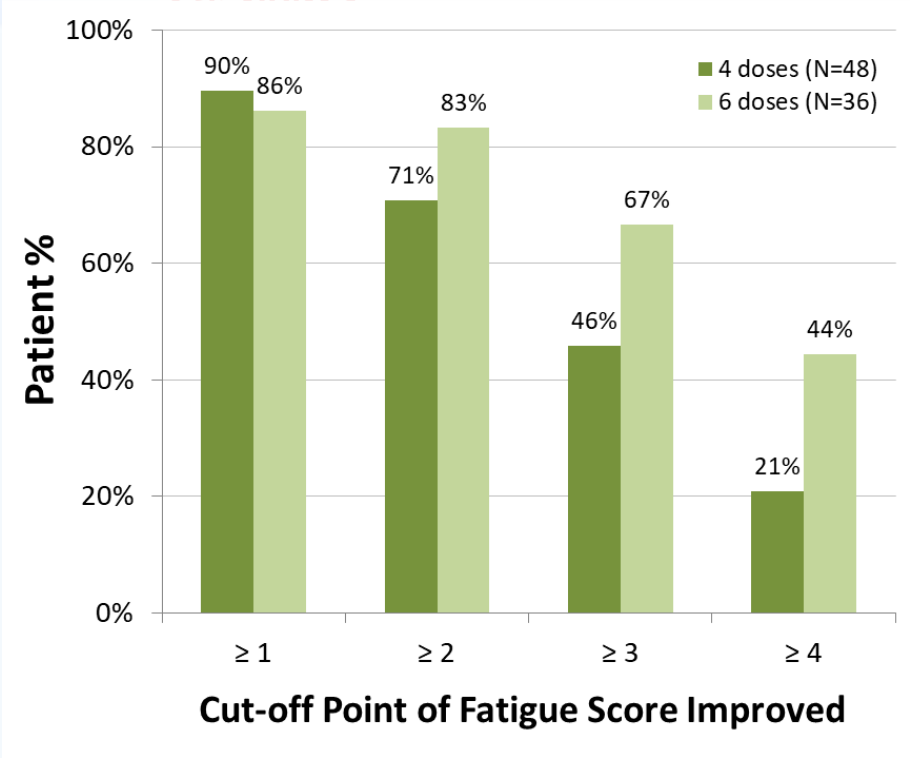
The WORST Level after the **Last Anti-cancer Treatment (or within 4 weeks**



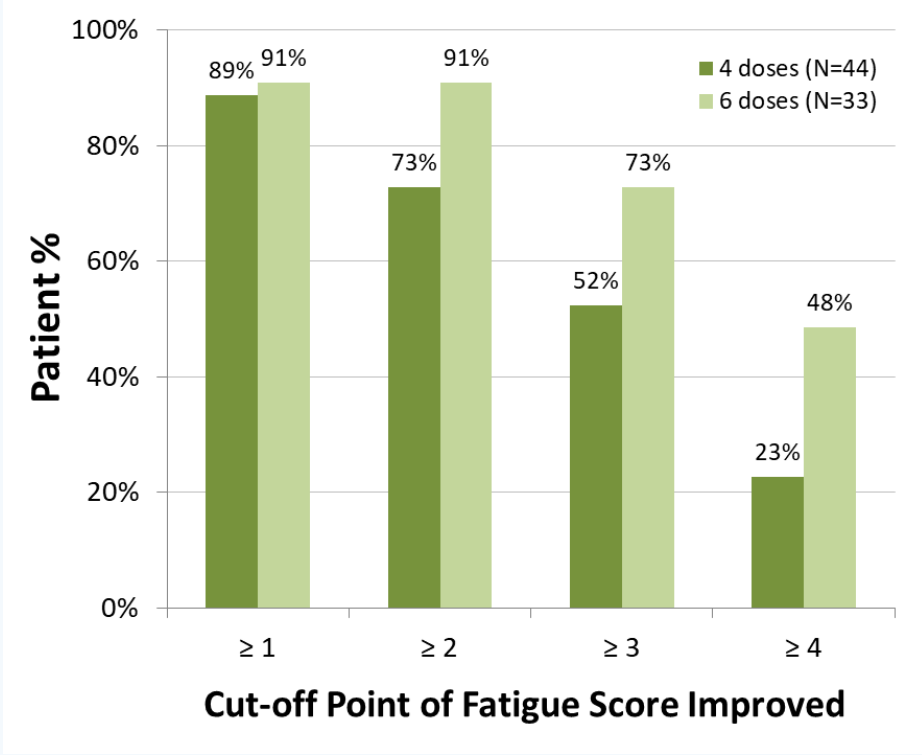
Fatigue scores improved from baseline by at least 30% in **81%~85%** of patients with 6 doses of PG2 Lyo. Injection.

