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Exploratory study on Anti-inflammatory effect and QOL by low molecular fucoidan (LMF) for advanced cancer patients in Japan.

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Disclosure of Conflict of Interest

Name of first author: Hidenori Takahashi

I have no COI

with regard to our presentation.

BACKGROUND -1

- Standard chemotherapy (Cx) against advanced cancer still face to their limited efficacies and side-effects.

- Therefore, patients are forced to search for various complementary and alternative therapies.

- One in Japan is fucoidan, a high molecular weight sulfated polysaccharide, extracted from seaweeds.

Cladosiphon **including fucoidan**
(Japanese name: “Mozuku”)

Fucoidan exhibits broad biological activities in basic research; such as anti-cancer, anti-oxidant and anti-inflammatory effects.

Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer

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Abstract. Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI) has become a standard regimen for advanced or recurrent colorectal cancer. Numerous studies have reported that long-term use of FOLFOX or FOLFIRI leads to better survival for these patients. Thus, control of the toxicity of these drugs may be crucial to prolonging survival. Fucoidan is one of the major sulfated polysaccharides of brown seaweeds and exhibits a wide range of biological activities. In the present study, we analyzed the effect of fucoidan on suppressing the toxicity of anti-cancer drugs. A total of 20 patients with unresectable advanced or recurrent colorectal cancer scheduled to undergo treatment with FOLFOX or FOLFIRI were randomly allocated into a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). Results showed that fucoidan regulated the occurrence

(LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) has become the standard regimen for advanced or recurrent colorectal cancer, and a high response rate has been reported (1-3). However, FOLFOX and FOLFIRI are associated with severe toxicity, such as nausea, vomiting, stomatitis, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia and liver dysfunction. A number of patients discontinue these effective chemotherapies due to toxicity. Thus, the prognosis of patients with unresectable advanced or recurrent colorectal cancer remains low despite advances in chemotherapeutic drugs.

To reduce the toxicity of chemotherapeutic drugs, various types of drugs or dietary supplements have been introduced (4-6). Among these supplements, fucoidan has been reported to exhibit anti-inflammatory, antiviral and anti-tumor activities (7-9). Fucoidan is a sulfated polysaccharide found mainly in various species of brown seaweeds such as kombu, wakame

Table II. Major adverse events.[a]

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Leukocytopenia	1	0	0.305
Neutropenia	3	4	0.639
Anemia	2	1	0.531
Thrombocytopenia	0	2	0.136
Nausea	1	1	1.000
Diarrhea	1	2	0.531
Stomatitis	3	1	0.264
Fatigue	1	6	0.019
Peripheral neuropathy	3	5	0.361
Liver dysfunction	0	2	0.136

[a]Adverse events ≥2.

General fatigue (≥ NCI-CTC Grade 2) due to Cx ; detected in 60% (6/10) of the control group, compared to 10% (1/10) in the fucoidan group (p=0.019)

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Overall survival with Fucoidan tended to be superior

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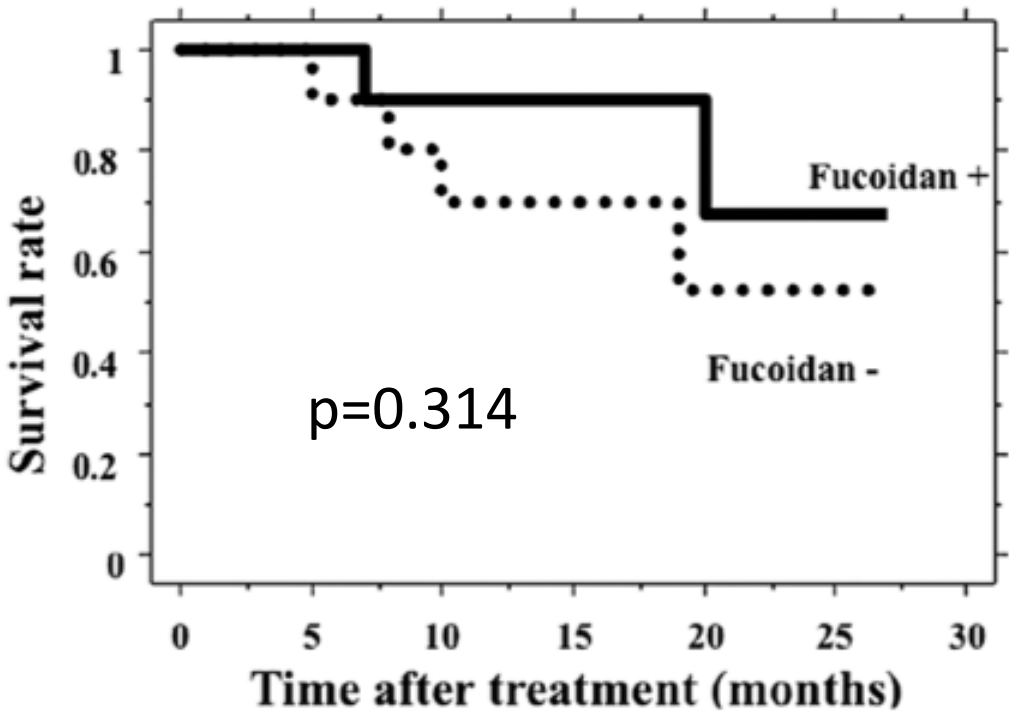


Figure 1. Survival curves of advanced or recurrent colorectal cancer patients. Solid line, survival curve of 10 patients who received fucoidan treatment. Dotted line, survival curve of 10 patients who did not receive fucoidan treatment. The difference was not significant (P=0.314).

The average number of Cx cycles (19.9 cycles) in the fucoidan group was significantly greater than that in the control group (10.8 cycles, P=0.016).

ONCOLOGY LETTERS 2: 319-322, 2011

BACKGROUND –2

- The recent prospective randomized clinical trial revealed that fucoidan significantly reduced fatigue caused by Cx for advanced cancer patients. (Oncology Letter 2011)

- However, the mechanism of alleviating Cx-induced fatigue by fucoidan remains to be determined.

- In addition, we experienced that an advanced pancreatic cancer patient under Cx + cancer vaccine “with fucoidan” showed a drastic tumor regression with a rapid improvement of QOL and C-reactive protein (CRP) value.

BACKGROUND –3

- Inflammation is known to affect the survival of tumor cells and the response to Cx or cancer immunotherapy.

