Table 2: Clinical trials stimulating innate immunity against bone and soft tissue sarcomas.

Agent	Number of patients	Diagnosis	Treatment	Follow-up	Clinical result
IL-2 [16]	6	Osteosarcoma, Ewing's sarcoma	$6–12 \times 10^6$ IU/m^2 for 5 days by every 3 weeks	7–71 months	Complete response (CR): 5 Progressive disease (PD): 5
IFNs [17]	3	Osteosarcoma	$2.5–5 \times 10^6$ IU/mL twice or thrice weekly	6–8 months	CR: 2 PD: 1
IFN-α2 [18]	20	Osteosarcoma, fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma	5×10^7 IU/m^2 thrice weekly	1–3 months	Partial response (PR): 3
IFN-α [19]	89	Osteosarcoma	Cohort 1 (70 patients); 3×10^6 IU daily for a month Cohort 2 (19 patients); 3×10^6 IU daily for 3–5 years	10 years	Metastatic free survival: 39% Sarcoma specific survival: 43%
IFN-β [20]	158	Osteosarcoma (COSS-80)	1×10^5 IU/kg for 22 weeks	30 months	Disease-free survival +IFN: 77% −IFN: 73% (N.S.)
Pegylated IFN-α2b [21]	715	Osteosarcoma (EURAMOS-1)	Methotrexate, adriamycin, and cisplatin (MAP) +/−IFN (0.5–1.0 μg/kg/wk) for 2 years	Median follow-up 3.1 years	Event-free survival +IFN: 77% −IFN: 74% (N.S.)
L-MTP-PE [22]	662	Osteosarcoma (INT 0133)	MAP alone, MAP + L-MTP-PE, MAP + ifosfamide, MAP + ifosfamide + L-MTP-PE	6 years	Overall survival +L-MTP-PE: 78% −L-MTP-PE: 70% Event free survival No significant difference

osteosarcoma achieved complete responses with a median follow-up time of 28 months (range: 11–36 months). However, all patients experienced adverse effects such as fatigue, anorexia, diarrhea, nausea, vomiting, and high-grade fever. Two patients could not undergo IL-2 therapy [16]. Furthermore, the other initial study reported treatment related death caused in 1-2% of patients [81]. Consequently, it limited the administration of high-dose IL-2 therapy for its adverse effect [81, 82].

The use of IFN-α as an adjuvant therapy was initiated at the Karolinska Hospital in 1971 [19]. The Karolinska Hospital group reported that 10-year results of adjuvant IFN-α therapy. The clinical outcome was improved by introducing adjuvant IFN-α therapy. The metastasis-free survival rate was 39% and the sarcoma-free survival rate was 43% in adjuvant IFN therapy group. These clinical results were better than the group of surgiral therapy only (15–20%) [83]. COSS-80 study investigated the effectiveness of use of adjuvant chemotherapy with IFN [20]. The 30-month disease-free survival rate of the IFN arm was 77% and that of non-IFN arm 73%. However, there was no significant difference between two groups; EURAMOS-1 study, a recent study in Europe, investigated the efficacy of the use of adjuvant chemotherapy with pegylated-IFNα-2b [21]. In the interim statement, the median follow-up time in EURAMOS-1 study was 3.1 years. The event-free survival rate was 77% in the group with chemotherapy and IFN and 73% in the group without IFN [19]. This difference was also not significant. These observations suggest that conventional chemotherapy with IFN improves the prognosis of bone and soft tissue sarcomas to some extent.

3.2. Mifamurtide. Mifamurtide, liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE), is a new agent that is a synthetic analog of a muramyl dipeptide (MDP) [22]. Although its pharmacological behavior is similar to that of MDP, L-MTP-PE has a longer half-life than MDP [84]. The intracellular pattern recognition molecule NOD2 detects MDP and enhances NF-κB signaling [85]. Therefore, recognition of L-MTP-PE by NOD2 stimulates the production of IL-1β, IL-6, and TNF-α via the activation of NF-κB signaling in monocytes and macrophages [86, 87].

The efficacy of L-MTP-PE treatment for osteosarcomas has been examined in dogs. Dogs with postoperative

Table 3: Clinical trials stimulating adaptive immunity against bone and soft tissue sarcomas.

Agent	Number of patients	Diagnosis	Treatment	Immune response	Clinical result
Autologous tumor cells [23]	23	Sarcoma	Total 1.0×10^7 cells	Delayed-type hypersensitivity (DTH) positive: 8 patients	Median survival DTH responder: 16.6 months Nonresponder: 8.2 months
Tumor translocation breakpoint specific peptide-pulsed DCs [24]	52	Ewing's sarcoma, rhabdomyosarcoma	Total $4.2–143.0 \times 10^6$ cells	39% with immune response to the translocation breakpoint, 25% with response to E7-specific	Overall survival Vaccination: 43% Control: 31%
Tumor-specific synthetic peptides or tumor lysates pulsed DCs [25]	5	Ewing's sarcoma, synovial sarcoma, neuroblastoma	$2–15 \times 10^6$ pulsed DCs injected 6–8 times	DTH positive: 1 patient	CR: 1 (77 months) PD: 4 (2–27 months)
A 9-mer peptide from SYT-SSX fusion site [26]	21	Synovial sarcoma	0.1 or 1.0 mg peptide +/− adjuvant 6 times at 14-day interval	Tetramer positive CD8: 7 patients	Stable disease (SD): 1/9 peptide alone 6/12 vaccine with adjuvant
Anti-CTLA-4 antibody [27]	6	Synovial sarcoma (expressed NY-ESO-1)	Ipilimumab 3 mg/kg every 3 weeks for 3 cycles	DTH: all patients negative	Time to progression 0.47–2.1 months (median 1.85), overall survival time 0.77–19.7 months (median 8.75)
T cell receptor- (TCR-) transduced T cells (NY-ESO-1 specific) [28]	6	Synovial sarcoma (expressed NY-ESO-1)	TCR-transduced T cells +720,000 IU/kg of IL-2	Tetramer positive CD8: 5 patients	PR: 4 PD: 2

osteosarcomas were treated by intravenous L-MTP-PE injections. The median survival time of dogs treated by L-MTP-PE (222 days) was longer than that of nontreated dogs (77 days) [88]. In human, intergroup study 0133 (INT 0133) began in 1993. 662 patients with osteosarcoma were recruited in this study. The aim of the study was to evaluate the efficacy of supplementation with ifosfamide (IFO) and L-MTP-PE in basic adjuvant chemotherapy (cisplatin, doxorubicin, and high-dose methotrexate (MAP)). Patients were randomly assigned to receive MAP alone, MAP + IFO, MAP + L-MTP-PE, and MAP + IFO + L-MTP-PE. It was observed that the addition of L-MTP-PE to chemotherapy improved the six-year overall survival rate from 70% to 78% ($P = 0.03$). The hazard ratio for overall survival with the addition of MTP was 0.71 (95% CI: 0.52–0.96) [22, 89]. Therefore, L-MTP-PE has been approved in Europe for the treatment of osteosarcoma with chemotherapy. However, it has not been approved by FDA in the United States [87].

3.3. Vaccines. Multiple clinical trials using vaccines that target whole cells, lysates, proteins, and peptides have been investigated in patients with sarcomas [90–92]. Vaccines are combined with costimulatory adjuvants such as GM-CSF or IL-2 to enhance the immune response [93]. Therapeutic tumor vaccines are presented as antigen epitopes on MHC molecules by APCs. Tumor antigen specific T cells are activated by APCs. The aim of cancer vaccines is to stimulate the patient's own immune system to eliminate the tumor [94].

Autologous sarcoma cell lysates can be used as a vaccine in patients with sarcomas. A clinical study was performed to treat patients using their autologous tumor cell lysate as vaccines [23]. The study recruited 86 patients with sarcomas and tryed to establish short-term cell lines in vitro. 25 patients, who had an established tumor cell line, were injected with the tumor lysate vaccine. Before vaccine treatment, patients were screened to ensure they were not positive for delayed-type hypersensitivity (DTH) to irradiated tumor cells. After treatment, eight patients became positive for DTH. The median survival time of patients who became positive for DTH (16.6 months) was eight months longer than that of DTH-negative patients (8.2 months). However, objective responses were not recorded [23]. In the result, tumor lysate vaccines improved the survival time, but tumor regression disappeared.

