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Case Report

Complete Remission of Multiple Pulmonary Metastases of Endometrial Adenocarcinoma Treated with a Mixture of Low Molecular Weight Fucoidan and *Canvaria gladiata* Extract: A Case Report

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ABSTRACT

Endometrial cancer (EC) is the most common malignant tumor in post-menopausal women, and the lung is one of the organs to which endometrial adenocarcinoma metastasizes. Chemotherapy is helpful for various malignancies, but not all are successful. A 71-year-old-Japanese-woman was diagnosed with metastatic lung cancer stage IV of primary endometrial adenocarcinoma. She received chemotherapy and hormone therapy after a total hysterectomy and pelvic lymphadenectomy. Subsequently, she visited this clinic for a second opinion as the metastatic lung cancer had repeated remissions and recurrences. Here, the authors report a case in which complete remission of metastatic lung cancer was achieved by using a product containing low molecular weight fucoidan extract (LMF) and *Canavalia gladiata* extract (CG) (LMF-CG) in combination with Medroxyprogesterone acetate (MPA) hormone therapy.

Keywords
Endometrioid adenocarcinoma; Pulmonary metastasis; Docetaxel+Carboplatin (DC) therapy; Hormone therapy; Low molecular weight fucoidan extract (LMF), *Canavalia gladiata* extract (CG).

INTRODUCTION

Endometrial carcinoma (EC) is the sixth most common gynecologic tumor in women worldwide and the fourth most common in incidence among women in Europe and North America.[1-3] EC is classified into several histological types, and its lung metastasis is the highest among gynecologic malignancies.[4] Advanced EC is less sensitive to chemotherapy, causes distant metastases, and has a poor prognosis.[3-5] Standard treatment for recurrent EC is chemotherapy; in this case, carboplatin and paclitaxel were combined with hormonal therapy. Bioactive ingredients derived from natural resources are considered suitable candidates as substitutes due to their low toxicity,[6] and fucoidan isolated from edible brown algae can be recommended as a natural active ingredient.

Fucoidan has a structure in which sulfate groups, fucose, etc., are bound to a heteropolysaccharide backbone,[6,7] and exhibits anticancer activity.[8-13] It induces autophagy and apoptosis in breast, ovarian, and endometrial cancers.[14] It inhibited the growth of 5 types of ovarian cancer cell lines but not on normal cells.[6] It also exhibits antitumor effects regardless of the presence or absence of estrogen receptors.[15,16] It induced apoptosis by increasing reactive oxygen species in cancer cells.[17] The suppression of PD-L1/PD-L2 expression by low molecular weight fucoidan extract (LMF) can be applied to treating other tumors.[18] Based on the above, the authors concluded that fucoidan is effective for this patient.

Thus, in addition to Medroxyprogesterone acetate (MPA) hormone therapy, we prescribed the fucoidan product

Low molecular weight fucoidan extract-*Canavalia gladiata* extract (LMF-CG) (trade name "Power Fucoidan® CG Jelly Type", Daiichi Sangyo Co., Ltd., Osaka, Japan) for lung metastasis of endometrial adenocarcinoma.