（Science 2013）

- The inflammatory cytokines are also considered to be associated with fatigue in cancer patients.

（Brain, Behavior, and Immunity 2007）

METHODS

- Study was carried out from January 2014 to February 2015 with Institutional Ethics Committee approval.

- Patients with advanced cancer were recruited to ingest 400ml/day of fucoidan for at least 4 weeks (wks).

- The changes of some inflammatory biomarkers (WBC、CRP,IL-1β、IL-6、TNF-α) and QOL score using EORTC QLQ-C30 were monitored before, after 2 wks, and after 4 wks.

The Fucoidan product used in this study

- Commercially available as a product named “Power Fucoidan”
- Including low-molecular-weight fucoidan (LMF) over 80%.

Mozuku from the Kingdom of Tonga

↓

High molecular Fucoidan Extract

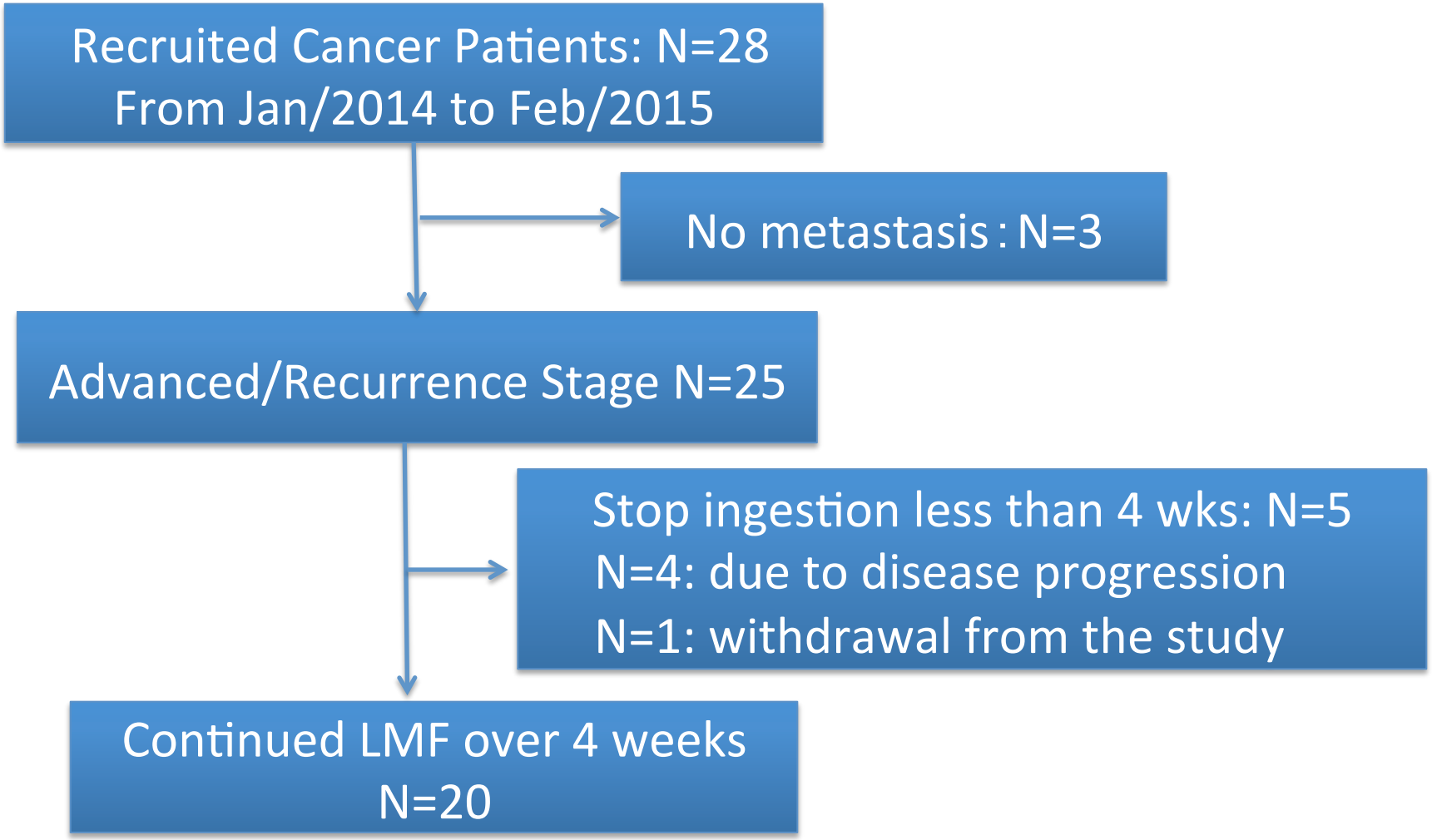
(Molecular weight :200,000～300,000)

↓ ← Enzymatic gradation

Low Molecular Fucoidan (LMF)

(Molecular weight <500 : over 80%)