Fatigue Improvement Response Rate (by Score Change)

The WORST Level during **Past 24 hours**



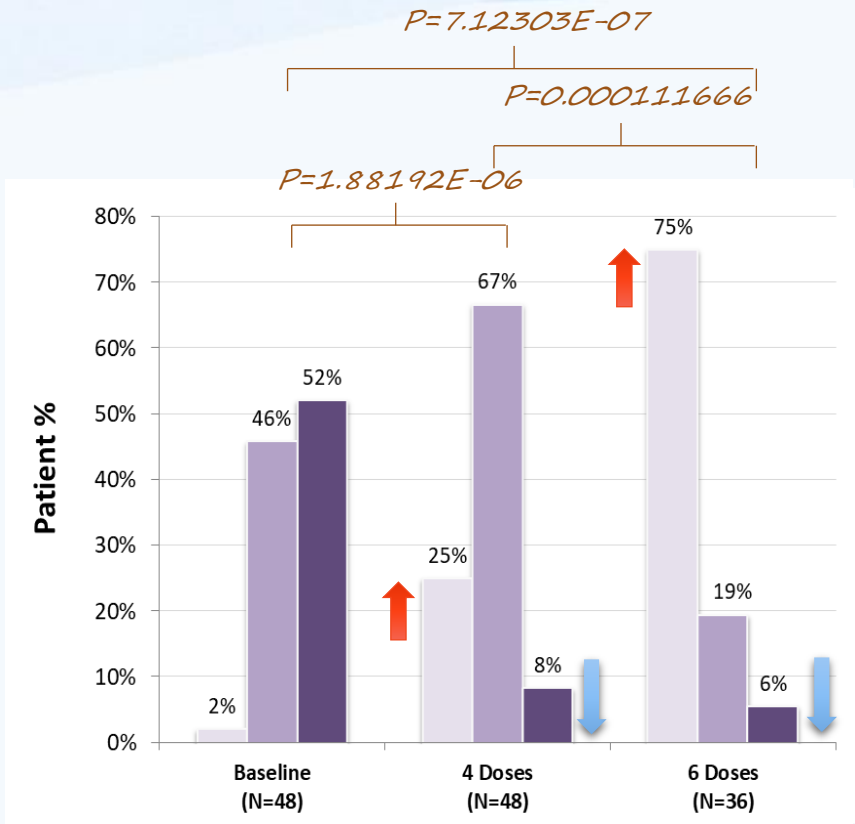
The WORST Level after the **Last Anti-cancer Treatment (or within 4 weeks**