Autologous DCs that are pulsed ex vivo with tumor cell lysate can stimulate host antitumor immunity [95, 96]. Adjuvant therapies using tumor lysate-pulsed DCs were investigated for children with solid tumors including bone

and soft tissue sarcomas. After tumor lysate-pulsed DC transfer, 70% of patients changed positively in the DTH test. This study resulted in one patient achieving complete remission and in five patients, the disease stabilized during the follow-up period of 16–30 months [97].

Tumor specific or overexpressed peptides are possible for therapeutic targets for antigen-specific immunotherapy [98, 99]. Bone and soft tissue sarcomas can have specific gene mutations and express mutated proteins [100]. Synovial sarcomas are known to have chromosomal translocation and synthesize the SYT-SSX mutated protein [101]. Kawaguchi et al. treated patients who had synovial sarcomas with SYT-SSX fusion gene-derived peptides [102]. The study enrolled 21 patients, who were injected subcutaneously with the 9 mer peptide with or without incomplete Freund's adjuvant (IFA) and IFN-α. Nine patients were injected with the peptide alone, and later in the study, 12 patients were injected the peptide with IFA and IFN-α. After treatment, in seven patients, the peptide tetramer-positive CD8 T cells appeared in PBMCs. With regard to the clinical result, in six patients, the disease stabilized during vaccination; however, in other patients, the disease progressed [26].

Tumor antigen-specific peptide pulsed DCs can stimulate peptide specific T cells 150 times more efficient than peptide alone [103]. Tumor-specific peptide pulsed DCs have been administered for immunotherapy against sarcoma, leukemia, and glioma [104]. 30 patients with Ewing's sarcomas and alveolar rhabdomyosarcoma were enrolled in a study for consolidative therapy. Patients were separated into three cohorts that received different dose of IL-2 (high, low, and none). Monocyte-derived DCs were cultured with tumor-derived breakpoint peptides (EWS-FLI1, EWS-FLI2, and PAX3/FKHR), and the E7 peptide was used as control [24]. After treatment, 39% of patients generated immune responses to the vaccinating peptide. The five-year overall survival of the immunotherapy group was 43% and that of the no-immunotherapy group was 31% [24]. Further, this treatment showed no severe adverse effect. For these reasons, vaccines from tumor cell lysate or tumor specific peptide can activate adaptive immune response against tumors. Antigen-specific peptide pulsed DCs can also enhance immune response. Vaccine therapies have validity for bone and soft tissue sarcomas.

CTAs are expressed only in germ line cells in humans; however, they are also expressed in various tumors [105]. More than 40 antigens have been identified [105]. For example, NY-ESO-1 is expressed in many osteosarcomas, leiomyosarcomas, and synovial sarcomas and LAGE-1 is expressed in liposarcomas, leiomyosarcomas, and synovial sarcomas (Table 1) [106]. MAGE-A3 was administered to patients with stage III/IV melanoma [107]. The effectiveness of MAGE-A3 against non-small-cell lung cancer (NSCLC) was reported in a phase II clinical trial [108, 109]. Thus CTAs have a potential to be immunotherapeutic targets against bone and soft tissue sarcomas.

3.4. Adoptive Cell Transfer. Adoptive cell transfer therapy is considered to provide large number of tumor reactive CD8T cells that secrete high levels of cytokines, IFNγ, TNFα, and IL-2 [110]. Tumor infiltrating lymphocytes (TILs) include tumor reactive CD8T cells. Antigen-specific T cells were sorted from patients. T cells were expanded and stimulated ex vivo. After ex vivo treatment, activated effector T cells were transferred to patients [110]. A small study examined six patients with synovial sarcomas or metastatic melanomas expressing NY-ESO-1. For inducing tumor lysis, T cell receptor (TCR) gene-modified T cells redirected towards NY-ESO-1 were generated [28]. Modified TCR displayed T cells were expanded with IL-2 ex vivo and then transferred to patients [111]. Two patients with melanoma showed complete regression, and 1 patient with synovial sarcoma showed disease stabilization for 18 months. Some types of adoptive cell transfer therapies are ongoing for patients with sarcomas, including autologous DC transport therapy for soft tissue sarcomas (NCT01347034) and hematopoietic cell transplantation and natural killer cell transport therapies for Ewing's sarcomas and rhabdomyosarcomas (NCT02100891).

3.5. Immune Checkpoint Blockade. Immune checkpoint blockade is likely to advance anticancer immunology. Ipilimumab, a fully human monoclonal antibody (IgG1), blocks CTLA-4 and promotes antitumor immunity [112]. Patients with metastatic melanomas treated with ipilimumab showed improved overall survival (from 6.4 months to 10.0 months) [113]. Six patients with advanced synovial sarcoma enrolled in a phase II study were treated with ipilimumab. The overall survival time ranged from 0.77 to 19.7 months (median: 8.75 months). Immunological responses after the treatment were different in each patient, and three patients showed an enhanced titer of CT24 (an uncharacterized CTA). All sarcomas expressed NY-ESO-1; however, NY-ESO-1 titers did not show any remarkable change [114].

Another immune checkpoint blockade agent is a human monoclonal anti-PD-1 antibody, called nivolumab [115]. Nivolumab has demonstrated efficacy against several types of cancers including melanoma, NSCLC, prostate cancer, renal cell carcinoma, and colorectal cancer [116]. The reported clinical outcomes of nivolumab therapies include a cumulative response rate of 18% among patients with NSCLC, 28% among patients with melanoma, and 27% among patients with renal cell carcinoma [116]. Furthermore, a phase I trial of nivolumab combined with ipilimumab enrolled 53 patients with advanced melanoma. This trial reported that 53% of patients experienced grade 3 or 4 adverse effects related to the therapy and 53% of patients had an objective response. Among patients treated with ipilimumab as a control, 20% had an objective response [117]. Thus, immune checkpoint blockade agents demonstrate efficacy in some types of tumors; however, further information is required to confirm the effectiveness of the immune blockade agents ipilimumab and nivolumab for bone and soft tissue sarcomas.

4. Conclusion and Future Directions

Conventional treatment for bone and soft tissue sarcomas consists of surgical resection, chemotherapy, and radiotherapy. However, clinical outcomes by these therapeutic modalities have not significantly improved in recent decades.

Under these circumstances, immunotherapy is expected to be a new therapeutic option for treatment. Cytokine therapies were initially regarded as a form of immunotherapy; however, their effectiveness was limited because of their toxicities. Only IFN-α-2 is used for maintenance therapy. Although L-MTP-PE induces antitumor effects via macrophage activation, the FDA has not approved its use because of the limited effectiveness. In Europe, L-MTP-PE efficacy has been confirmed in an international multicenter study. Vaccine therapy using tumor lysates or lysate-derived DCs has been investigated only in small-scale studies and in nonsarcoma patients. CTA peptide and fusion protein peptide therapies are expected to be novel sarcoma-effective vaccines. Addition of L-MTP-PE as an adjuvant may improve the vaccine therapy outcome. Novel microparticle-based drug delivery systems, such as microemulsion, nanoemulsion, nanoparticles, liposomes, and others, can load many kinds of various drugs and improve the drug delivery to target sites [118–121]. It has been reported that these systems improve the efficacy of vaccine and reduce adverse effects of cytokines [122–124]. Tuftsin, a tetrapeptide (Thr-Lys-Pro-Arg) fraction of immunoglobulin G molecule, binds to neutrophils and macrophages [125–127]. Tuftsin stimulates their phagocytic activity and enhances expression of nitric oxide synthase in macrophages. It has been demonstrated that tuftsin improves the efficacy of antibiotics against protozoan, bacterial, and fungal infections. Besides, tuftsin-bearing liposomized etoposide enhanced the therapeutic efficacy in murine fibrosarcoma models [128].