Flow Diagram of the patients



Patient Characteristics

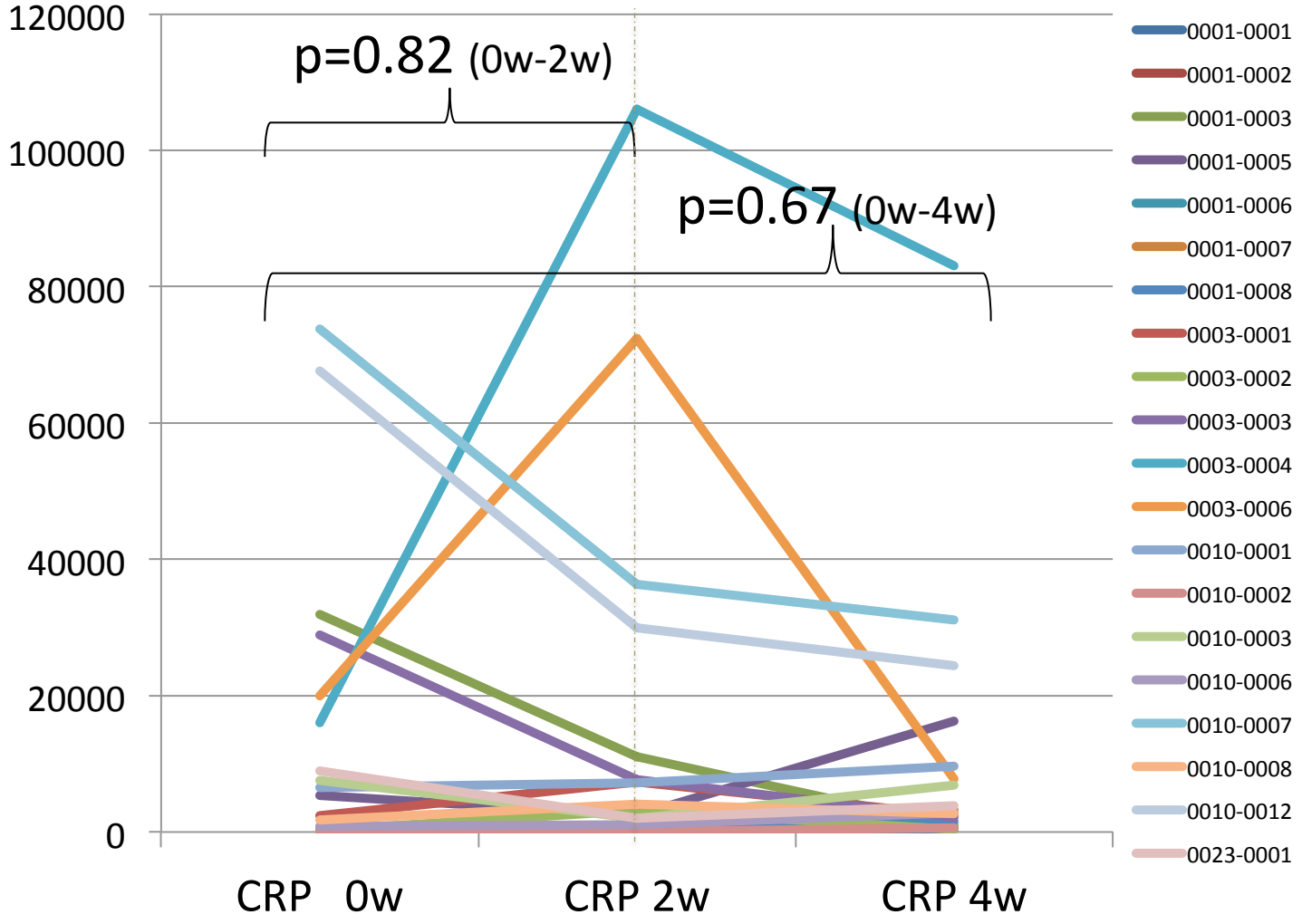
N=20		N (=20)	%
Age (range)		58.9 (18-76)	
Sex	Male	12	60.0%
Primary Organ of Cancer	Lung	4	20.0%
	Colon	4	20.0%
	Liver	2	10.0%
	Stomach	2	10.0%
	Pancreas	2	10.0%
	Sarcoma	2	10.0%
	Uterus	1	5.0%
	Breast	1	5.0%
	Prostate	1	5.0%
	Head & Neck	1	5.0%
Histological Subtype	Adeno-Ca.	13	65.0%
	Squamous Cell Ca	3	15.0%
	Others	4	20.0%
Standard Therapy before the Trial	Surgery	10	50.0%
	Chemotherapy	18	90.0%
	Radiotherapy	4	20.0%

Result 1. Change of biomarkers

N=20	Before	2 w	4 w	p-value (0w-2w)	p-value (0w-4w)
Blood Cell Counts					
WBC	6135 (±3519)	–	6195 (±3148)	–	0.94
Hb	11.2 (±1.9)	–	11.4 (±1.9)	–	0.64
Plt	23.1 (±13.3)	–	24.9 (±17.2)	–	0.50
Neu%	58.2 (±14.2)	–	56.1 (±14.4)	–	0.64
Lym%	29.5 (±14.1)	–	31.0 (±10.9)	–	0.72
N/L	2.7 (±1.8)	–	2.3 (±1.6)	–	0.42
CRP (ng/ml)	20019 (±33133)	21494 (±38580)	17738 (±37284)	0.82	0.67
Main Inflammatory Cytokines					
IL-1 β (pg/ml)	358.2 (±280.4)	189.9 (±143.0)	273.4 (±336.4)	0.006*	0.40
IL-6 (pg/ml)	2198.6 (±2523.6)	1522.8 (±1641.4)	1624.1 (±1347.6)	0.03*	0.24
TNF-α (pg/ml)	4819.4 (±3452.6)	3257.2 (±2900.5)	3985.1 (±2453.4)	0.03*	0.15