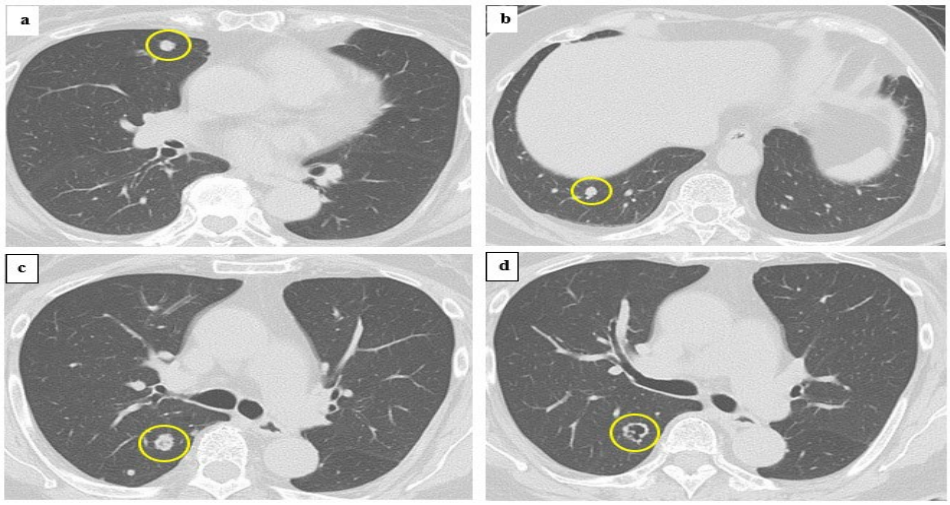
CASE REPORT

A 71-year-old Japanese female was diagnosed with a metastatic lung tumor (stage IV) of primary endometrioid adenocarcinoma in 2018. She underwent a total hysterectomy and pelvic lymphadenectomy. After that, she received six cycles of adjuvant chemotherapy (docetaxel plus carboplatin (DC) therapy). Multiple pulmonary metastases were found three months later, and three nodules were detected in the right lung despite receiving DC therapy for an additional seven months (Figure 1 a-c). Then, MPA hormone therapy (600 mg/day) was initiated to suppress the progression of metastatic lung cancer (Figure 2).

The patient visited Clinic Ginowan for a second opinion because she felt her condition did not seem to improve after receiving MPA therapy. Considering the patient's chief complaint and physical condition, six pouches of LMF-CG (50 g/pouch) were prescribed daily in addition to MPA therapy. A positron emission tomography (PET) scan showed a cavitated nodule in the right lung three months later. In addition to the PET findings, as natural killer (NK) cell activity increased, LMF-CG intake was reduced to 3 pouches per day (Figure 2). At the same time, to reduce her anxiety, she was presented with advice for sleeplessness and information on hormones and diet. After four months, the LMF-CG was decreased to two pouches per day as the tumor had almost disappeared.

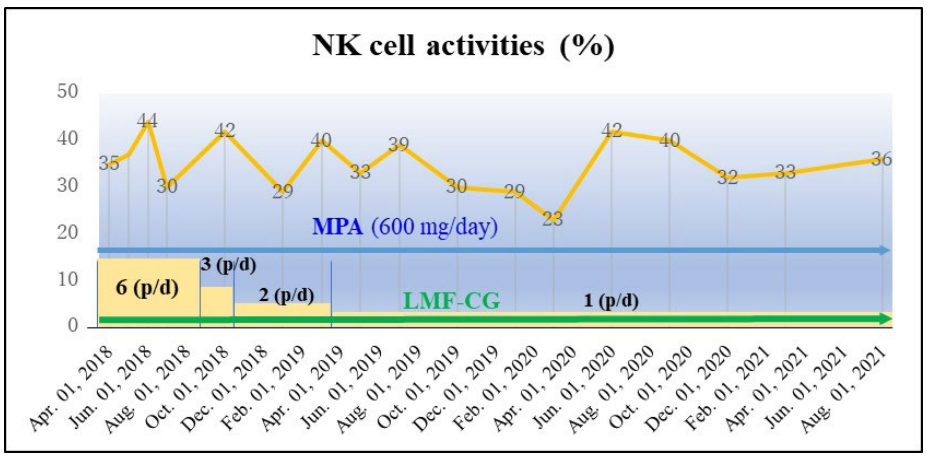
Because there was neither new cancer metastasis nor worsening of the symptoms during the LMF-CG intake period, the intake of LMF-CG was reduced to one pouch per day, and she is still taking LMF-CG. A computed tomography (CT) scan

Figure 1. *Computed Tomography (CT) Image Taken on March 12, 2018. Multiple Metastatic Tumors in the Right Lung (a-d)*



Metastasis to the Middle Lobe (a), Metastasis to the Lower Lobe (b), (c). Image (d) is the Same Tumor as (C) Taken at a Different Position.

