Supplementary Material

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

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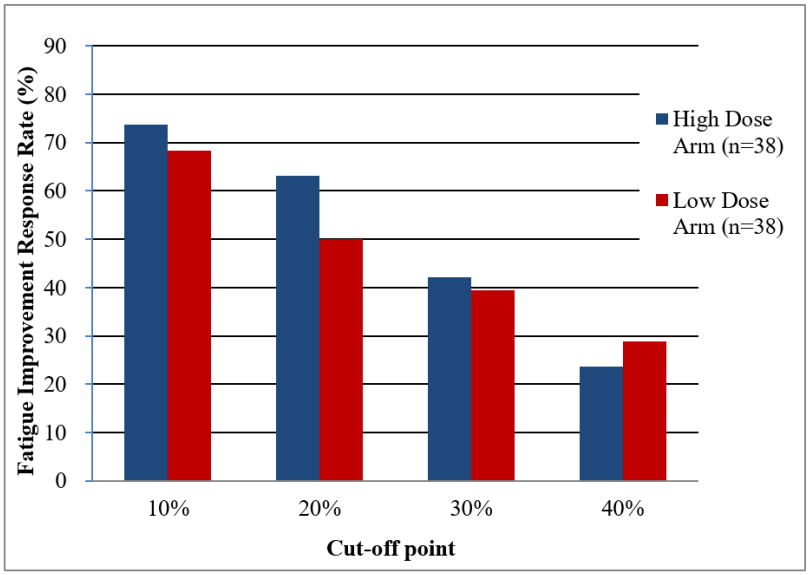

Co-variable Controlled ITT Population			
	N = 38	*N* = 38	
10%	28 (73.68%)	26 (68.42%)	(−0.15, 0.26)
20%	24 (63.16%)	19 (50.00%)	(−0.09, 0.35)
30%	16 (42.11%)	15 (39.47%)	(−0.19, 0.25)
40%	9 (23.68%)	11 (28.95%)	(−0.25, 0.15)

Figure S1. Summary of Fatigue Improvement Response Rate at Cycle 1 Week 4 (Patients without chemotherapy, radiation therapy, or steroid treatments).

Table S1. List of IRB approval information.

IRB	Approval Dated	IRB No.
Joint Institutional Review Board	2012/05/02	12-010-A
Institutional Review Board of Tri-Service General Hospital	2012/04/18	2-101-01-001
China Medical University & Hospital Research Ethics Committee	2012/05/18	DMR101-IRB2-032
Taipei Medical University–Joint Institutional Review Board	2012/07/03	201205017
Institutional Review Board of the Chi Mei Medical Center	2012/08/09	10108-L04
Chang Gung Medical Foundation Institutional Review Board	2012/11/02	101-2875A1
Mackay Memorial Hospital Institutional Review Board	2012/10/15	12CT026A
Institutional Review Board Changhua Christian Hospital	2012/09/13	120803

Table S2. Cancer types of patients enrolled in this study.