Immune checkpoint mechanism inhibits CD8 T cell function in tumor microenvironment [129]. Although immune checkpoint blockade molecules, anti-CTLA-4 antibody and anti-PD-1 antibody, have not been proven currently to have the effectiveness, there is too little information to decide efficacy of ipilimumab and nivolumab in sarcomas. Thus, immune checkpoint blockade medicines should be evaluated in the future. Adoptive cell transfer approaches are also the subject of new sarcoma treatment trials. Overall, these trials and successes suggest that immunotherapy is moving to the forefront of therapy for bone and soft tissue sarcomas.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The authors acknowledge a grant-in-aid for Scientific Research on Applying Health Technology from the Ministry of Health, Labor and Welfare of Japan, and a grant-in-aid for Health and Labour Sciences Research Expenses for Commission, Applied Research for Innovative Treatment of Cancer from the Ministry of Health, Labour and Welfare (H26-084).

References

[1] Z. Burningham, M. Hashibe, L. Spector et al., "The epidemiology of sarcoma," *Clinical Sarcoma Research*, vol. 2, no. 1, p. 14, 2012.

[2] National Cancer Institute, *A Snapshot of Sarcoma*, 2013.

[3] T. A. Damron, W. G. Ward, and A. Stewart, "Osteosarcoma, chondrosarcoma, and Ewing's sarcoma: national cancer data base report," *Clinical Orthopaedics and Related Research*, no. 459, pp. 40–47, 2007.

[4] L. A. Doyle, "Sarcoma classification: an update based on the 2013 world health organization classification of tumors of soft tissue and bone," *Cancer*, vol. 120, no. 12, pp. 1763–1774, 2014.

[5] A. Italiano, A. le Cesne, J. Mendiboure et al., "Prognostic factors and impact of adjuvant treatments on local and metastatic relapse of soft-tissue sarcoma patients in the competing risks setting," *Cancer*, vol. 120, no. 21, pp. 3361–3369, 2014.

[6] M. A. Tucker, G. J. D'Angio, J. D. Boice Jr. et al., "Bone sarcomas linked to radiotherapy and chemotherapy in children," *The New England Journal of Medicine*, vol. 317, no. 10, pp. 588–593, 1987.

[7] A. N. van Geel, U. Pastorino, K. W. Jauch et al., "Surgical treatment of lung metastases: the European organization for research and treatment of cancer-soft tissue and bone sarcoma group study of 255 patients," *Cancer*, vol. 77, no. 4, pp. 675–682, 1996.

[8] S. S. Bielack, B. Kempf-Bielack, G. Delling et al., "Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols," *Journal of Clinical Oncology*, vol. 20, no. 3, pp. 776–790, 2002.

[9] L. Mulder Renée, M. Paulides, T. Langer, L. C. Kremer, and E. C. van Dalen, "Cyclophosphamide versus ifosfamide for paediatric and young adult bone and soft tissue sarcoma patients," *Cochrane Database of Systematic Reviews*, vol. 17, no. 2, Article ID CD006300, 2012.

[10] W. B. Coley, "II. Contribution to the knowledge of sarcoma," *Annals of Surgery*, vol. 14, no. 3, pp. 199–220, 1891.

[11] J. Kluwe, A. Mencin, and R. F. Schwabe, "Toll-like receptors, wound healing, and carcinogenesis," *Journal of Molecular Medicine*, vol. 87, no. 2, pp. 125–138, 2009.

[12] F. Balkwill, "Tumour necrosis factor and cancer," *Nature Reviews Cancer*, vol. 9, no. 5, pp. 361–371, 2009.

[13] R. L. Modlin, "Innate immunity: ignored for decades, but not forgotten," *Journal of Investigative Dermatology*, vol. 132, no. 3, pp. 882–886, 2012.

[14] J. F. M. Jacobs, F. Brasseur, C. A. Hulsbergen-van de Kaa et al., "Cancer-germline gene expression in pediatric solid tumors using quantitative real-time PCR," *International Journal of Cancer*, vol. 120, no. 1, pp. 67–74, 2007.

[15] K. M. Skubitz, S. Pambuccian, J. C. Carlos, and A. P. N. Skubitz, "Identification of heterogeneity among soft tissue sarcomas by gene expression profiles from different tumors," *Journal of Translational Medicine*, vol. 6, article 23, 2008.

[16] W. Schwinger, V. Klass, M. Benesch et al., "Feasibility of high-dose interleukin-2 in heavily pretreated pediatric cancer patients," *Annals of Oncology*, vol. 16, no. 7, pp. 1199–1206, 2005.

[17] H. Ito, K. Murakami, T. Yanagawa et al., "Effect of human leukocyte interferon on the metastatic lung tumor of osteosarcoma: case reports," *Cancer*, vol. 46, no. 7, pp. 1562–1565, 1980.

[18] J. H. Edmonson, H. J. Long, S. Frytak, W. A. Smithson, and L. M. Itri, "Phase II study of recombinant alfa-2a interferon in patients with advanced bone sarcomas," *Cancer Treatment Reports*, vol. 71, no. 7-8, pp. 747–748, 1987.

[19] C. R. Müller, S. Smeland, H. C. F. Bauer, G. Sæter, and H. Strander, "Interferon-α as the only adjuvant treatment in high-grade osteosarcoma: long term results of the Karolinska

Hospital series," *Acta Oncologica*, vol. 44, no. 5, pp. 475–480, 2005.

[20] K. Winkler, G. Beron, R. Kotz et al., "Neoadjuvant chemotherapy for osteogenic sarcoma: Results of a cooperative German/Austrian study," *Journal of Clinical Oncology*, vol. 2, no. 6, pp. 617–624, 1984.

[21] S. S. Bielack, S. Smeland, J. Whelan et al., "MAP plus maintenance pegylated interferon alpha-2b (MAPIfn) versus MAP alone in patients with resectable high-grade osteosarcoma and good histologic response to preoperative MAP: first results of the EURAMOS-1 "good response" randomization," *Journal of Clinical Oncology*, vol. 31, no. 18, 2013.

[22] L. Kager, U. Potschger, and S. Bielack, "Review of mifamurtide in the treatment of patients with osteosarcoma," *Therapeutics and Clinical Risk Management*, vol. 6, no. 279–286, 2010.

[23] R. Dillman, N. Barth, S. Selvan et al., "Phase I/II trial of autologous tumor cell line-derived vaccines for recurrent or metastatic sarcomas," *Cancer Biotherapy and Radiopharmaceuticals*, vol. 19, no. 5, pp. 581–588, 2004.

[24] C. L. Mackall, E. H. Rhee, E. J. Read et al., "A pilot study of consolidative immunotherapy in patients with high-risk pediatric sarcomas," *Clinical Cancer Research*, vol. 14, no. 15, pp. 4850–4858, 2008.

[25] A. Suminoe, A. Matsuzaki, H. Hattori, Y. Koga, and T. Hara, "Immunotherapy with autologous dendritic cells and tumor antigens for children with refractory malignant solid tumors," *Pediatric Transplantation*, vol. 13, no. 6, pp. 746–753, 2009.

[26] S. Kawaguchi, T. Tsukahara, K. Ida et al., "SYT-SSX breakpoint peptide vaccines in patients with synovial sarcoma: a study from the Japanese Musculoskeletal Oncology Group," *Cancer Science*, vol. 103, no. 9, pp. 1625–1630, 2012.

[27] R. G. Maki, A. A. Jungbluth, S. Gnjatic et al., "A pilot study of anti-CTLA4 antibody ipilimumab in patients with synovial sarcoma," *Sarcoma*, vol. 2013, Article ID 168145, 8 pages, 2013.

[28] P. F. Robbins, R. A. Morgan, S. A. Feldman et al., "Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1," *Journal of Clinical Oncology*, vol. 29, no. 7, pp. 917–924, 2011.

[29] G. Schuler, B. Schuler-Thurner, and R. M. Steinman, "The use of dendritic cells in cancer immunotherapy," *Current Opinion in Immunology*, vol. 15, no. 2, pp. 138–147, 2003.

[30] L. Gattinoni, D. J. Powell Jr., S. A. Rosenberg, and N. P. Restifo, "Adoptive immunotherapy for cancer: building on success," *Nature Reviews Immunology*, vol. 6, no. 5, pp. 383–393, 2006.

[31] S. A. Rosenberg, N. P. Restifo, J. C. Yang, R. A. Morgan, and M. E. Dudley, "Adoptive cell transfer: a clinical path to effective cancer immunotherapy," *Nature Reviews Cancer*, vol. 8, no. 4, pp. 299–308, 2008.

[32] S. A. Rosenberg, J. J. Mule, P. J. Spiess, C. M. Reichert, and S. L. Schwarz, "Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2," *The Journal of Experimental Medicine*, vol. 161, no. 5, pp. 1169–1188, 1985.