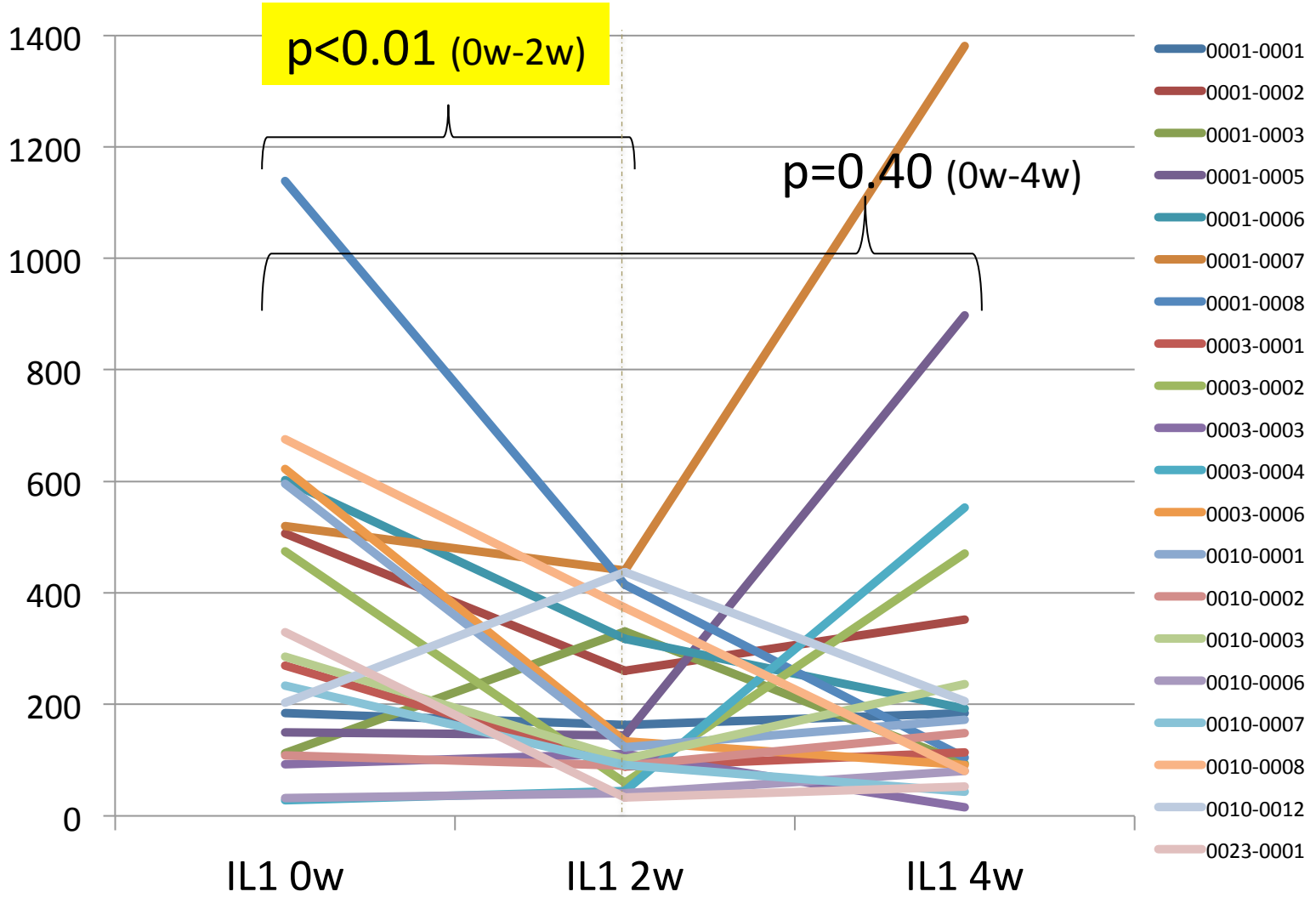
*p<0.05: statistically significant

High Sensitivity CRP (ex. 1000ng/ml=0.1mg/dl)



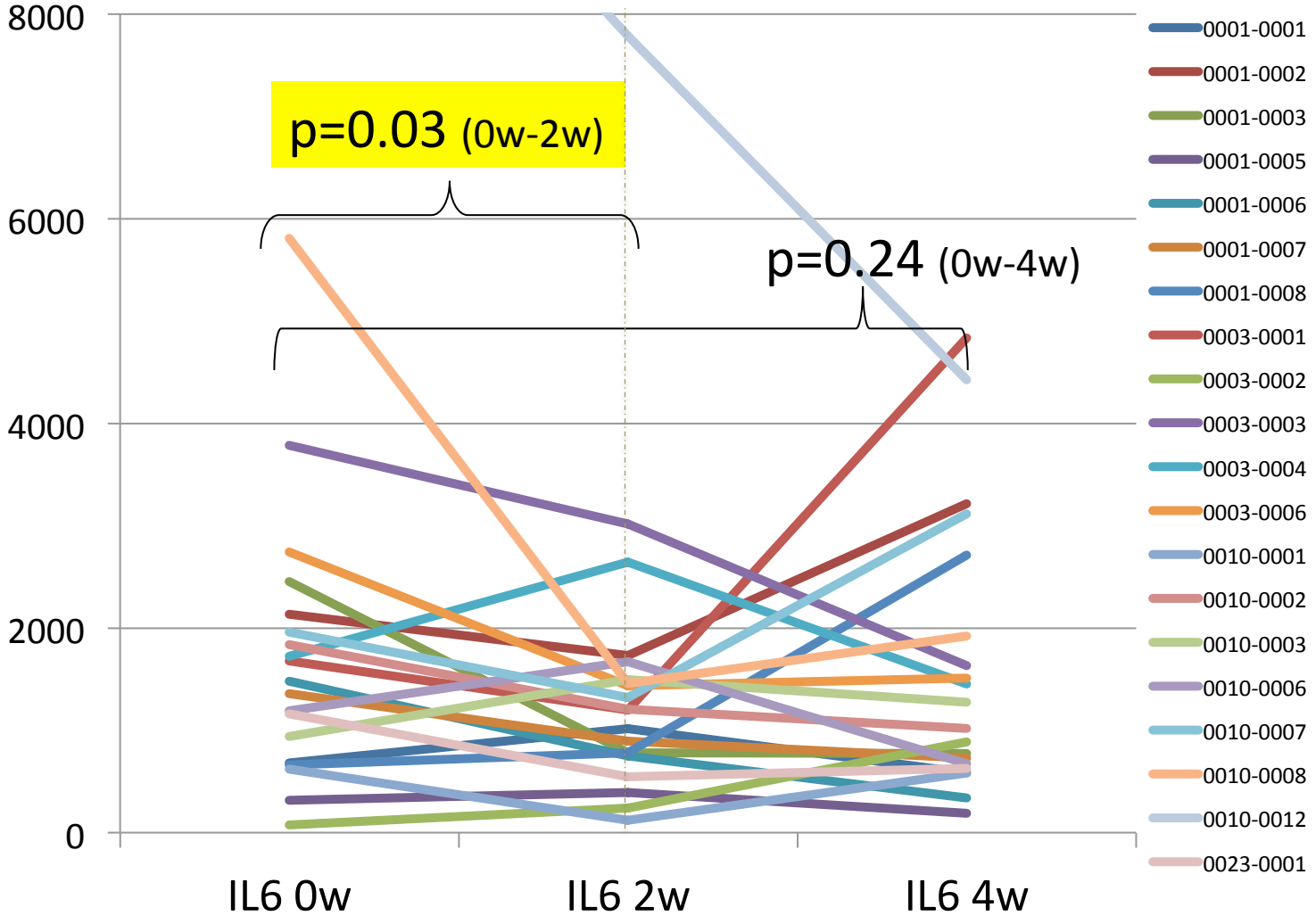
Response Rate (2w CRP < 0w CRP) during the first 2 wks : 50%（10/20; p=0.82)