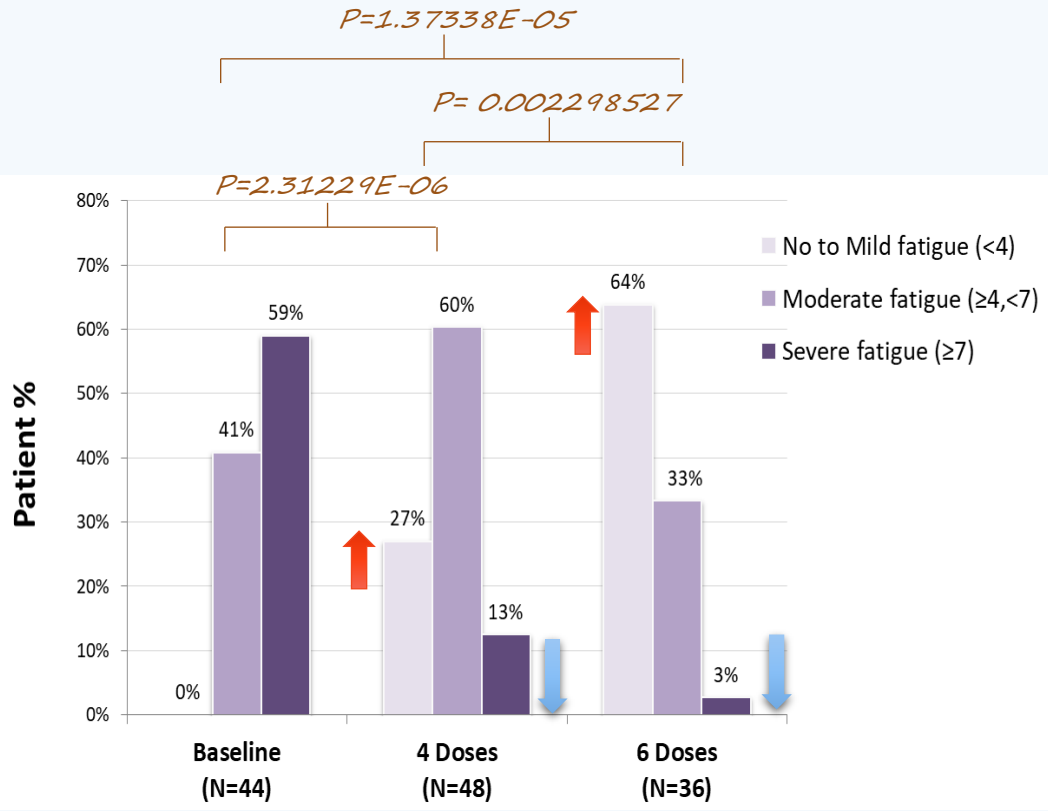
Fatigue scores improved from baseline by **at least 3 was observed in 67%~73%** of patients with 6 doses of PG2 Lyo. Injection administration.

Categorized of Fatigue Severity

The WORST Level during **Past 24 hours**



The WORST Level after the **Last Anti-cancer Treatment (or within 4 weeks until now)**



- **Less** patients suffering from **severe** fatigue (3-13%) and **more** patients who had **no** fatigue or experiencing **mild** fatigue (25-75%) after PG2 Lyo. Injection treatment were observed.
- The distribution of patient groups experiencing different levels of fatigue severity compared between before and after PG2 Lyo. Injection treatment were shown a significantly **statistical difference**.

Fatigue treatment satisfaction:

Clinical Global Impression-Improvement (CGI-I) by Patients

CGI-I Score	4-Doses		6-Doses		
N	47		36		
Missing Data	1		0		
Improved (1-3)	**42**	**89.36%**	**33**		**91.67%**
Very much improved	6	12.77%	5	26/	13.89%
Much improved	16	34.04%	22	33=	61.11%
Minimally improved	20	42.55%	6	82%	16.67%
No Improved (4-7)	5	10.64%	3		8.33%
No change	4	8.51%	1		2.78%
Minimally worse	1	2.13%	0		0.00%
Much worse	0	0.00%	2		5.56%
Very much worse	0	0.00%	0		0.00%

*chi-square between improved/no Improved and 4-Doses/6-Doses is 1.

- **92%** of patients with 6 doses of PG2 Lyo. Injection treatment reported fatigue improvement.
- Of these improved patients, **82%** of patients reported " **Much improved**" and "**Very much improved**" after 6 doses of PG2 Lyo. Injection treatment.

Fatigue treatment satisfaction:

Patient Expectations for Continuous Use

Patient expectations for continuous use		
N	36	
Yes	28	77.78%
No	8	22.22%
Change to other pharmacological CRF therapy	0	0.00%
Change to non-pharmacological CRF therapy	0	0.00%
No fatigue without CRF therapy	0	0.00%
Patient's willingness	4	11.11%
Other reason	4	11.11%

78% of patients were willing to receive PG2 Lyo. Injection treatment continuously.

Fatigue treatment satisfaction:

Overall Clinical Evaluation by Physicians

Overall Outcome Evaluation	No. of subject/proportion (%)	
N	36	
Excellent	4	11.11%
Good	31	86.11%
Fair	1	2.78%

Recommendations for Continuous Use	No. of subject/proportion (%)	
N	36	
Very High	8	22.22%
High	20	55.56%
Moderate	8	22.22%

97% of patients had positive overall outcome evaluated by physicians after 6 doses of PG2 Lyo. Injection treatment, and 78% of patients were recommended to continue receiving PG2 Lyo. Injection treatment.