[33] W. H. West, K. W. Tauer, J. R. Yannelli et al., "Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer," *The New England Journal of Medicine*, vol. 316, no. 15, pp. 898–905, 1987.

[34] S. A. Rosenberg, P. Spiess, and R. Lafreniere, "A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes," *Science*, vol. 233, no. 4770, pp. 1318–1321, 1986.

[35] S. A. Rosenberg, J. C. Yang, and N. P. Restifo, "Cancer immunotherapy: moving beyond current vaccines," *Nature Medicine*, vol. 10, no. 9, pp. 909–915, 2004.

[36] K. E. de Visser, A. Eichten, and L. M. Coussens, "Paradoxical roles of the immune system during cancer development," *Nature Reviews Cancer*, vol. 6, no. 1, pp. 24–37, 2006.

[37] R. Medzhitov and C. A. Janeway Jr., "Innate immunity: the virtues of a nonclonal system of recognition," *Cell*, vol. 91, no. 3, pp. 295–298, 1997.

[38] C. A. Janeway Jr. and R. Medzhitov, "Innate immune recognition," *Annual Review of Immunology*, vol. 20, no. 1, pp. 197–216, 2002.

[39] T. Kawai and S. Akira, "TLR signaling," *Cell Death & Differentiation*, vol. 13, no. 5, pp. 816–825, 2006.

[40] K. Takeda and S. Akira, "TLR signaling pathways," *Seminars in Immunology*, vol. 16, no. 1, pp. 3–9, 2004.

[41] H. R. MacDonald and M. Nabholz, "T-cell activation," *Annual Review of Cell Biology*, vol. 2, pp. 231–253, 1986.

[42] J. E. Smith-Garvin, G. A. Koretzky, and M. S. Jordan, "T cell activation," *Annual Review of Immunology*, vol. 27, pp. 591–619, 2009.

[43] A. Grakoui, S. K. Bromley, C. Sumen et al., "The immunological synapse: a molecular machine controlling T cell activation," *Science*, vol. 285, no. 5425, pp. 221–227, 1999.

[44] S. M. Kaech, E. J. Wherry, and R. Ahmed, "Effector and memory T-cell differentiation: implications for vaccine development," *Nature Reviews Immunology*, vol. 2, no. 4, pp. 251–262, 2002.

[45] S. M. Kaech, S. Hemby, E. Kersh, and R. Ahmed, "Molecular and functional profiling of memory CD8 T cell differentiation," *Cell*, vol. 111, no. 6, pp. 837–851, 2002.

[46] D. Mauri, T. Wyss-Coray, H. Gallati, and W. J. Pichler, "Antigen-presenting T cells induce the development of cytotoxic $CD4^+$ T cells. I. Involvement of the CD80-CD28 adhesion molecules," *The Journal of Immunology*, vol. 155, no. 1, pp. 118–127, 1995.

[47] I. S. Grewal and R. A. Flavell, "A central role of CD40 ligand in the regulation of $CD4^+$ T-cell responses," *Immunology Today*, vol. 17, no. 9, pp. 410–414, 1996.

[48] S. R. M. Bennett, F. R. Carbone, F. Karamalis, R. A. Flaveli, J. F. A. P. Miller, and W. R. Heath, "Help for cytotoxic-T-cell responses is mediated by CD40 signalling," *Nature*, vol. 393, no. 6684, pp. 478–480, 1998.

[49] K. Murali-Krishna, J. D. Altman, M. Suresh et al., "Counting antigen-specific CD8 T cells: a reevaluation of bystander activation during viral infection," *Immunity*, vol. 8, no. 2, pp. 177–187, 1998.

[50] R. M. Steinman, "The dendritic cell system and its role in immunogenicity," *Annual Review of Immunology*, vol. 9, pp. 271–296, 1991.

[51] J. Banchereau and R. M. Steinman, "Dendritic cells and the control of immunity," *Nature*, vol. 392, no. 6673, pp. 245–252, 1998.

[52] M. L. Albert, B. Sauter, and N. Bhardwaj, "Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLS," *Nature*, vol. 392, no. 6671, pp. 86–89, 1998.

[53] M. Corr, A. E. Slanetz, L. F. Boyd et al., "T cell receptor-MHC class I peptide interactions: affinity, kinetics, and specificity," *Science*, vol. 265, no. 5174, pp. 946–949, 1994.

[54] P. R. Scholl, P. R. Scholl, R. S. Geha, and R. S. Geha, "MHC class II signaling in B-cell activation," *Immunology Today*, vol. 15, no. 9, pp. 418–422, 1994.

[55] W. R. Heath and F. R. Carbone, "Cross-presentation, dendritic cells, tolerance and immunity," *Annual Review of Immunology*, vol. 19, no. 1, pp. 47–64, 2001.

[56] H. Udono, T. Yamano, Y. Kawabata, M. Ueda, and K. Yui, "Generation of cytotoxic T lymphocytes by MHC class I ligands fused to heat shock cognate protein 70," *International Immunology*, vol. 13, no. 10, pp. 1233–1242, 2001.

[57] A. L. Ackerman and P. Cresswell, "Cellular mechanisms governing cross-presentation of exogenous antigens," *Nature Immunology*, vol. 5, no. 7, pp. 678–684, 2004.

[58] M. Chiriva-Internati, A. Pandey, R. Saba et al., "Cancer testis antigens: a novel target in lung cancer," *International Reviews of Immunology*, vol. 31, no. 5, pp. 321–343, 2012.

[59] E. Stockert, E. Jäger, Y.-T. Chen et al., "A survey of the humoral immune response of cancer patients to a panel of human tumor antigens," *Journal of Experimental Medicine*, vol. 187, no. 8, pp. 1349–1354, 1998.

[60] C. Coppin, F. Porzsolt, J. Kumpf, A. Coldman, and T. Wilt, "Immunotherapy for advanced renal cell cancer," *Cochrane Database of Systematic Reviews*, 2004.

[61] A. D. Sasse, E. C. Sasse, L. G. O. Clark, L. Ulloa, and O. A. C. Clark, "Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma," *Cochrane Database of Systematic Reviews*, Article ID CD005413, 2007.

[62] G. A. Rabinovich, D. Gabrilovich, and E. M. Sotomayor, "Immunosuppressive strategies that are mediated by tumor cells," *Annual Review of Immunology*, vol. 25, pp. 267–296, 2007.

[63] T. L. Walunas, D. J. Lenschow, C. Y. Bakker et al., "CTLA-4 can function as a negative regulator of T cell activation," *Immunity*, vol. 1, no. 5, pp. 405–413, 1994.

[64] P. S. Linsley, J. L. Greene, W. Brady et al., "Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors," *Immunity*, vol. 1, no. 9, pp. 793–801, 1994.

[65] K. Wing, Y. Onishi, P. Prieto-Martin et al., "CTLA-4 control over Foxp3$^+$ regulatory T cell function," *Science*, vol. 322, no. 5899, pp. 271–275, 2008.

[66] E. R. Kearney, T. L. Walunas, R. W. Karr et al., "Antigen-dependent clonal expansion of a trace population of antigen-specific CD4$^+$ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4," *The Journal of Immunology*, vol. 155, no. 3, pp. 1032–1036, 1995.

[67] D. L. Barber, E. J. Wherry, D. Masopust et al., "Restoring function in exhausted CD8 T cells during chronic viral infection," *Nature*, vol. 439, no. 7077, pp. 682–687, 2006.

[68] C. Petrovas, J. P. Casazza, J. M. Brenchley et al., "PD-1 is a regulator of virus-specific CD8$^+$ T cell survival in HIV infection," *The Journal of Experimental Medicine*, vol. 203, no. 10, pp. 2281–2292, 2006.

[69] K. Sakuishi, L. Apetoh, J. M. Sullivan, B. R. Blazar, V. K. Kuchroo, and A. C. Anderson, "Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity," *Journal of Experimental Medicine*, vol. 207, no. 10, pp. 2187–2194, 2010.

[70] Y. Latchman, C. R. Wood, T. Chernova et al., "PD-L2 is a second ligand for PD-1 and inhibits T cell activation," *Nature Immunology*, vol. 2, no. 3, pp. 261–268, 2001.