< IL-1β >



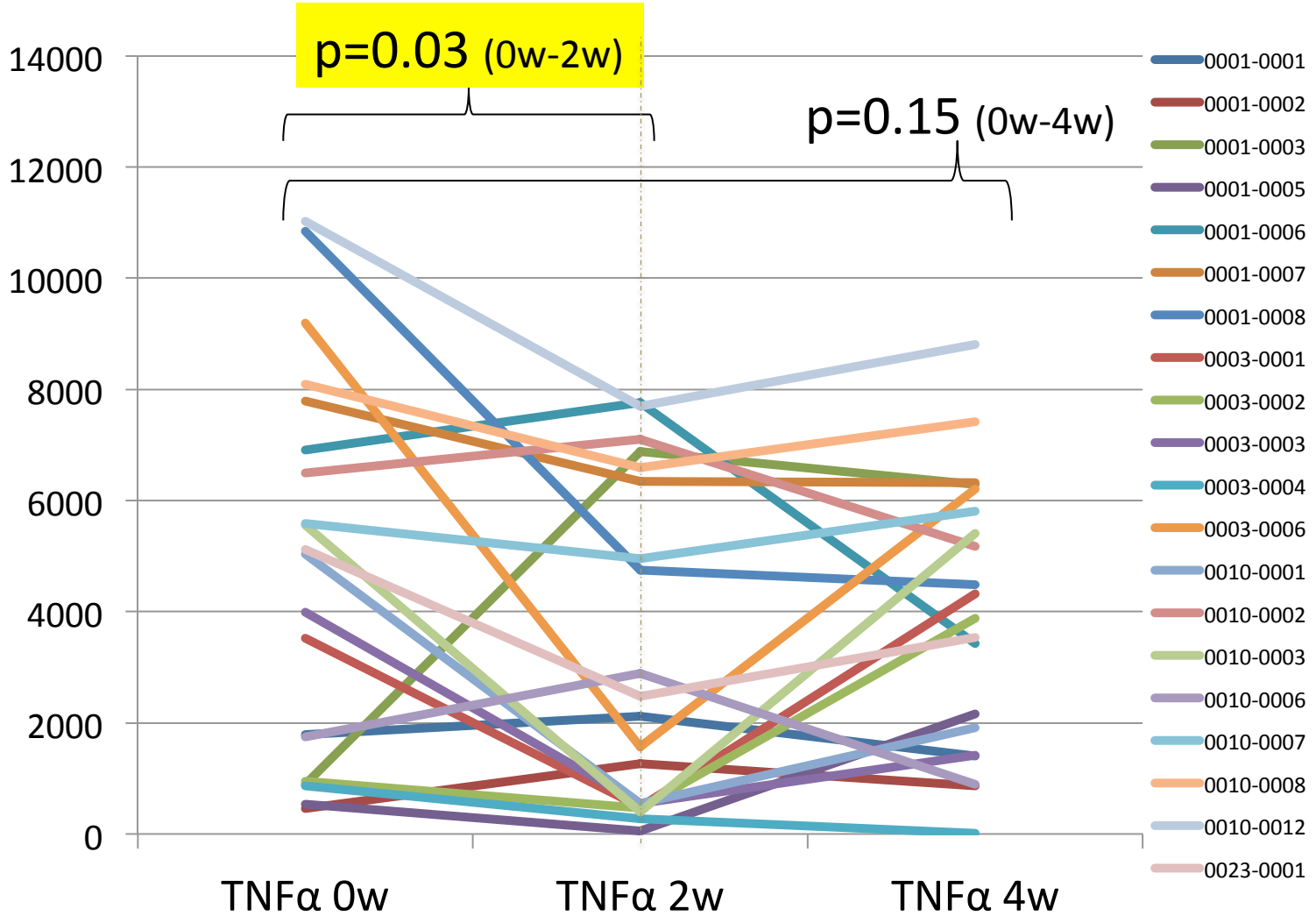
Response Rate (2w IL-1β < 0w IL-1β) during the first 2 wks :
75%（15/20; p<0.01)