Variable/Statistics	High Dose Arm (*N* = 111)	Low Dose Arm (*N* = 103)
Cancer type		
Transitional cell carcinoma	1 (0.90%)	0 (0.00%)
bile duct cancer	4 (3.60%)	5 (4.85%)
bladder cancer	1 (0.90%)	0 (0.00%)
breast cancer	16 (14.41%)	12 (11.65%)
colon cancer	13 (11.71%)	11 (10.68%)
duodenal caner	1 (0.90%)	0 (0.00%)
esophageal cancer	6 (5.41%)	8 (7.77%)
gallbladder cancer	1 (0.90%)	0 (0.00%)
gastric cancer	10 (9.01%)	10 (9.71%)
gastrointestinal stromal cancer	0 (0.00%)	1 (0.97%)
hepatobiliary cancer	1 (0.90%)	0 (0.00%)
hypopharyngeal cancer	1 (0.90%)	0 (0.00%)
laryngeal cancer	0 (0.00%)	2 (1.94%)
leukemia	1 (0.90%)	0 (0.00%)
lip and/or oral cavity cancer	4 (3.60%)	2 (1.94%)
liposarcoma	2 (1.80%)	2 (1.94%)
liver cancer	4 (3.60%)	6 (5.83%)
liver cancer, bile duct cancer	0 (0.00%)	1 (0.97%)
lung cancer	20 (18.02%)	14 (13.59%)
lymphoma	1 (0.90%)	2 (1.94%)
malignant peripheral nerve sheath tumor	0 (0.00%)	1 (0.97%)
nasopharyngeal cancer	1 (0.90%)	3 (2.91%)
oropharyngeal cancer	0 (0.00%)	1 (0.97%)
ovarian cancer	2 (1.80%)	3 (2.91%)
pancreatic cancer	9 (8.11%)	9 (8.74%)
pleural mesothelioma	1 (0.90%)	0 (0.00%)
Prostate cancer	2 (1.80%)	1 (0.97%)
rectal cancer	2 (1.80%)	3 (2.91%)
renal cancer	1 (0.90%)	1 (0.97%)
thymic cancer	4 (3.60%)	2 (1.94%)
tonsil cancer	0 (0.00%)	1 (0.97%)
ureteric cancer	1 (0.90%)	0 (0.00%)
uterine cancer	0 (0.00%)	1 (0.97%)
UNKNOWN	1 (0.90%)	1 (0.97%)

Table S3. Change in Brief Fatigue Inventory-Taiwanese version score at each evaluation time point.

Cycle/Visit	High Dose Arm (*N* = 111)	Low Dose Arm (*N* = 103)	Differences among Groups with 95% CI
Cycle 1			
Baseline			
n	111	103	
Mean (SD)	6.80 (1.52)	6.75 (1.25)	(−0.33, 0.43)
Median (min, max)	6.55 (4, 10)	6.88 (4.11, 9.44)	
95% CI	(6.51, 7.08)	(6.50, 6.99)	
Week 1 Visit 3			
n	110	102	
Mean (SD)	6.05 (1.77)	5.94 (1.58)	(−0.34, 0.57)
Median (min, max)	6 (0, 9.33)	5.88 (2.11, 9.55)	
95% CI	(5.72, 6.39)	(5.63, 6.25)	
Week 1 Visit 3 Change from Baseline			
n	110	102	
Mean (SD)	−0.75 (1.25)	−0.80 (1.13)	(−0.28, 0.37)
Median (min, max)	−0.725 (−4.78, 2.89)	−0.78 (−4.34, 1.78)	
95% CI	(−0.99, −0.52)	(−1.02, −0.58)	
* *p*-value	<0.0001	<0.0001	
Week 2			
n	108	102	
Mean (SD)	5.72 (1.89)	5.49 (1.87)	(−0.29, 0.74)
Median (min, max)	5.88 (0.55, 9.66)	5.55 (1.22, 9.44)	
95% CI	(5.36, 6.08)	(5.13, 5.86)	
Week 2 Change from Baseline			
n	108	102	
Mean (SD)	−1.12 (1.49)	−1.25 (1.71)	(−0.31, 0.57)
Median (min, max)	−1.11 (−5.22, 3.34)	−1.275 (−6.55, 3.23)	
95% CI	(−1.40, −0.83)	(−1.58, −0.91)	
* *p*-value	<0.0001	<0.0001	
Week 3			
n	110	100	
Mean (SD)	5.58 (2.02)	5.40 (1.85)	(−0.35, 0.71)
Median (min, max)	5.605 (0, 10)	5.33 (0.55, 9.44)	
95% CI	(5.20, 5.97)	(5.03, 5.77)	
Week 3 Change from Baseline			
n	110	100	
Mean (SD)	−1.21 (1.80)	−1.37 (1.65)	(−0.31, 0.63)
Median (min, max)	−1 (−6.78, 3.89)	−1.28 (−7.22, 2.56)	
95% CI	(−1.55, −0.87)	(−1.70, −1.04)	
* *p*-value	<0.0001	<0.0001	
Week 4			
n	109	103	
Mean (SD)	5.47 (1.95)	5.29 (1.88)	(−0.34, 0.70)
Median (min, max)	5.55 (0, 9.77)	5.11 (0.33, 9.44)	
95% CI	(5.10, 5.84)	(4.93, 5.66)	
Week 4 Change from Baseline			
n	109	103	
Mean (SD)	−1.32 (1.77)	−1.45 (1.83)	(−0.35, 0.62)
Median (min, max)	−1.44 (−6.23, 3.34)	−1.22 (−7.44, 3.11)	
95% CI	(−1.65, −0.98)	(−1.81, −1.10)	
* *p*-value	<0.0001	<0.0001	
Cycle 2			
Week 1 Visit 3			
n	99	77	
Mean (SD)	5.11 (2.12)	4.89 (2.02)	(−0.41, 0.84)
Median (min, max)	5 (0, 9.77)	4.77 (0, 9.66)	