Figure 2. *NK Cell Activity Measurement, and MPA, LMF-CG Treatment Plans. NK Cell Activity was Evaluated as having High Immunity when the Values are 20 or more.*[44,45]



MPA (600 mg/day): Treatment Period (blue right-pointing arrow). The Dose of LMF-CG was Gradually Reduced to 6, 3, 2, 1 pouches/day (p/d) (green right-pointing arrow). According to the Decrease of LMF, NK Cell Activity Decreased toward April 2020, but after 3 Years when the Tumor Disappeared NK Cell Activity Recovered to the Normal Range.

in September 2020 showed that the third nodule observed in Figures 1c and 1d wholly disappeared (Figure 2), and the other two nodules were undetectable. The third nodule (Figures 1c and 1d) image taken on March 12, 2018, appeared likely undergoing apoptosis and thus was followed up. C.T. scans taken on September 4, 2020 (Figure 3) and June 4, 2021 (Figure 4).

Supported by favorable results such as CT images and NK cell activity (Figure 2), the patient regained physical and mental health and physical condition and returned to farm work in September 2023, which she continues.

DISCUSSION

In this case, despite the patient with metastatic lung cancer having received chemotherapy, it recurred three months later. This patient had been on MPA hormone therapy as standard care following the initial surgery. MPA exerts its effects through risk.[19-23] Chemotherapy- and radiation-induced necrosis is the disordered destruction of cells, releasing intracellular components and triggering an inflammatory response in the surrounding tissue. Chemotherapy, despite its effectiveness, causes acute and long-term side effects on normal cells and tissues in the human body.[24] Thus, it is necessary to consider the appropriate dose when applying chemotherapy.[25] Apoptosis is distinct from necrosis because harmful intracellular components released from dead cells are phagocytosed by surrounding phagocytic cells. Thus, MPA-induced effects are an anti-cancer strategy to switch the necrotic- to apoptotic-tumor cell death.[26]

Fucoidans, mainly extracted from *Undaria pinnatifida* and *Fucus vesiculosus*, have been regarded as a "Generally Recognized As Safe (GRAS)" agent by the United States Food and Drug Administration (USFDA). These extracts were also approved as a novel food by the Commission Implementing Regulation (E.U.) as of December 20, 2017, admitting to taking up to 250 mg daily. Canadian and Australian agencies have approved pharmaceutical products containing fucoidan extracts from such two algae species.[27,28]

Figure 3. *CT Image taken on September 4, 2020.The Image Shows the Metastatic Tumor Detected in Figure 1(c) Disappeared by Apoptosis (Inset: enlarged image of d)*

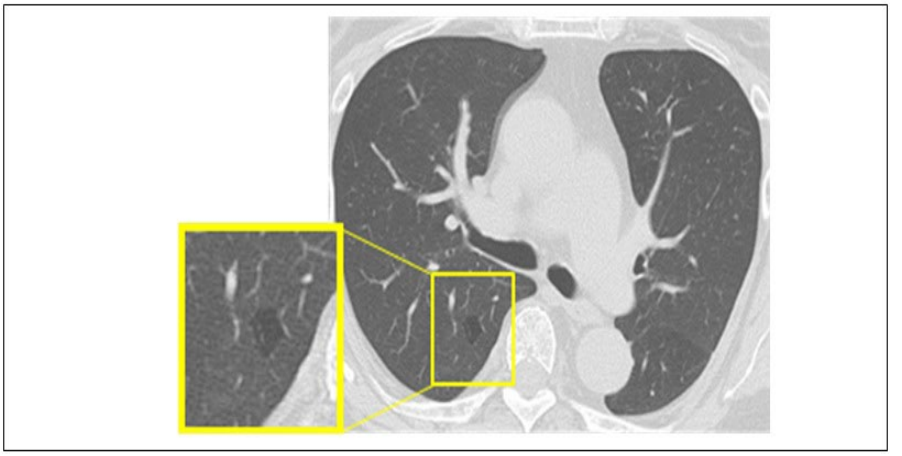
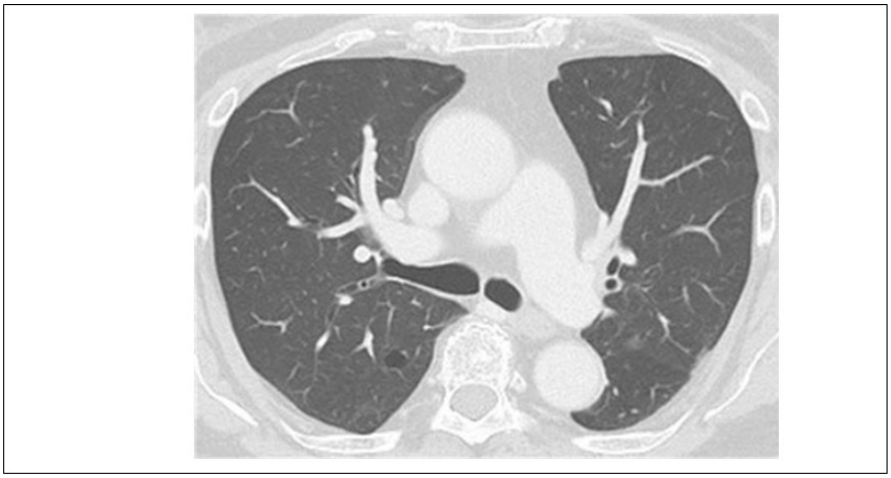