< IL-6 >



Response Rate (2w IL-6 < 0w IL-6) during the first 2 wks:
65%（13/20; p=0.03）

< TNF-α >

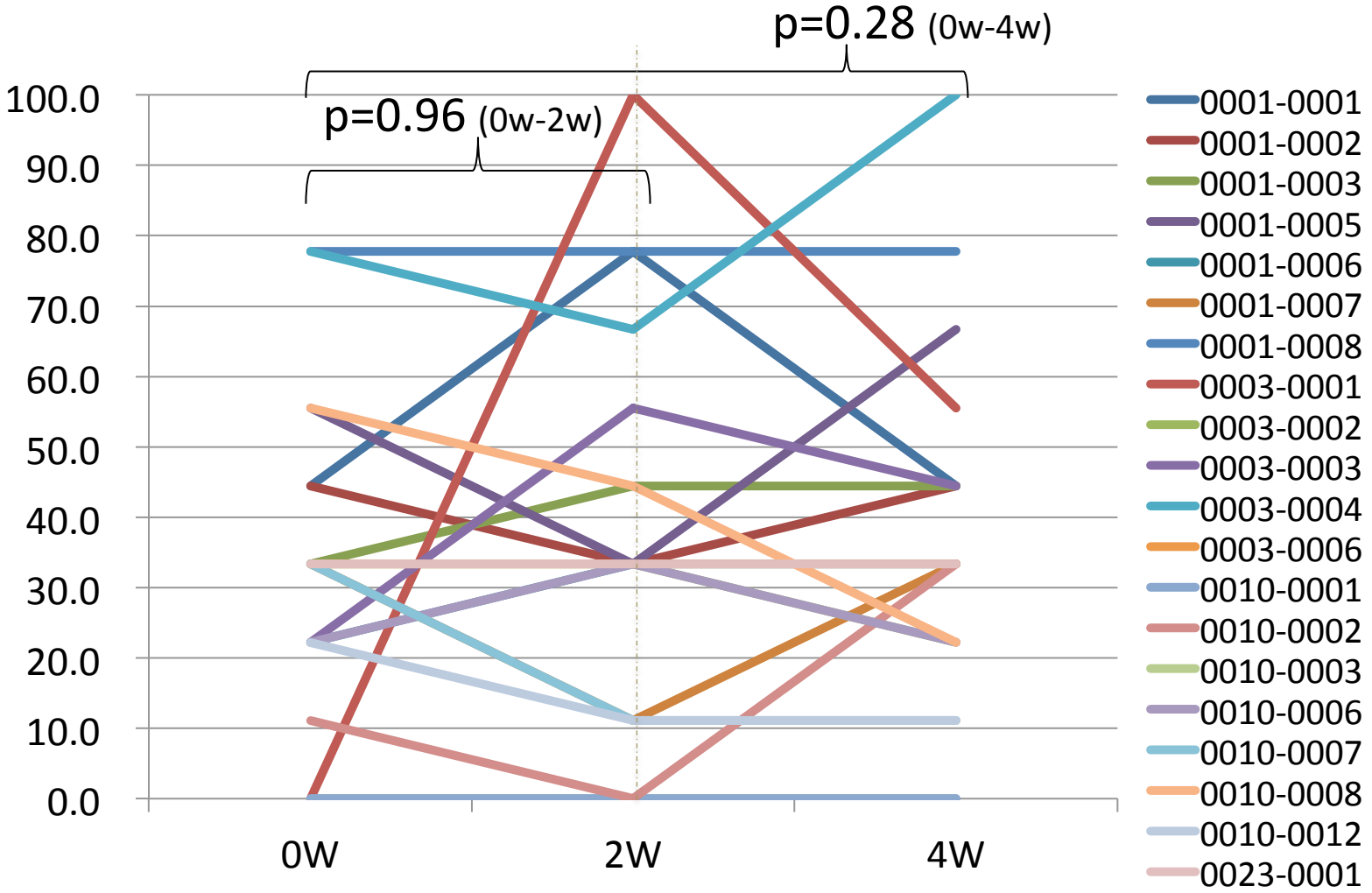


Response Rate (2w TNF-α < 0w TNF-α) during the first 2 wks：
70%（14/20; p=0.03）

RESULTS 2： Change of EORTC QLQ-C30 scores

N=20		Before	2w	4w	p-value (0w-2w)	p-value (0w-4w)
QOL (higher is better)	Global health status / QoL	58.3 (±23.9)	53.5 (±29.4)	58.3 (±21.6)	0.18	0.77
Functional Scales (higher is better)	Physical functioning	79.7 (±19.4)	76.8 (±23.7)	77.7 (±22.5)	0.34	0.43
	Role functioning	76.7 (±28.3)	76.5 (±26.4)	72.5 (±29.3)	0.78	0.61
	Emotional functioning	82.9 (±13.5)	78.5 (±19.7)	80.8 (±22.1)	0.45	0.75
	Cognitive functioning	83.3 (±20.2)	75.4 (±25.7)	80 (±23.3)	0.91	0.65
	Social functioning	86.7 (±19.2)	76.3 (±30.1)	81.7 (±24.7)	0.16	0.33
Symptom Scales (higher is worse)	Fatigue	35.0 (±21.1)	38.6 (±27.3)	38.6 (±24.1)	0.54	0.36
	Nausea and vomiting	6.7 (±11.3)	4.4 (±12.2)	8.3 (±23.9)	0.38	0.75
	Pain	24.2 (±27.3)	20.4 (±25.9)	21.7 (±27.6)	0.21	0.52
	Dyspnoea	20.0 (±27.4)	19.3 (±27.9)	18.3 (±27.5)	0.54	1
	Insomnia	22.8 (±33.4)	19.3 (±25.6)	21.7 (±29.1)	1	1
	Appetite loss	25.0 (±28.4)	29.8 (±29.2)	23.3 (±26.7)	0.48	0.72
	Constipation	13.3 (±25.1)	12.3 (±25.4)	10.0 (±24.4)	0.58	0.33
	Diarrhoea	23.3 (±32.6)	26.3 (±32.5)	21.7 (±22.4)	0.63	0.79

The change of “Fatigue” score



Response Rate (2w Fatigue < 0w Fatigue) during the first 2 wks : 42%（8/19; p=0.54）

Conclusion & Discussion

- Fucoidan could reduce the three main pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) of advanced cancer patients during the first 2 wks.

- This anti-inflammatory cytokine effect of fucoidan in a short time might contribute to the reduction of Cx-related side-effects, especially fatigue.

- Controlled studies are required to confirm the efficacy of fucoidan as supportive care for advanced cancer patients especially undergoing chemotherapy.

Discussion-suppl.

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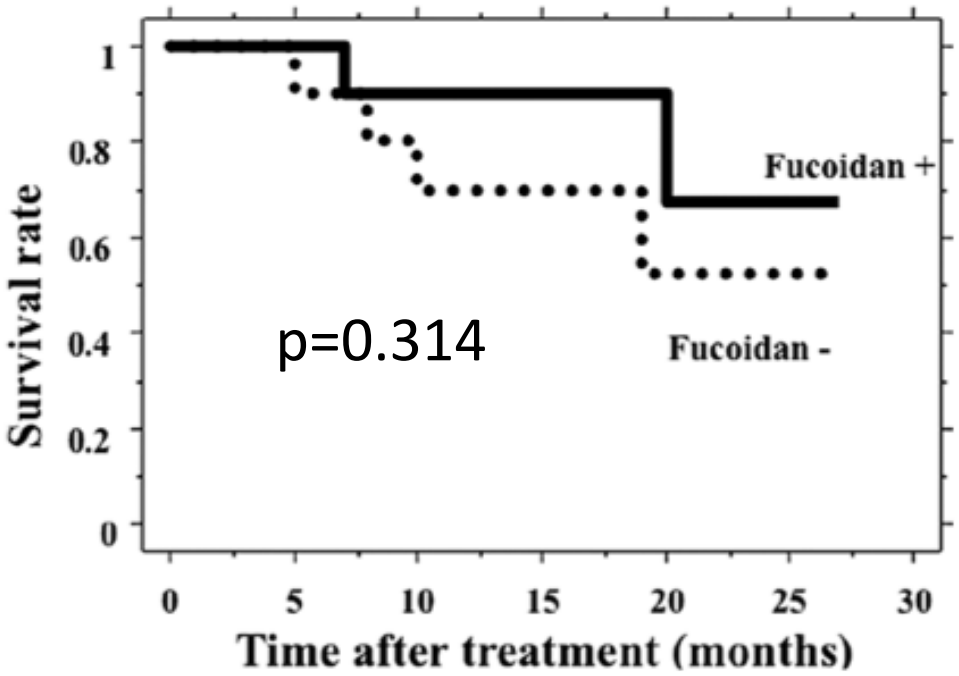