95% CI	(4.68, 5.53)	(4.43, 5.35)	
Week 1 Visit 3 Change from Baseline			
n	99	77	
Mean (SD)	−1.75 (1.81)	−1.83 (1.96)	(−0.48, 0.64)
Median (min, max)	−2 (−5.77, 2.44)	−1.78 (−7.88, 3.11)	
95% CI	(−2.11, −1.39)	(−2.27, −1.38)	
* *p*-value	<0.0001	<0.0001	
Week 2			
n	89	71	
Mean (SD)	4.99 (2.22)	5.12 (1.97)	(−0.79, 0.54)
Median (min, max)	4.66 (0.22, 9.66)	4.66 (1, 9.66)	
95% CI	(4.52, 5.46)	(4.65, 5.58)	
Week 2 Change from Baseline			
n	89	71	
Mean (SD)	−1.80 (2.16)	−1.60 (1.92)	(−0.85, 0.45)
Median (min, max)	−2.11 (−6, 3.56)	−1.77 (−7.33, 3.22)	
95% CI	(−2.26, −1.35)	(−2.06, −1.15)	
* *p*-value	<0.0001	<0.0001	
Week 3			
n	81	67	
Mean (SD)	4.82 (2.08)	4.70 (2.05)	(−0.56, 0.79)
Median (min, max)	4.55 (0, 9.88)	4.22 (0.33, 8.77)	
95% CI	(4.36, 5.28)	(4.20, 5.20)	
Week 3 Change from Baseline			
n	81	67	
Mean (SD)	−2.00 (2.15)	−1.96 (2.06)	(−0.73, 0.65)
Median (min, max)	−1.89 (−6.78, 3.78)	−2 (−6.55, 3.22)	
95% CI	(−2.48, −1.53)	(−2.46, −1.46)	
* *p*-value	<0.0001	<0.0001	
Week 4			
n	75	65	
Mean (SD)	4.76 (2.24)	4.54 (2.14)	(−0.52, 0.95)
Median (min, max)	4.44 (0.11, 10)	4.33 (0, 9.11)	
95% CI	(4.24, 5.28)	(4.01, 5.07)	
Week 4 Change from Baseline			
n	75	65	
Mean (SD)	−2.06 (2.07)	−2.09 (2.23)	(−0.69, 0.74)
Median (min, max)	−2.22 (−7.23, 3.45)	−2.11 (−7.55, 3.22)	
95% CI	(−2.54, −1.59)	(−2.64, −1.54)	
* *p*-value	<0.0001	<0.0001	
[Cycle 2- Week 4 change from baseline]-[Cycle 1- Week 4 change from baseline]			
n	75	65	
Mean (SD)	−0.56 (1.56)	−0.37 (1.66)	(−0.72, 0.35)
Median (min, max)	−0.55 (−5.44, 3.56)	−0.11 (−5.22, 3.89)	
95% CI	(−0.91, −0.20)	(−0.78, 0.04)	
* *p*-value	0.0028	0.0768	

* Compared to baseline.

Table S4. Summary of adverse events.