ECOG

ECOG Score Distribute

ECOG score	Baseline		4-Doses		6-Doses	
N	48		46		32	
Missing Data	0		2		4	
2 or below	48	100.00%	46	100.00%	31	96.88%
0	20	41.67%	20	43.48%	12	37.50%
1	24	50.00%	21	45.65%	17	53.13%
2	4	8.33%	5	10.87%	2	6.25%
3 or above	0	0.00%	0	0.00%	1	3.13%
3	0	0.00%	0	0.00%	1	3.13%
4	0	0.00%	0	0.00%	0	0.00%

*chi-square between 2 or below /3 or above and baseline/4-Dose is not calculable
*chi-square between 2 or below /3 or above and baseline/6-Doses is 0.313499946
*chi-square between 2 or below /3 or above and 4-Doses/6-Doses is 0.313499946

ECOG Score Change from Baseline

ECOG score change from Baseline	4-Doses		6-Doses	
N	46		32	
Missing Data	2		4	
increase	4	8.70%	5	15.63%
remain	38	82.61%	25	78.13%
decrease	4	8.70%	2	6.25%

*chi-square 6-Doses against 4-Doses is 0.93673067

Weight

Weight(kg)

visit	N	Missing Data	Mean	SD	Median	Min	Max	95% confidence range			paired t-test from baseline
Baseline	48	0	59.62	10.37	57.85	41.00	89.10	56.69	~	62.56	
4-Doses	46	2	58.48	10.46	58.00	40.00	87.00	55.46	~	61.50	0.1513
6-Doses	34	2	58.47	9.40	57.70	43.90	89.00	55.31	~	61.63	0.069

*paired t-test between 4-Doses and 6-Doses is 0.911

Weight Change from Baseline (%)

visit	N	Missing Data	Mean	SD	Median	Min	Max	95% confidence range		
4-Doses	46	2	-1.20%	5.08%	0.00%	-16.67%	12.12%	-2.67%	~	0.26%
6-Doses	34	2	-1.71%	5.75%	0.00%	-16.67%	8.93%	-3.64%	~	0.23%

*paired t-test between 4-Doses and 6- Doses is 0.911

Categorized Weight Change from Baseline Distribution

items	4-Doses		6-Doses	
N	46		34	
Missing Data	2		2	
Decrease >= 5%	11	23.91%	9	26.47%
Stable change between 5%	32	69.57%	23	67.65%
Increase >= 5%	3	6.52%	2	5.88%

*Chi-square between 4-Doses and 6-Doses is 0.962767147

CTCAE Statistical Summary

CTCAE Term	Grade	V1	Occurrence	V2	Occurrence	V3	Occurrence
Anemia	N	47		44		33	
	Missing Data	1		4		3	
	0	21	44.68%	0	0.00%	13	39.39%
	1	16	34.04%	15	34.09%	11	33.33%
	2	8	17.02%	20	45.45%	7	21.21%
	3	2	4.26%	7	15.91%	2	6.06%
Neutrophil count decreased	N	46		41		31	
	Missing Data	2		7		5	
	0	35	76.09%	34	82.93%	27	87.10%
	1	3	6.52%	0	0.00%	0	0.00%
	2	5	10.87%	6	14.63%	3	9.68%
	Above grade 3	3	6.52%	1	2.44%	1	3.23%
	3	2	4.35%	1	2.44%	1	3.23%
	4	1	2.17%	0	0.00%	0	0.00%
Platelet count decreased	N	47		44		33	
	Missing Data	1		4		3	
	0	37	78.72%	35	79.55%	22	66.67%
	1	9	19.15%	6	13.64%	9	27.27%
	2	1	2.13%	3	6.82%	1	3.03%
	Above grade 3	0	0.00%	0	0.00%	1	3.03%
	3	0	0.00%	0	0.00%	1	3.03%
	4	0	0.00%	0	0.00%	0	0.00%
White blood cell decreased	N	47		45		33	
	Missing Data	1		3		3	
	0	35	74.47%	29	64.44%	23	69.70%
	1	5	10.64%	8	17.78%	7	21.21%
	2	4	8.51%	8	17.78%	2	6.06%
	Above grade 3	3	6.38%	0	0.00%	1	3.03%
	3	3	6.38%	0	0.00%	1	3.03%
	4	0	0.00%	0	0.00%	0	0.00%

III. Summary

- The advanced breast cancer patients received 6 doses of PG2 Lyo. Injection had significantly lower fatigue scores than baseline (VAS score 3.33~3.56; <4 of treatment goal).