Figure 4. *CT Image Taken on June 4, 2021. Similar to the Image in Figure 2, it shows a Cavitated Tumor by Apoptosis*



Low molecular weight fucoidan extrac (LMF) is prepared by digesting crude fucoidan obtained from the brown seaweed *Mozuku* with abalone glycosidase and has different characteristics from other fucoidans.[18,29,30] The molecular size composition of LMF consists of a digested low molecular weight fraction (72%) of less than 500 Da.[31-33] Patients with advanced cancers of lung, uterine, and breast received 4 g of LMF daily for four weeks, pro-inflammatory cytokines (interleukin-1β, interleukin-6, and tumor necrosis factor-α) significantly reduced in two weeks.[18]

Recently, attention has focused on the role of immune checkpoint inhibitors that suppress the programmed cell death protein-1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway by activating the immune system against cancer cells.[18,34] Inhibition of PD-1 has been demonstrated to exert anti-tumor activity in certain solid tumors.[34-36] Immunotherapy is effective for renal cell carcinoma and patients with non-small cell lung cancer and other cancers. However, anti-PD-1/PD-L1 therapeutics like other anti-cancer agents, also have various side effects.[37]

The authors devised a therapeutic strategy combining LMF-CG and hormone therapy for recurred metastatic lung cancer and succeeded in eradicating it. LMF was selected not only for its anti-cancer activity but also for its various biological effects.

Considering above drawbacks of immune checkpoint inhibitors, LMF can be recommended as an ideal drug.[18] Presently prescribed fucoidan product LMF-CG consists of 91.03% LMF extract as the main constituent and 2.40% CG extract containing a minute amount of concanavalin A (Con A) as a minor ingredient in a 50 g pouch.[38] Con A has been known as a Ca^{2+}/Mn^{2+}-dependent and mannose/glucose-binding legume lectin to induce cell death in cultured cancer cells and to exert anti-inflammatory activity.[39-43] Anti-cancer effects of Con A by induction of autophagy and apoptosis and inhibition of angiogenesis would be a model of LMF-CG.[42]

Still, the natural killer cells (NK cells) activities and quality-of-life (QoL) scores were mostly stable.[43,44] Anti-inflammatory agents have anti-cancer effects, Increased NK cell activity after the disappearance of tumors suggested a good prognosis. Multiple biological function of LMF needs to be confirmed by more case reports and clinical trials.[45]

These co-treatments significantly induced cell-growth inhibition, apoptosis, as well as cell cycle modifications in MDA-MB-231 and MCF-7 cells. LMF enhanced apoptosis in cancer cells that responded to treatment with chemotherapeutic drugs with downregulation of the anti-apoptotic proteins B-cell lymphoma-extra large (Bcl-xL) and Myeloid cell leukemia 1 (Mcl-1). The combination treatments led to an obvious decrease in the phosphorylation of ERK and Akt in MDA-MB-231 cells, but increased the phosphorylation of ERK in MCF-7 cells.[46] LMF deserves further investigation as a natural anti-cancer and cancer preventive agent.