Status/Category	High Dose Arm (*N* = 152)		Low Dose Arm (*N* = 155)	
	Event	Subject	Event	Subject
	E	n (%)	E	n (%)
Total number of adverse events				
-	872 (100%)	141 (92.76%)	878 (100.00%)	148 (95.48%)
Treatment-related adverse events				
-	76 (8.72%)	33 (21.71%)	57 (6.49%)	21 (13.55%)
Total number of severe adverse events				
-	64 (7.34%)	53 (34.87%)	81 (9.23%)	72 (46.45%)
Severity				
Grade 1 Mild	442 (50.69%)	112 (73.68%)	391 (44.53%)	116 (74.84%)
Grade 2 Moderate	302 (34.63%)	100 (65.79%)	290 (33.03%)	93 (60.00%)
Grade 3 Severe	86 (9.86%)	48 (31.58%)	117 (13.33%)	57 (36.77%)
Grade 4 Life-threatening or disabling	19 (2.18%)	14 (9.21%)	43 (4.90%)	18 (11.61%)
Grade 5 Death	23 (2.64%)	22 (14.47%)	37 (4.21%)	37 (23.87%)
Relationship to Study Drug				
Unrelated	729 (83.60%)	129 (84.87%)	769 (87.59%)	140 (90.32%)
Unlikely	67 (7.68%)	26 (17.11%)	52 (5.92%)	19 (12.26%)
Possibly	33 (3.78%)	17 (11.18%)	47 (5.35%)	14 (9.03%)
Probably	24 (2.75%)	9 (5.92%)	5 (0.57%)	4 (2.58%)
Definitely	19 (2.18%)	8 (5.26%)	5 (0.57%)	3 (1.94%)
Outcome				
Recovered	417 (47.82%)	109 (71.71%)	377 (42.94%)	110 (70.97%)
Recovered with residual effects	3 (0.34%)	3 (1.97%)	7 (0.80%)	5 (3.23%)
Continuing	314 (36.01%)	98 (64.47%)	304 (34.62%)	
Death	123 (14.11%)	23 (15.13%)	181 (20.62%)	37 (23.87%)
Lost to follow-up	15 (1.72%)	1 (0.66%)	9 (1.03%)	1 (0.65%)
Action Taken with Study Drug				
No action	353 (40.48%)	111 (73.03%)	320 (36.45%)	106 (68.39%)
Treatment given	500 (57.34%)	124 (81.58%)	527 (60.02%)	130 (83.87%)
Withdrawn from study	19 (2.18%)	19 (12.50%)	31 (3.53%)	29 (18.71%)

Table S5. Logistic regression analysis of fatigue improvement response rate for high dose arm subjects.

	High Dose Arm				
	Cut-off Points = 10%			Multivariate Analysis	
Variable/Status	**Responder (*N* = 73)**	**Non-Responder (*N* = 38)**	**Univariate Analysis *p*-Value ***	**Odds Ratio (95% CI)**	***p*-Value ****
Age (years)					
n	73	38	0.1018 [T]	0.979 (0.931, 1.029)	0.4074
Mean (SD)	61.00 (10.90)	64.50 (10.00)			
Median (min, max)	62 (28, 84)	65 (40, 81)			
95% CI	(58.46, 63.54)	(61.21, 67.79)			
Gender					
Male	35 (47.95 %)	20 (52.63 %)	0.6394 [C]	1.088 (0.403, 2.933)	0.8683
Female	38 (52.05 %)	18 (47.37 %)			
Body mass index (BMI) (kg/m^2)					
<19	20 (28.17 %)	13 (34.21 %)	0.5130 [C]	0.760 (0.263, 2.198)	0.6126
≥19	51 (71.83 %)	25 (65.79%)			
number of missing	2	0			
Body weight loss in previous 6 months					
<5%	26 (36.62 %)	17 (44.74%)	0.4086 [C]	0.601 (0.215, 1.680)	0.3319
≥5%	45 (63.38%)	21 (55.26 %)			
NA	2	0			
Baseline KPS score					
30–50	11 (15.07 %)	19 (50.00 %)	<0.0001 [C]	0.138 (0.048, 0.400)	0.0003
60–90	62 (84.93 %)	19 (50.00 %)			
Baseline BFI score					
4–6	39 (53.42 %)	22 (57.89 %)	0.6533 [C]	0.662 (0.255, 1.716)	0.3959
7–10	34 (46.58 %)	16 (42.11 %)			
Cancer Type: three category					
Lung cancer	13 (17.81 %)	7 (18.42 %)	0.6994 [C]		
Breast cancer	12(16.44 %)	4 (10.53 %)		0.944 (0.155, 5.743)	0.9504
other	48 (65.75 %)	27 (71.05 %)		0.960 (0.288, 3.200)	0.9464
Albumin (g/dL)					
<3.0	10 (13.70 %)	5 (13.16 %)	0.9370 [C]	1.799 (0.426, 7.602)	0.4245
≥3.0	63 (86.30 %)	33 (86.84 %)			
Hemoglobin (g/dL)					
<10	27 (36.99 %)	17 (44.74 %)	0.4283 [C]	0.508 (0.195, 1.322)	0.1651