- Fatigue scores improved from baseline by at least 30% in 81%~85% of patients with 6 doses of PG2 Lyo. Injection.

- Less patients suffering from severe fatigue (3-13%) and more patients who had experiencing mild or no fatigue (25-75%) after PG2 Lyo. Injection treatment were observed.

III. Summary

- 92% of patients with 6 doses of PG2 Lyo. Injection treatment reported fatigue improvement.

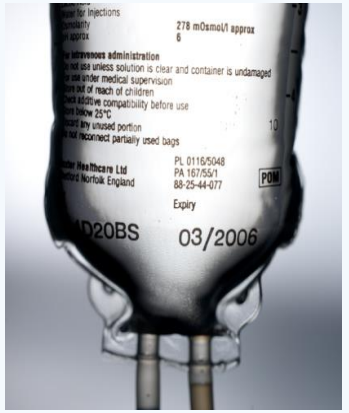
- Of these improved patients, 82% of patients reported “ Much improved” and “Very much improved” after 6 doses of PG2 Lyo. Injection treatment.

- Total 97% of patients had positive overall outcome evaluated by physicians after 6 doses of PG2 Lyo. Injection treatment, and 78% of patients were recommended to continue receiving PG2 Lyo. Injection treatment.

IV. Conclusion

In these preliminary data, the results shown advanced breast cancer patients received 6 doses of PG2 Lyo. Injection had good satisfaction and efficacious improvement on fatigue.