[71] M. K. Callahan and J. D. Wolchok, "At the bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy," *Journal of Leukocyte Biology*, vol. 94, no. 1, pp. 41–53, 2013.

[72] D. M. Pardoll, "The blockade of immune checkpoints in cancer immunotherapy," *Nature Reviews Cancer*, vol. 12, no. 4, pp. 252–264, 2012.

[73] A. Chaudhry, D. Rudra, P. Treuting et al., "CD4$^+$ regulatory T cells control TH17 responses in a stat3-dependent manner," *Science*, vol. 326, no. 5955, pp. 986–991, 2009.

[74] J. R. Brahmer, S. S. Tykodi, L. Q. M. Chow et al., "Safety and activity of anti-PD-L1 antibody in patients with advanced cancer," *The New England Journal of Medicine*, vol. 366, no. 26, pp. 2455–2465, 2012.

[75] Y. Iwai, M. Ishida, Y. Tanaka, T. Okazaki, T. Honjo, and N. Minato, "Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 19, pp. 12293–12297, 2002.

[76] L. M. Francisco, V. H. Salinas, K. E. Brown et al., "PD-L1 regulates the development, maintenance, and function of induced regulatory T cells," *Journal of Experimental Medicine*, vol. 206, no. 13, pp. 3015–3029, 2009.

[77] S. Lee and K. Margolin, "Cytokines in cancer immunotherapy," *Cancers*, vol. 3, no. 4, pp. 3856–3893, 2011.

[78] J.-P. Shaw, P. J. Utz, D. B. Durand, J. J. Toole, E. A. Emmel, and G. R. Crabtree, "Indentification of a putative regulator of early T cell activation genes," *Science*, vol. 241, no. 4862, pp. 202–205, 1988.

[79] M. T. Lotze, A. E. Chang, C. A. Seipp, C. Simpson, J. T. Vetto, and S. A. Rosenberg, "High-dose recombinant interleukin 2 in the treatment of patients with disseminated cancer. Responses, treatment-related morbidity, and histologic findings," *The Journal of the American Medical Association*, vol. 256, no. 22, pp. 3117–3124, 1986.

[80] M. B. Atkins, M. T. Lotze, J. P. Dutcher et al., "High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993," *Journal of Clinical Oncology*, vol. 17, no. 7, pp. 2105–2116, 1999.

[81] R. N. Schwartz, L. Stover, and J. Dutcher, "Managing toxicities of high-dose interleukin-2," *Oncology*, vol. 16, no. 11, pp. 11–20, 2002.

[82] D. J. Schwartzentruber, "Guidelines for the safe administration of high-dose interleukin-2," *Journal of Immunotherapy*, vol. 24, no. 4, pp. 287–293, 2001.

[83] M. P. Link, A. M. Goorin, A. W. Miser et al., "The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity," *The New England Journal of Medicine*, vol. 314, no. 25, pp. 1600–1606, 1986.

[84] K. Ando, K. Mori, N. Corradini, F. Redini, and D. Heymann, "Mifamurtide for the treatment of nonmetastatic osteosarcoma," *Expert Opinion on Pharmacotherapy*, vol. 12, no. 2, pp. 285–292, 2011.

[85] P. M. Anderson, M. Tomaras, and K. McConnell, "Mifamurtide in osteosarcoma-a practical review," *Drugs of Today*, vol. 46, no. 5, pp. 327–337, 2010.

[86] K. Geddes, J. G. Magalhães, and S. E. Girardin, "Unleashing the therapeutic potential of NOD-like receptors," *Nature Reviews Drug Discovery*, vol. 8, no. 6, pp. 465–479, 2009.

[87] J. E. Frampton, P. M. Anderson, A. J. Chou et al., "Mifamurtide: a review of its use in the treatment of osteosarcoma," *Pediatric Drugs*, vol. 12, no. 3, pp. 141–153, 2010.

[88] E. G. MacEwen, I. D. Kurzman, R. C. Rosenthal et al., "Therapy for osteosarcoma in dogs with intravenous injection of liposome-encapsulated muramyl tripeptide," *Journal of the National Cancer Institute*, vol. 81, no. 12, pp. 935–938, 1989.

[89] P. A. Meyers, C. L. Schwartz, M. D. Krailo et al., "Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival—a report from the children's oncology group," *Journal of Clinical Oncology*, vol. 26, no. 4, pp. 633–638, 2008.

[90] M. Ayyoub, R. N. Taub, M. L. Keohan et al., "The frequent expression of cancer/testis antigens provides opportunities for immunotherapeutic targeting of sarcoma," *Cancer Immunity*, vol. 4, no. 7, 2004.

[91] R. Takahashi, Y. Ishibashi, K. Hiraoka et al., "Phase II study of personalized peptide vaccination for refractory bone and soft tissue sarcoma patients," *Cancer Science*, vol. 104, no. 10, pp. 1285–1294, 2013.

[92] S. E. Finkelstein, M. Fishman, A. P. Conley, D. Gabrilovich, S. Antonia, and A. Chiappori, "Cellular immunotherapy for soft tissue sarcomas," *Immunotherapy*, vol. 4, no. 3, pp. 283–290, 2012.

[93] C. Harrison, "Vaccines: nanorings boost vaccine adjuvant effects," *Nature Reviews Drug Discovery*, vol. 13, no. 7, pp. 496–496, 2014.

[94] M. Vergati, C. Intrivici, N.-Y. Huen, J. Schlom, and K. Y. Tsang, "Strategies for cancer vaccine development," *Journal of Biomedicine and Biotechnology*, vol. 2010, Article ID 596432, 13 pages, 2010.

[95] F. J. Hsu, C. Benike, F. Fagnoni et al., "Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells," *Nature Medicine*, vol. 2, no. 1, pp. 52–58, 1996.

[96] C. M. Celluzzi, J. I. Mayordomo, W. J. Storkus, M. T. Lotze, and L. D. Falo Jr., "Peptide-pulsed dendritic cells induce antigen-specific, CTL-mediated protective tumor immunity," *Journal of Experimental Medicine*, vol. 183, no. 1, pp. 283–287, 1996.

[97] J. D. Geiger, R. J. Hutchinson, L. F. Hohenkirk et al., "Vaccination of pediatric solid tumor patients with tumor lysate-pulsed dendritic cells can expand specific T cells and mediate tumor regression," *Cancer Research*, vol. 61, no. 23, pp. 8513–8519, 2001.

[98] H. L. Chen and D. P. Carbone, "p53 as a target for anti-cancer immunotherapy," *Molecular Medicine Today*, vol. 3, no. 4, pp. 160–167, 1997.

[99] S. Gnjatic, H. Nishikawa, A. A. Jungbluth et al., "NY-ESO-1: review of an immunogenic tumor antigen," *Advances in Cancer Research*, vol. 95, pp. 1–30, 2006.

[100] S. A. Rosenberg, "A new era for cancer immunotherapy based on the genes that encode cancer antigens," *Immunity*, vol. 10, no. 3, pp. 281–287, 1999.

[101] A. Kawai, J. Woodruff, J. H. Healey, M. F. Brennan, C. R. Antonescu, and M. Ladanyi, "*SYT-SSX* gene fusion as a determinant of morphology and prognosis in synovial sarcoma," *The New England Journal of Medicine*, vol. 338, no. 3, pp. 153–160, 1998.

[102] S. Kawaguchi, T. Wada, K. Ida et al., "Phase I vaccination trial of SYT-SSX junction peptide in patients with disseminated synovial sarcoma," *Journal of Translational Medicine*, vol. 3, article 1, 2005.

[103] L. He, H. Feng, A. Raymond et al., "Dendritic-cell-peptide immunization provides immunoprotection against *bcr-abl*-positive leukemia in mice," *Cancer Immunology, Immunotherapy*, vol. 50, no. 1, pp. 31–40, 2001.

[104] R. Yamanaka, N. Yajima, T. Abe et al., "Dendritic cell-based glioma immunotherapy (review)," *International Journal of Oncology*, vol. 23, no. 1, pp. 5–15, 2003.

[105] A. J. G. Simpson, O. L. Caballero, A. Jungbluth, Y.-T. Chen, and L. J. Old, "Cancer/testis antigens, gametogenesis and cancer," *Nature Reviews Cancer*, vol. 5, no. 8, pp. 615–625, 2005.