CONCLUSION

This case is the first report of complete remission of EC-derived metastatic lung cancer by combining hormone therapy and LMF-CG. Further clinical studies are expected for various other cancers.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

CONSENT

The authors obtained the written consent from the patients to report.

REFERENCES

1. Dendl K, Koerber SA, Finck R, et al. 68Ga-FAPI-PET/CT in patients with various gynecological malignancies. *Eur J Nucl Med Mol Imaging.* 2021; 48: 4089-4100. doi: 10.1007/s00259-021-05378-0

2. Liu Y, Jin Y, Lu Y, et al. Comparison of the outcomes between laparoscopic surgery and conventional open surgery in treating patients with stage II endometrial carcinoma. *Medicine.* 2021; 100: 38. doi: 10.1097/MD.0000000000027148

3. Baiden-Amissah REM, Annibali D, Tuyaerts S, et al. Endometrial cancer molecular characterization: the key to identifying high-risk patients and defining guidelines for clinical decision-making? *Cancers.* 2021; 13: 3988. doi: 10.3390/cancers13163988

4. Kurra V, Krajewski KM, Jagannathan J, et al. Typical and atypical metastatic sites of recurrent endometrial carcinoma. *Canc Imag.* 2013; 13(1): 113-122. doi: 10.1102/1470-7330.2013.0011

5. Mandato VD, Mastrofilippo V, Palicelli A, et al. Solitary vulvar metastasis from early-stage endometrial cancer: Case report and literature review. *Medicine.* 2021; 100: 22(e25863). doi: 10.1097/MD.0000000000025863

6. Liu S, Yang J, Peng X, et al. The natural product fucoidan inhibits proliferation and induces apoptosis of human ovarian cancer cells: Focus on the PI3K/Akt signaling pathway. *Cancer Manag Res.* 2020; 12: 6195-6207. doi: 10.2147/CMAR.S254784

7. Mak W, Wang SK, Liu T, et al. Anti-proliferation potential and content of fucoidan extracted from sporophyll of New Zealand Undaria pinnatifida. *Front Nutr.* 2014; 1: Article 9, 1-10. doi: 10.3389/fnut.2014.00009

8. Aisa Y, Miyakawa Y, Nakazato T, et al. Fucoidan Induces apoptosis of human HS-Sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways. *Am J Hematol.* 2005; 78: 7-14. doi: 10.1002/ajh.20182

9. Hyun J-H, Kim S-C, Kang J-I, et al. Apoptosis inducing activity of fucoidan in HCT-15 colon carcinoma. *Cells Biol Pharm Bull.* 2009; 32(10): 1760-1764. doi: 10.1248/bpb.32.1760

10. Park HS, Kim G-Y, Nam T-J, et al. Antiproliferative activity

of fucoidan was associated with the induction of apoptosis and autophagy in AGS human gastric cancer cells. *J Food Sci*. 2011; 76, Nr. 3: T77-T83. doi: 10.1111/j.1750-3841.2011.02099.x

11. Yamasaki Y, Yamasaki M, Tachibana H, et al. Important role of β1-integrin in fucoidan-induced apoptosis via caspase-8 activation. *Biosci Biotechnol Biochem*. 2012; 76 (6): 1163-1168. doi: 10.1271/bbb.111001

12. Atashrazm F, Lowenthal RM, Woods GM, et al. Fucoidan suppresses the growth of human acute promyelocytic leukemia cells in vitro and in vivo. *J Cell. Physiol*. 2016; 231: 688-697. doi: 10.1002/jcp.25119

13. Shen J, Li J, Yu P, et al. Research status and hotspots of anticancer natural products based on the patent literature and scientific articles. *Front Pharmacol*. 2022; 13: 903239. doi: 10.3389/fphar.2022.903239

14. Bobiński M, Okła K, Bednarek W, et al. The effect of fucoidan, a potential new, natural, anti-neoplastic agent on uterine sarcomas and carcinosarcoma cell lines: ENITEC Collaborative Study. *Arch Immunol Ther Exp (Warsz)*. 2019; 67: 125-131. doi: 10.1007/s00005-019-00534-9