懷特血寶注射劑 (PG2® Injection)
臨床用藥資訊



- 機轉：增強免疫功能及刺激骨髓造血功能
- 適應症：適用於癌症末期因疾病進展所導致中重度疲勞症狀之改善
- 用法及用量：

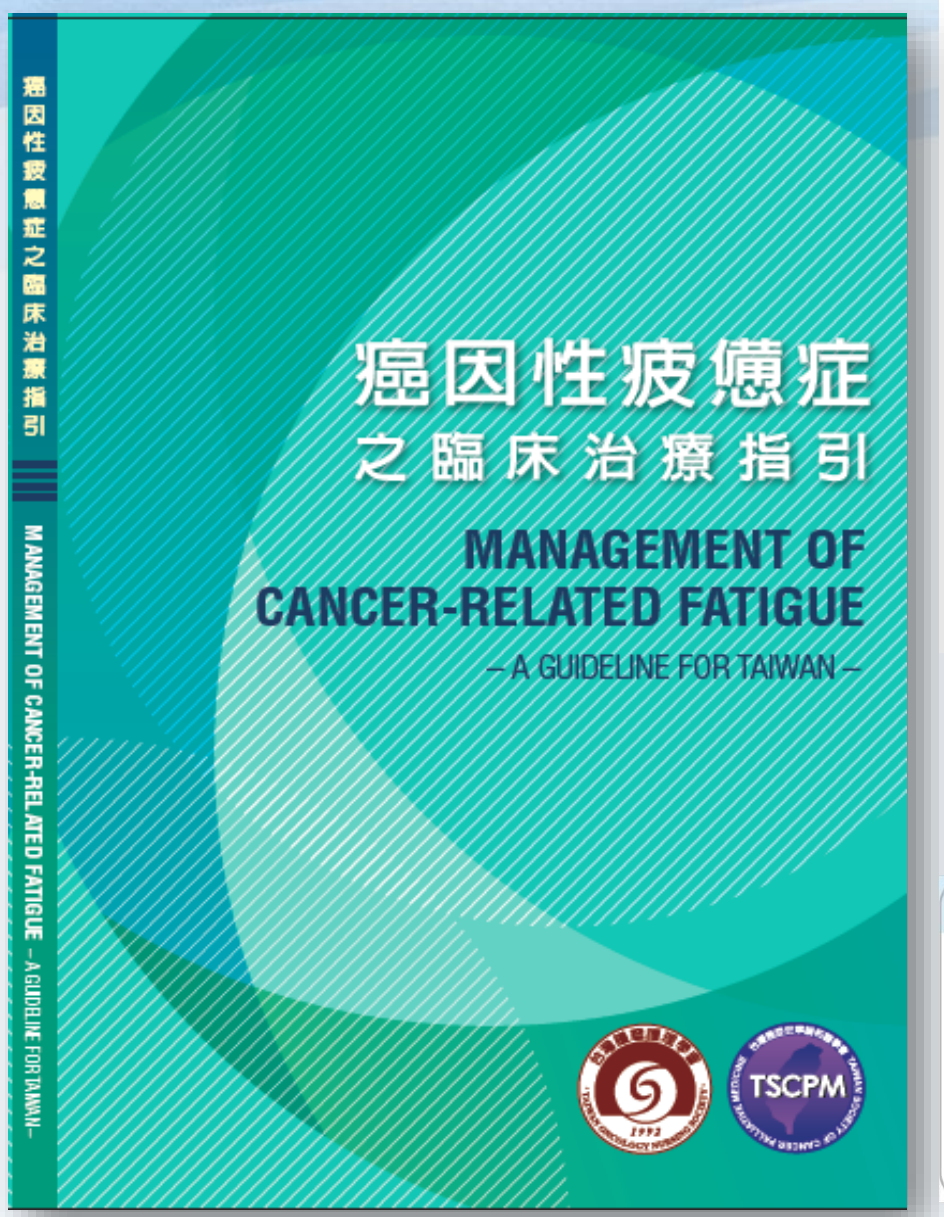
  成人每次劑量 500 mg，以 2.5 - 3.5 小時點滴靜脈滴注。

  每週2 - 4次，使用2 - 4週。
- 靜脈滴注溶液製備:
  - ✓ 從500 mL注射用生理食鹽水點滴瓶中抽取10mL，注入本品藥瓶中，充分混合至完全溶解後，注射回原500 mL生理食鹽水點滴瓶中，混合均勻，即完成製備。。
- 安全性:

  依據上市後第四期臨床試驗，懷特血寶注射劑常見的不良反應(>2%)包括皮疹(9.21%)、發燒(7.24%)、感覺冷(5.26%)、寒顫(2.63%)及過敏(2.63%)。預防輸注反應可考慮事先給予抗組織胺，及/或以較慢輸住速率，延長輸注時間完成輸注療程

Clinical Experiences in CRF Treatment

Case sharing



癌因性疲憊症之臨床治療指引電子版連結由此去

「藥品給付規定」修訂對照表

第 3 節 代謝及營養劑 Metabolic & nutrient agents

（自110年3月1日生效）

修訂後給付規定	原給付規定
3.3.20.Polysaccharides of Astragalus membranaceus(如 PG2 Lyo. Injection)：(110/3/1) 使用本藥品應符合下列各條件： 1.限用於第四期因疾病進展導致中重度疲憊之乳癌成人患者(不含住院安寧療護病患)。 2.臨床上需符合 ICD-10 診斷標準，病歷上應詳細記載疲憊分數≧4(BFI-T 或 VAS)，經其他處置無效之中重度癌因性疲憊症患者。 3.ECOG 需為 0-2 之患者。 4.每位病人終生給付 6 支為上限。 5.需經事前審查核准後使用。	無

備註：劃線部分為新修訂規定

Polysaccharides of Astragalus membranaceus(PG2 Lyo. Injection)
健保給付規定

第三節 代謝及營養劑 (自110年3月1日生效)

使用本藥品應符合下列各條件：

1. 用於**第四期乳癌成人患者**因疾病進展導致中重度疲憊**(不含住院安寧療護病患)**。
2. 臨床上需符合ICD-10診斷標準，病歷上應詳細記載疲憊分數≥4 (BFI-T或 VAS)，**經其他處置無效**之中重度癌因性疲憊症患者。
3. ECOG需為0-2之患者。
4. 每位病人終生給付6支為上限。
5. 需經事先審查核准後使用。

”Cure sometimes, treat often, comfort always“

Hippocrates