[106] R. L. Jones, S. M. Pollack, E. T. Loggers, E. T. Rodler, and C. Yee, "Immune-based therapies for sarcoma," *Sarcoma*, vol. 2011, Article ID 438940, 7 pages, 2011.

[107] C. Roeder, B. Schuler-Thurner, S. Berchtold et al., "MAGE-A3 is a frequent tumor antigen of metastasized melanoma," *Archives of Dermatological Research*, vol. 296, no. 7, pp. 314–319, 2005.

[108] W. Sienel, C. Varwerk, A. Linder et al., "Melanoma associated antigen (MAGE)-A3 expression in Stages I and II non-small cell lung cancer: results of a multi-center study," *European Journal of Cardio-Thoracic Surgery*, vol. 25, no. 1, pp. 131–134, 2004.

[109] O. L. Caballero and Y.-T. Chen, "Cancer/testis (CT) antigens: potential targets for immunotherapy," *Cancer Science*, vol. 100, no. 11, pp. 2014–2021, 2009.

[110] M. E. Dudley and S. A. Rosenberg, "Adoptive-cell-transfer therapy for the treatment of patients with cancer," *Nature Reviews Cancer*, vol. 3, no. 9, pp. 666–675, 2003.

[111] D. W. Lee, D. M. Barrett, C. Mackall, R. Orentas, and S. A. Grupp, "The future is now: chimeric antigen receptors as new targeted therapies for childhood cancer," *Clinical Cancer Research*, vol. 18, no. 10, pp. 2780–2790, 2012.

[112] J. Weber, "Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events," *The Oncologist*, vol. 12, no. 7, pp. 864–872, 2007.

[113] F. S. Hodi, S. J. O'Day, D. F. McDermott et al., "Improved survival with ipilimumab in patients with metastatic melanoma," *The New England Journal of Medicine*, vol. 363, no. 8, pp. 711–723, 2010.

[114] K. Wiater, T. Witaj, J. Mackiewicz et al., "Efficacy and safety of ipilimumab therapy in patients with metastatic melanoma: a retrospective multicenter analysis," *Contemporary Oncology*, vol. 17, no. 3, pp. 257–262, 2013.

[115] E. D. Deeks, "Nivolumab: a review of its use in patients with malignant melanoma," *Drugs*, vol. 74, no. 11, pp. 1233–1239, 2014.

[116] S. L. Topalian, F. S. Hodi, J. R. Brahmer et al., "Safety, activity, and immune correlates of anti-PD-1 antibody in cancer," *The New England Journal of Medicine*, vol. 366, no. 26, pp. 2443–2454, 2012.

[117] J. D. Wolchok, H. Kluger, M. K. Callahan et al., "Nivolumab plus Ipilimumab in advanced melanoma," *The New England Journal of Medicine*, vol. 369, no. 2, pp. 122–133, 2013.

[118] M. Farazuddinm, B. Sharma, A. A. Khan, B. Joshi, and M. Owais, "Anticancer effcacy of perillyl alcohol-bearing PLGA microparticles," *International Journal of Nanomedicine*, vol. 7, pp. 35–47, 2012.

[119] A. Khan, Y. Shukla, N. Kalra et al., "Potential of diallyl sulfide bearing pH-sensitive liposomes in chemoprevention against DMBA-induced skin papilloma," *Molecular Medicine*, vol. 13, no. 7-8, pp. 443–451, 2007.

[120] M. Farazuddin, B. Dua, Q. Zia, A. A. Khan, B. Joshi, and M. Owais, "Chemotherapeutic potential of curcumin-bearing microcells against hepatocellular carcinoma in model animals," *International Journal of Nanomedicine*, vol. 9, no. 1, pp. 1139–1152, 2014.

[121] A. Chauhan, S. Zubair, A. Nadeem, S. A. Ansari, M. Y. Ansari, and O. Mohammad, "Escheriosome-mediated cytosolic

delivery of PLK1-specific siRNA: potential in treatment of liver cancer in BALB/c mice," *Nanomedicine*, vol. 9, no. 4, pp. 407–420, 2014.

[122] A. Chauhan, S. Zubair, S. Tufail et al., "Fungus-mediated biological synthesis of gold nanoparticles: potential in detection of liver cancer," *International Journal of Nanomedicine*, vol. 6, pp. 2305–2319, 2011.

[123] H. Singha, A. I. Mallick, C. Jana, N. Fatima, M. Owais, and P. Chaudhuri, "Co-immunization with interlukin-18 enhances the protective efficacy of liposomes encapsulated recombinant Cu-Zn superoxide dismutase protein against Brucella abortus," *Vaccine*, vol. 29, no. 29-30, pp. 4720–4727, 2011.

[124] M. A. Khan, A. Aljarbou, A. Khan, and M. Owais, "Immune stimulating and therapeutic potential of tuftsin-incorporated nystatin liposomes against *Cryptococcus neoformans* in leukopenic BALB/C mice," *FEMS Immunology and Medical Microbiology*, vol. 66, no. 1, pp. 88–97, 2012.

[125] M. A. Khan, A. Khan, and M. Owais, "Prophylactic use of liposomized tuftsin enhances the susceptibility of *Candida albicans* to fluconazole in leukopenic mice," *FEMS Immunology and Medical Microbiology*, vol. 46, no. 1, pp. 63–69, 2006.

[126] M. A. Khan and M. Owais, "Toxicity, stability and pharmacokinetics of amphotericin B in immunomodulator tuftsin-bearing liposomes in a murine model," *Journal of Antimicrobial Chemotherapy*, vol. 58, no. 1, pp. 125–132, 2006.

[127] M. A. Khan, S. M. Faisal, and O. Mohammad, "Safety, efficacy and pharmacokinetics of tuftsin-loaded nystatin liposomes in murine model," *Journal of Drug Targeting*, vol. 14, no. 4, pp. 233–241, 2006.

[128] A. Khan, A. A. Khan, V. Dwivedi, M. G. Ahmad, S. Hakeem, and M. Owais, "Tuftsin augments antitumor efficacy of liposomized etoposide against fibrosarcoma in Swiss albino mice," *Molecular Medicine*, vol. 13, no. 5-6, pp. 266–276, 2007.

[129] J. Crespo, H. Sun, T. H. Welling, Z. Tian, and W. Zou, "T cell anergy, exhaustion, senescence, and stemness in the tumor microenvironment," *Current Opinion in Immunology*, vol. 25, no. 2, pp. 214–221, 2013.

臨研様式5号

整理番号	m12004	
区分	■ 医薬品	□ 医療機器

西暦　2014年 6月 17日

臨床研究審査結果通知書

岡山大学病院長　殿

岡山大学大学院医歯薬学総合研究科長　殿

臨床研究審査専門委員会
岡山大学医療系部局臨床研究審査専門委員会　岡山市北区鹿田町二丁目5番1号
委員長　　柳井　広之

審査依頼のあった件についての審査結果を下記のとおり通知いたします。

記

試験薬の化学名又は識別記号	メトホルミン	臨床研究実施計画書番号	
研究課題名	健常者におけるメトホルミンの免疫機能への影響の検討		
審査事項（審査資料）	■ 研究の実施の適否（臨床研究依頼書　（西暦　2014年4月28日　付臨研様式1号写））		
	□ 研究の継続の適否		
	□ 重篤な有害事象等		
	（□ 重篤な有害事象に関する報告書　（西暦　年　月　日　付臨床様式9-1、9-2号写））		
	□ 安全性情報等		
	（□ 安全性情報等に関する報告書　（西暦　年　月　日　付臨床様式10号写））		
	□ 臨床研究に関する変更		
	（臨床研究に関する変更申請書　（西暦　年　月　日　付臨床様式7号写））		
	□ 緊急の危険を回避するための臨床研究実施計画書からの逸脱		
	（緊急の危険を回避するための臨床研究実施計画書からの逸脱に関する報告書　（西暦　年　月　日　付臨床様式6号写））		
	□ 継続審査		
	（臨床研究実施状況報告書　（西暦　年　月　日　付臨床様式8号写））		
	□ その他（　）		
審査区分	■	委員会審査（審査日　：西暦　2014年6月17日　）	
	□	迅速審査（審査終了日　：西暦　年　月　日　）	
審査結果	■ 承認　□ 修正の上で承認　□ 却下　□ 既承認事項の取り消し　□ 保留		
「承認」以外の場合の理由等			
備考			