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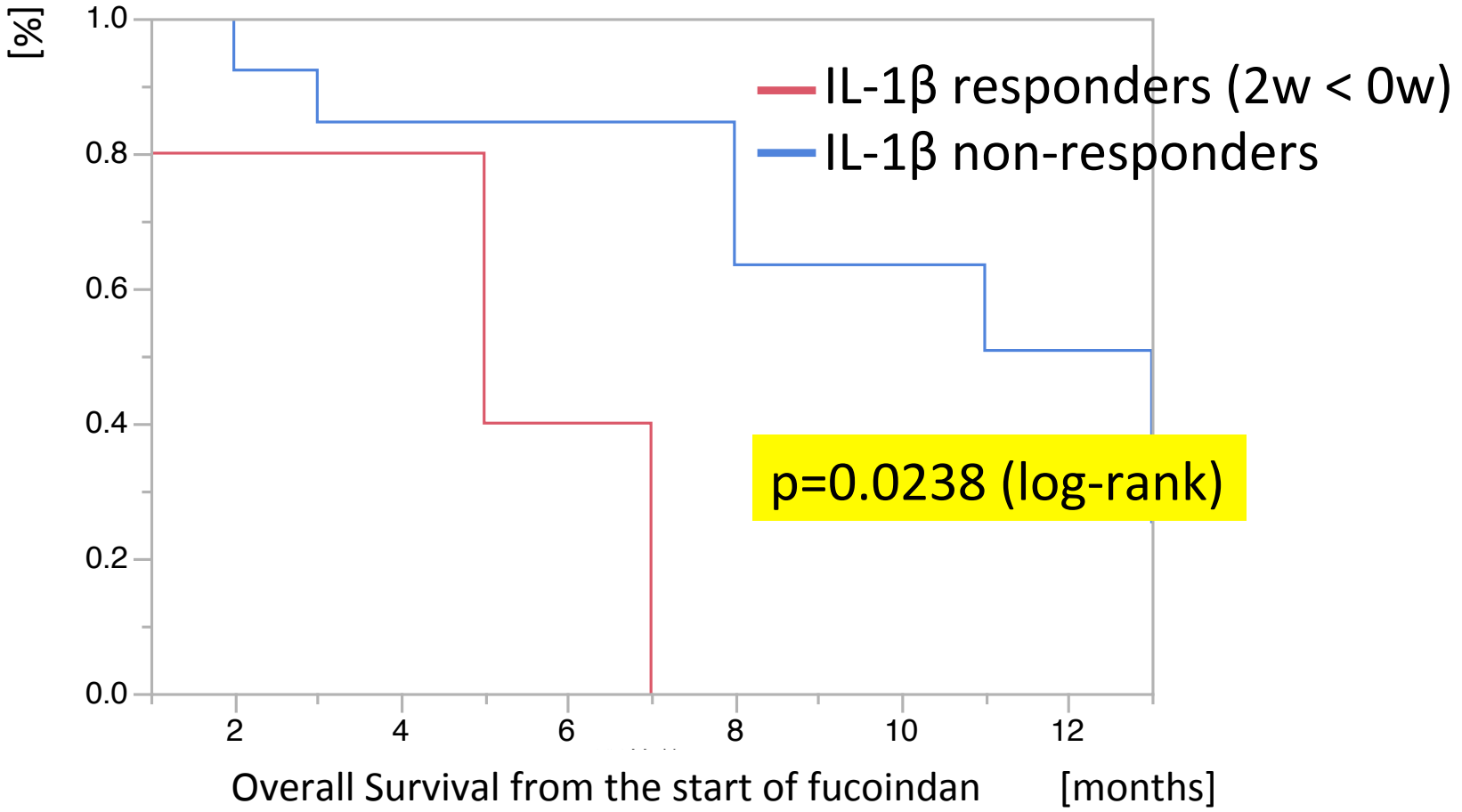
ONCOLOGY LETTERS 2: 319-322, 2011

Overall survival of “IL-1β responders (2w < 0w)” was superior compared to that of non-responders.



Chemotherapy induce IL-1β production, leading to suppress anticancer immunity and promote tumor growth.