15. Zhang Z, Teruya K, Yoshida T, et al. Fucoidan extract enhances the anti-cancer activity of chemotherapeutic agents in MDA-MB-231 and MCF-7 breast cancer cells. Mar. *Drugs*. 2013; 11(1): 81-98. doi: 10.3390/md11010081

16. Zhang J, Riby JE, Conde L, et al. A fucus vesiculosus extract inhibits estrogen receptor activation and induces cell death in female cancer cell lines. *BMC Complement Altern Med*. 2016; 16: 151. doi: 10.1186/s12906-016-1129-6

17. Hsu H-Y, Lin T-Y, Lu M-K, et al. Fucoidan induces toll-like receptor 4-regulated reactive oxygen species and promotes endoplasmic reticulum stress-mediated apoptosis in lung cancer. *Sci Rep*. 2017; 7: 44990. doi: 10.1038/srep44990

18. Teruya K, Kusumoto Y, Eto H, et al. Selective suppression of cell growth and programmed cell death-ligand 1 expression in HT1080 fibrosarcoma cells by low molecular weight fucoidan extract. *Mar Drugs*. 2019; 17: 421. doi: 10.3390/md17070421

19. Mio H. A case of postoperative recurrent breast cancer with multiple lung metastases that completely responded to combination therapy of docetaxel (TXT) and medroxyprogesterone acetate (MPA) [In Japanese]. *Jpn J Cancer Chemother*. 2003; 30(7): 985-988.

20. Verma MK., Miki Y, Sasano H. Sex steroid receptors in human lung diseases. *J Steroid Biochem Mol Bio*. 2011; 127: 216-222. doi: 10.1016/j.jsbmb.2011.07.013

21. Reis FM, Coutinho LM, Vannuccini S, Batteux F, et al. Progesterone receptor ligands for the treatment of endometriosis: The mechanisms behind therapeutic success and failure. *Hum Reprod Update*. 2020; 26(4): 565-585. doi: 10.1093/humupd/dmaa009

22. Fedotcheva TA. Clinical use of progestins and their mechanisms of action: Present and future (Review). *Sovrem Tehnologii Med*. 2021; 13(1): 93. doi: 10.17691/stm2021.13.1.11

23. Mikuła Pietrasik J, Witucka A, Pakuła M, et al. Comprehensive review on how platinum and taxane based chemotherapy of ovarian cancer affects biology of normal cells. *Cell Mol Life Sci*. 2019; 76: 681-697. doi: 10.1007/s00018-018-2954-1

24. Ho MY, Mackey JR. Presentation and management of docetaxel-related adverse effects in patients with breast cancer. *Cancer Manag Res*. 2014; 6: 253-259. doi: 10.2147/CMAR.S40601

25. Gaughran G, Qayyum K, Smyth L, et al. Carboplatin and hypomagnesemia: Is it really a problem? *Asia-Pac J Clin Oncol*. 2020; 1-8. doi: 10.1111/ajco.13481

26. Numata T, Sato-Numata K, Okada Y. TRPM7 is involved in acid-induced necrotic cell death in a manner sensitive to progesterone in human cervical cancer cells. *Physiol Rep*. 2019; 7(13): e14157. doi: 10.14814/phy2.14157

27. Citkowska A, Szekalska M, Winnicka K. Possibilities of fucoidan utilization in the development of pharmaceutical dosage forms. *Mar Drugs*. 2019; 17: 458. doi: 10.3390/md17080458

28. Fitton JH, Stringer DN, Park AY, et al. Therapies from fucoidan: New developments. *Mar Drugs*. 2019; 17: 571. doi: 10.3390/md17100571

29. Zhang Z, Teruya K, Eto H, et al. Induction of apoptosis by low-molecular-weight fucoidan through calcium- and caspase-dependent mitochondrial pathways in MDA-MB-231 breast cancer cells. *Biosci Biotechnol Biochem*. 2013; 77(2): 235-242. doi: 10.1271/bbb.120631