診療科長　三好 新一郎　殿
研究責任者　豊岡 伸一　殿

西暦　2014年6月17日

依頼のあった臨床研究に関する審査事項について上記のとおり決定しましたので通知いたします。

岡山大学病院長
岡山大学大学院医歯薬学総合研究科長

臨研様式5号

整理番号	m12004

西暦　2014年6月17日

臨床研究審査専門委員会委員出欠リスト

氏名	職業、資格及び所属	委員区分	出欠	備考
深　松　紘　子	皮膚科・助教	④	○	内規第4条第1号
佃　　和　憲	低侵襲治療センター・講師	④	○	内規第4条第1号
石　原　嘉　人	矯正歯科・助教	④	×	内規第4条第1号
前　田　嘉　信	血液，腫瘍内科・講師/医局長	④	×	内規第4条第2号
元　木　崇　之	消化管外科・助教/医局長	④	○	内規第4条第2号
尾　崎　敏　文	検査部・部長	④	○	内規第4条第3号
柳　井　広　之	病理部・副部長	④	○	内規第4条第4号
北　村　佳　久	薬剤部・副薬剤部長	④	○	内規第4条第5号
三　村　　瞳	看護部・副看護部長	④	○	内規第4条第6号
西　堀　正　洋	大学院医歯薬学総合研究科・教授	④	×	内規第4条第7号
岡　　久　雄	大学院保健学研究科・教授	④	※－	内規第4条第8号
近　藤　真紀子	大学院保健学研究科・准教授	④	○	内規第4条第9号
津　田　敏　秀	大学院環境生命科学研究科・教授	④	○	内規第4条第10号
吉　岡　文　夫	大学院社会文化科学研究科・教授	①	○	内規第4条第11号
山　崎　英　男	医事課・総括主査	①	○	内規第4条第11号
芳　井　増　稔	元福山市立市民病院看護部長	②, ③	○	内規第4条第12号
古　野　勝　志	元医療法人長光会長島病院薬局長	②, ③	○	内規第4条第12号
坂　口　幸　司	弁護士・坂口法律事務所	②, ③	○	内規第4条第12号
犬　飼　茂　子	元岡山市立京山中学校校長	②, ③	○	内規第4条第12号

注）委員区分については以下の区分により番号で記載する。

①非専門委員
②実施医療機関と利害関係を有しない委員（①に定める委員を除く）
③臨床研究審査専門委員会の設置者と利害関係を有しない委員（①に定める委員を除く）
④①～③以外の委員

また、出欠については以下の区分により記号で記載する。

○（出席し、かつ当該試験に関与しない委員）
－（出席したが、当該試験に関与するため審議及び採決に不参加の委員）
×（欠席した委員）
※(本臨床研究審査専門委員会内規にて医療機器に関する審議事項がない場合は、成立要件に含まないため不参加(欠席)の委員)
※－(出席したが、本臨床研究審査専門委員会内規で医療機器審査のみ審議および採決に参加の為、医薬品審議及び採決に不参加の委員)

本臨床研究審査専門委員会は、本委員会の標準業務手順書に従って組織され、活動していることを確認し、保証いたします。

臨研様式5号

整理番号	m12004	
区分	■ 医薬品	□ 医療機器

西暦　2014年 6月 17日

臨床研究審査結果通知書

岡山大学病院長　殿

岡山大学大学院医歯薬学総合研究科長　殿

臨床研究審査専門委員会
岡山大学医療系部局臨床研究審査専門委員会　岡山市北区鹿田町二丁目5番1号
委員長　　柳井　広之

審査依頼のあった件についての審査結果を下記のとおり通知いたします。

記

試験薬の化学名又は識別記号	メトホルミン	臨床研究実施計画書番号	
研究課題名	健常者におけるメトホルミンの免疫機能への影響の検討		
審査事項（審査資料）	■ 研究の実施の適否（臨床研究依頼書　（西暦　2014年4月28日　付臨研様式1号写））		
	□ 研究の継続の適否		
	□ 重篤な有害事象等		
	（□ 重篤な有害事象に関する報告書　（西暦　年　月　日　付臨床様式9-1、9-2号写））		
	□ 安全性情報等		
	（□ 安全性情報等に関する報告書　（西暦　年　月　日　付臨床様式10号写））		
	□ 臨床研究に関する変更		
	（臨床研究に関する変更申請書　（西暦　年　月　日　付臨床様式7号写））		
	□ 緊急の危険を回避するための臨床研究実施計画書からの逸脱		
	（緊急の危険を回避するための臨床研究実施計画書からの逸脱に関する報告書　（西暦　年　月　日　付臨床様式6号写））		
	□ 継続審査		
	（臨床研究実施状況報告書　（西暦　年　月　日　付臨床様式8号写））		
	□ その他（　）		
審査区分	■	委員会審査（審査日　：西暦　2014年6月17日　）	
	□	迅速審査（審査終了日　：西暦　年　月　日　）	
審査結果	■ 承認　□ 修正の上で承認　□ 却下　□ 既承認事項の取り消し　□ 保留		
「承認」以外の場合の理由等			
備考			

診療科長　三好 新一郎　殿　　西暦　2014年6月17日
研究責任者　豊岡 伸一　殿

依頼のあった臨床研究に関する審査事項について上記のとおり決定しましたので通知いたします。

岡山大学病院長
岡山大学大学院医歯薬学総合研究科長

臨研様式5号

整理番号	m12004

西暦　2014年6月17日

臨床研究審査専門委員会委員出欠リスト

氏名	職業、資格及び所属	委員区分	出欠	備考
深　松　紘　子	皮膚科・助教	④	○	内規第4条第1号
佃　　和　憲	低侵襲治療センター・講師	④	○	内規第4条第1号
石　原　嘉　人	矯正歯科・助教	④	×	内規第4条第1号
前　田　嘉　信	血液，腫瘍内科・講師/医局長	④	×	内規第4条第2号
元　木　崇　之	消化管外科・助教/医局長	④	○	内規第4条第2号
尾　崎　敏　文	検査部・部長	④	○	内規第4条第3号
柳　井　広　之	病理部・副部長	④	○	内規第4条第4号
北　村　佳　久	薬剤部・副薬剤部長	④	○	内規第4条第5号
三　村　　瞳	看護部・副看護部長	④	○	内規第4条第6号
西　堀　正　洋	大学院医歯薬学総合研究科・教授	④	×	内規第4条第7号
岡　　久　雄	大学院保健学研究科・教授	④	※－	内規第4条第8号
近　藤　真紀子	大学院保健学研究科・准教授	④	○	内規第4条第9号
津　田　敏　秀	大学院環境生命科学研究科・教授	④	○	内規第4条第10号
吉　岡　文　夫	大学院社会文化科学研究科・教授	①	○	内規第4条第11号
山　崎　英　男	医事課・総括主査	①	○	内規第4条第11号
芳　井　増　稔	元福山市立市民病院看護部長	②，③	○	内規第4条第12号
古　野　勝　志	元医療法人長光会長島病院薬局長	②，③	○	内規第4条第12号
坂　口　幸　司	弁護士・坂口法律事務所	②，③	○	内規第4条第12号
犬　飼　茂　子	元岡山市立京山中学校校長	②，③	○	内規第4条第12号

注）委員区分については以下の区分により番号で記載する。

①非専門委員
②実施医療機関と利害関係を有しない委員（①に定める委員を除く）
③臨床研究審査専門委員会の設置者と利害関係を有しない委員（①に定める委員を除く）
④①～③以外の委員

また、出欠については以下の区分により記号で記載する。

○（出席し、かつ当該試験に関与しない委員）
－（出席したが、当該試験に関与するため審議及び採決に不参加の委員）
×（欠席した委員）
※（本臨床研究審査専門委員会内規にて医療機器に関する審議事項がない場合は、成立要件に含まないため不参加（欠席）の委員）
※－（出席したが、本臨床研究審査専門委員会内規で医療機器審査のみ審議および採決に参加の為、医薬品審議及び採決に不参加の委員）