≥10	46 (63.01 %)	21 (55.26 %)			
Peripheral blood TLC (/uL)					
<700	24 (32.88 %)	10 (26.32 %)	0.4768 [C]	1.624 (0.556, 4.743)	0.3751
≥700	49 (67.12 %)	28 (73.68 %)			

* The two sample *t*-test [T] 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.

Table S6. Logistic regression analysis of fatigue improvement response rate for low dose arm subjects.

	Low Dose Arm				
	Cut-off Points = 10%			**Multivariate Analysis**	
Variable/Status	**Responder (*N* = 67)**	**Non-responder (*N* = 36)**	**Univariate Analysis *p*-Value ***	**Odds Ratio (95% CI)**	***p*-Value ****
Age (years)					
n	67	36	0.8735 [W]	1.019 (0.980, 1.060)	0.3457
Mean (SD)	63.21 (11.65)	62.22 (11.34)			
Median (min, max)	64 (28, 91)	65 (22, 76)			
95% CI	(60.37, 66.05)	(58.38, 66.06)			
Gender					
Male	40 (59.70 %)	26 (72.22 %)	0.2066 [C]	0.676 (0.224, 2.036)	0.4864
Female	27 (40.30 %)	10 (27.78 %)			
Body mass index (BMI) (kg/m^2)					
<19	19 (28.36 %)	14 (40.00 %)	0.2328 [C]	0.700 (0.250, 1.958)	0.4965
≥19	48 (71.64 %)	21 (60.00%)			
number of missing	0	1			
Body weight loss in previous 6 months					
<5%	37 (55.22 %)	13 (36.11 %)	0.0642 [C]	1.709 (0.661, 4.421)	0.2691
≥5%	30 (44.78%)	23 (63.89 %)			
Baseline KPS score					
30–50	11 (16.42 %)	12 (33.33 %)	0.0494 [C]	0.335 (0.117, 0.960)	0.0417
60–90	56 (83.58 %)	24 (66.67 %)			
Baseline BFI score					
4–6	33 (49.25 %)	19 (52.78 %)	0.7330 [C]	0.932 (0.381, 2.280)	0.8767
7–10	34 (50.75 %)	17 (47.22 %)			
Cancer Type: three category					
Lung cancer	9 (13.43 %)	5 (13.89 %)	0.4040 [F]		

Breast cancer	10 (14.93 %)	2 (5.56 %)		1.948 (0.214, 17.735)	0.5541
other	48 (71.64 %)	29 (80.56 %)		1.045 (0.286, 3.819)	0.9468
Albumin (g/dL)					
<3.0	10 (14.93 %)	6 (16.67 %)	0.8161 [C]	0.841 (0.230, 3.076)	0.7934
≥3.0	57 (85.07 %)	30 (83.33 %)			
Hemoglobin (g/dL)					
<10	21 (31.34 %)	13 (36.11 %)	0.6237 [C]	1.286 (0.467, 3.539)	0.6266
≥10	46 (68.66 %)	23 (63.89 %)			
Peripheral blood TLC (/uL)					
<700	22 (32.84 %)	8 (22.22 %)	0.2583 [C]	1.866 (0.656, 5.304)	0.2419
≥700	45 (67.16 %)	28 (77.78 %)			

* 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] or Fisher's exact test [F] 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.

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