30. Takahashi H, Kawaguchi M, Kitamura K, et al. An exploratory study on the anti-inflammatory effects of fucoidan in relation to quality of life in advanced cancer patients. *Integr Cancer Ther*. 2018; 17(2): 282-291. doi: 10.1177/1534735417692097

31. Ye J, Li Y, Teruya K, et al. Enzyme-digested fucoidan extracts derived from seaweed Mozuku of Cladosiphon novae-caledoniae kylin inhibit invasion and angiogenesis of tumor cells. *Cytotechnology*. 2005; 47: 117-126. doi: 10.1007/s10616-005-3761-8

32. Coussens LM, Zitvoge L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: A magic bullet? *Science*. 2013; 339: 286-291. doi: 10.1126/science.1232227

33. Bruchard M, Mignot G, Derangère V, et al. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. *Nat Med*. 2013; 19: 57-64. doi: 10.1038/nm.2999

34. Wagner G, Stollenwerk HK, Klerings I, et al. Efficacy and

safety of immune checkpoint inhibitors in patients with advanced non– small cell lung cancer (NSCLC): A systematic literature review. *Oncoimmunology*. 2020; 9 (1): 1-16. doi: 10.1080/2162402X.2020.1774314

35. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti–programmed death-1 (MDX-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010; 28: 3167-3175. doi: 10.1200/JCO.2009.26.7609

36. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther*. 2015; 37(4): 764-782. doi: 10.1016/j.clinthera.2015.02.018

37. Su C, Wang H, Liu Y, et al. Adverse effects of anti-PD-1/PD-L1 therapy in non-small cell lung cancer. *Front Oncol*. 2020; 10: 554313. doi: 10.3389/fonc.2020.554313

38. Shirahata S, Katakura Y, Teruya K, et al. Inventors. kit for inducing changes in sugar chain structure on the surface of cancer cells. Patent publication number: JP5201499B2. 2013.6.5.

39. Pinto NV, Cavada BS, Brito LF, et al. Effects of canavalia lectins on acute inflammation in sensitized and non-sensitized rats. *Inflammation*. 2013; 36(3): 713-722. doi: 10.1007/s10753-013-9596-0

40. Yau T, Dan X, Ng CCW, et al. Lectins with potential for anti-cancer therapy. *Molecules*. 2015; 20: 3791-3810. doi: 10.3390/molecules20033791

41. Une S, Nonaka K, Akiyama J. Lectin isolated from Japanese red sword beans (*Canavalia gladiata*) as a potential cancer chemopreventive agent. *J Food Sci*. 2018; 83: Nr. 3. doi: 10.1111/1750-3841.14057

42. Li W-w, Yu J-y, Xu H-l et al. Concanavalin A: A potential anti-neoplastic agent targeting apoptosis, autophagy and anti-angiogenesis for cancer therapeutics. *Biochem Biophys Res Commun*. 2011; 414: 282-286. doi: 10.1016/j.bbrc. 2011.09.072

43. Chung H-J, Park C-J, Lim J-H, et al. Establishment of a reference interval for natural killer cell activity through flow cytometry and its clinical application in the diagnosis of hemophagocytic lymphohistiocytosis. *Int Jnl Lab Hem*. 2010; 32: 239-247. doi: 10.1111/j.1751-553X. 2009.01177.x

44. Hou H, Mao L, Wang J, et al. Establishing the reference intervals of NK cell functions in healthy adults. *Hum Immunol*. 2016; 77: 637-642. doi: 10.1016/j.humimm.2016.05.022

45. Zhang Z, Teruya K, Eto H, et al., Fucoidan extract induces apoptosis in MCF-7 cells via a mechanism involving the ROS-dependent JNK activation and mitochondria-mediated pathways. *PLoS One*. 2011; 6(11): e27441. pii: e27441.

46. Zhang Z, Teruya K, Yoshida T, et al., Fucoidan extract enhances the anti-cancer activity of chemotherapeutic agents in MDA-MB-231 and MCF-7 breast cancer cells. *Marine drugs*. 2013 Jan 09;11(1): 81-98. doi: 10.3390/md11010081