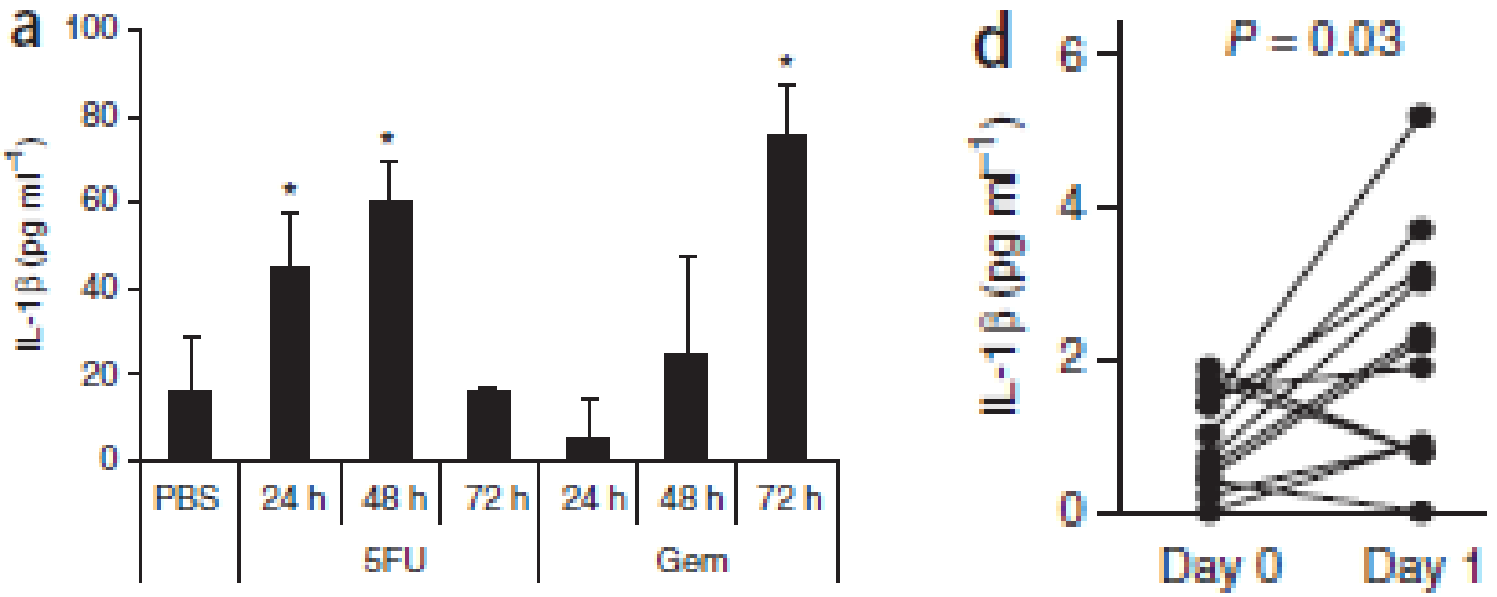
nature medicine

Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth

Mélanie Bruchard[1,2,8], Grégoire Mignot[1,2,8], Valentin Derangère[1,2], Fanny Chalmin[1,2], Angélique Chevriaux[1–3], Frédérique Végran[1,2], Wilfrid Boireau[4], Benoit Simon[4], Bernhard Ryffel[5], Jean Louis Connat[6], Jean Kanellopoulos[7], François Martin[1,2], Cédric Rébé[1–3], Lionel Apetoh[1–3,8] & François Ghiringhelli[1–3,8]

Chemotherapeutic agents are widely used for cancer treatment. In addition to their direct cytotoxic effects, these agents harness the host's immune system, which contributes to their antitumor activity. Here we show that two clinically used chemotherapeutic agents, gemcitabine (Gem) and 5-fluorouracil (5FU), activate the NOD-like receptor family, pyrin domain containing-3 protein (Nlrp3)-dependent caspase-1 activation complex (termed the inflammasome) in myeloid-derived suppressor cells (MDSCs), leading to production of interleukin-1β (IL-1β), which curtails anticancer immunity. Chemotherapy-triggered IL-1β secretion relied on lysosomal permeabilization and the release of cathepsin B, which bound to Nlrp3 and drove caspase-1 activation. MDSC-derived IL-1β induced secretion of IL-17 by CD4+ T cells, which blunted the anticancer efficacy of the chemotherapy. Accordingly, Gem and 5FU exerted higher antitumor effects when tumors were established in *Nlrp3*$^{-/-}$ or *Casp1*$^{-/-}$ mice or wild-type mice treated with interleukin-1 receptor antagonist (IL-1Ra). Altogether, these results identify how activation of the Nlrp3 inflammasome in MDSCs by 5FU and Gem limits the antitumor efficacy of these chemotherapeutic agents.

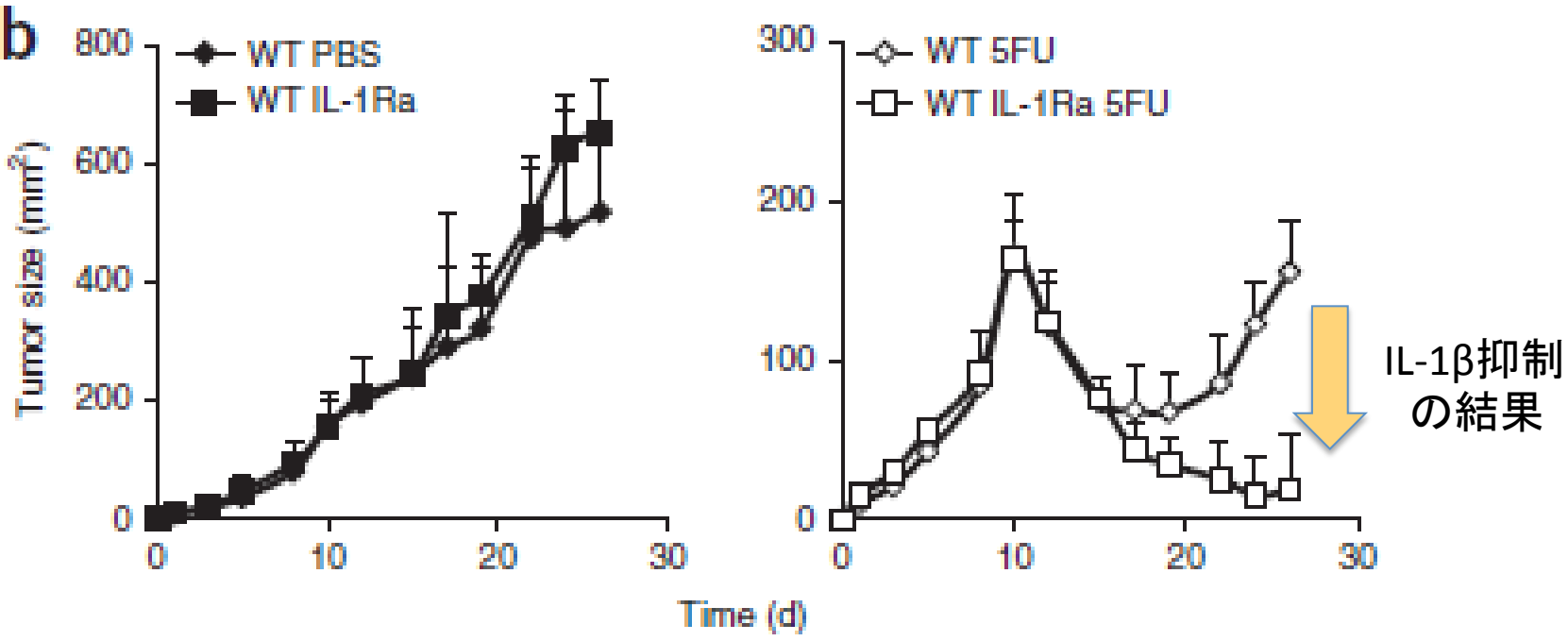
5FU and Gem promote the secretion of IL-1β



(a) MDSCs from wild-type tumor-bearing mice treated with Gem or 5FU secreted IL-1β.

(d) In the cohort of patients with metastatic colorectal cancer who were treated with 5FU-based chemotherapy, IL-1β serum concentrations were increased in 9 out of 12 patients 24 h after 5FU administration (P = 0.03)

IL-1β production restrains 5FU antitumor effect



Administration of anti IL-1 (IL-1Ra: Anakinra®) enhanced the antitumor efficacy of 5FU in the tumor-bearing model and the combination induced cure in 45% of the mice (**Fig. b**).

※IL-1Ra: Anakinra®: IL-1R antagonist

- Would you expect to see this same