本臨床研究審査専門委員会は、本委員会の標準業務手順書に従って組織され、活動していることを確認し、保証いたします。

臨研様式4号

整理番号	m12004
区分	■ 医薬品 □ 医療機器

西暦　2014年4月21日

臨床研究分担者・臨床研究協力者リスト　（ ■ 新規 □ 変更

岡山大学病院長 殿

岡山大学大学院医歯薬学総合研究科長

臨床研究責任者

（診療科名）　呼吸器外科

（氏名）　豊岡 伸一

下記の研究において、下に示す者を臨床研究分担者・臨床研究協力者として業務を分担したく提出いたします。

記

試験薬の化学名又は識別記号	メトホルミン	臨床研究実施計画書番号	
研究課題名	健常者におけるメトホルミンの免疫機能への影響の検討		

臨床研究分担者の氏名、所属又は職名及び分担業務の内容（10名を上回る場合別紙に記載）

氏名	所属又は職名	分担業務の内容			利益相反の有無
鵜殿　平一郎	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 腫瘍制御学講座 免疫学分野・教授	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
樋之津　史郎	岡山大学病院新医療研究開発センター・教授	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
和田　淳	岡山大学病院　腎臓・糖尿病・内分泌内科・准教授	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
平田　泰三	岡山大学病院新医療研究開発センター・准教授	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
山本　寛斉	岡山大学病院　呼吸器外科・助教	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
榮川　伸吾	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 腫瘍制御学講座 免疫学分野・助教	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
渡邊　元嗣	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 腫瘍制御学講座 呼吸器・乳腺内分泌外科学分野・大学院生	■	臨床研究業務全般	□ （ ）	□ 有 ■ 無
		□	臨床研究業務全般	□ （ ）	□ 有 □ 無
		□	臨床研究業務全般	□ （ ）	□ 有 □ 無

臨床研究協力者の氏名、所属又は職名及び分担業務の内容（10名を上回る場合別紙に記載）

氏名	所属又は職名	分担業務の内容			
		□	臨床研究業務全般	□	（ ）
		□	臨床研究業務全般	□	（ ）
		□	臨床研究業務全般	□	（ ）
		□	臨床研究業務全般	□	（ ）
		□	臨床研究業務全般	□	（ ）

西暦　2014年6月17日

上記の研究において、臨床研究分担者及び臨床研究協力者のリストを了承いたします。

岡山大学病院長
岡山大学大学院医歯薬学総合研究科長

臨研様式5号

整理番号	m12005	
区分	■ 医薬品	□ 医療機器

西暦　2014年7月15日

臨床研究審査結果通知書

岡山大学病院長　殿

岡山大学大学院医歯薬学総合研究科長　殿

臨床研究審査専門委員会

岡山大学医療系部局臨床研究審査専門委員会
岡山市北区鹿田町二丁目5番1号

委員長　柳井　広之

審査依頼のあった件についての審査結果を下記のとおり通知いたします。

記

試験薬の化学名又は識別記号	メトホルミン	臨床研究実施計画書番号	
研究課題名	悪性腫瘍患者におけるメトホルミンの免疫機能への影響の検討		
審査事項（審査資料）	■ 研究の実施の適否（臨床研究依頼書　（西暦　2014年5月26日　付臨研様式1号写））		
	□ 研究の継続の適否		
	□ 重篤な有害事象等		
	（□ 重篤な有害事象に関する報告書　（西暦　年　月　日　付臨床様式9-1、9-2号　写））		
	□ 安全性情報等		
	（□ 安全性情報等に関する報告書　（西暦　年　月　日　付臨床様式10号写））		
	□ 臨床研究に関する変更		
	（臨床研究に関する変更申請書　（西暦　年　月　日　付臨床様式7号写））		
	□ 緊急の危険を回避するための臨床研究実施計画書からの逸脱		
	（緊急の危険を回避するための臨床研究実施計画書からの逸脱に関する報告書　（西暦　年　月　日　付臨床様式6号写））		
	□ 継続審査		
	（臨床研究実施状況報告書　（西暦　年　月　日　付臨床様式8号写））		
	□ その他（　）		
審査区分	■	委員会審査（審査日　：西暦　2014年7月15日　）	
	□	迅速審査（審査終了日　：西暦　年　月　日　）	
審査結果	■ 承認　□ 修正の上で承認　□ 却下　□ 既承認事項の取り消し　□ 保留		
「承認」以外の場合の理由等			
備考			

西暦　2014年7月15日

診療科長　三好 新一郎　殿
研究責任者　豊岡 伸一　殿

依頼のあった臨床研究に関する審査事項について上記のとおり決定しましたので通知いたします。

岡山大学病院長
岡山大学大学院医歯薬学総合研究科長

臨研様式5号

整理番号	m12005

西暦　2014年7月15日

臨床研究審査委員専門会委員出欠リスト

氏名	職業、資格及び所属	委員区分	出欠	備考
深　松　紘　子	皮膚科・助教	④	○	内規第4条第1号
佃　　和　憲	低侵襲治療センター・講師	④	○	内規第4条第1号
石　原　嘉　人	矯正歯科・助教	④	×	内規第4条第1号
前　田　嘉　信	血液，腫瘍内科・講師/医局長	④	○	内規第4条第2号
元　木　崇　之	消化管外科・助教/医局長	④	○	内規第4条第2号
尾　崎　敏　文	検査部・部長	④	○	内規第4条第3号
柳　井　広　之	病理部・副部長	④	○	内規第4条第4号
北　村　佳　久	薬剤部・副薬剤部長	④	×	内規第4条第5号
三　村　　瞳	看護部・副看護部長	④	×	内規第4条第6号
西　堀　正　洋	大学院医歯薬学総合研究科・教授	④	×	内規第4条第7号
桐　田　泰　三	研究推進産学官連携機構産学官連携コーディネーター	④	※－	内規第4条第8号
近　藤　真紀子	大学院保健学研究科・准教授	④	×	内規第4条第9号
津　田　敏　秀	大学院環境生命科学研究科・教授	④	×	内規第4条第10号
吉　岡　文　夫	大学院社会文化科学研究科・教授	①	○	内規第4条第11号
山　崎　英　男	医事課・総括主査	①	○	内規第4条第11号
芳　井　増　稔	元福山市立市民病院看護部長	②，③	○	内規第4条第12号
古　野　勝　志	元医療法人長光会長島病院薬局長	②，③	○	内規第4条第12号
坂　口　幸　司	弁護士・坂口法律事務所	②，③	○	内規第4条第12号
犬　飼　茂　子	元岡山市立京山中学校校長	②，③	○	内規第4条第12号

注）委員区分については以下の区分により番号で記載する。

①非専門委員
②実施医療機関と利害関係を有しない委員（①に定める委員を除く）
③臨床研究審査専門委員会の設置者と利害関係を有しない委員（①に定める委員を除く）
④①～③以外の委員

また、出欠については以下の区分により記号で記載する。

○（出席し、かつ当該試験に関与しない委員）
－（出席したが、当該試験に関与するため審議及び採決に不参加の委員）
×（欠席した委員）
※(本臨床研究審査専門委員会内規にて医療機器に関する審議事項がない場合は、成立要件に含まないため不参加(欠席)の委員)
※－(出席したが、本臨床研究審査専門委員会内規で医療機器審査のみ審議および採決に参加の為、医薬品審議及び採決に不参加の委員)

本臨床研究審査専門委員会は、本委員会の標準業務手順書に従って組織され、活動していることを確認し、保証いたします。

臨研様式5号

整理番号	m12005	
区分	■ 医薬品	□ 医療機器

西暦　2014年7月15日

臨床研究審査結果通知書

岡山大学病院長　殿

岡山大学大学院医歯薬学総合研究科長　殿

臨床研究審査専門委員会
岡山大学医療系部局臨床研究審査専門委員会
岡山市北区鹿田町二丁目5番1号
委員長　柳井　広之

審査依頼のあった件についての審査結果を下記のとおり通知いたします。

記

試験薬の化学名又は識別記号	メトホルミン	臨床研究実施計画書番号	
研究課題名	悪性腫瘍患者におけるメトホルミンの免疫機能への影響の検討		
審査事項（審査資料）	■ 研究の実施の適否（臨床研究依頼書　（西暦　2014年5月26日　付臨研様式1号写））		
	□ 研究の継続の適否		
	□ 重篤な有害事象等		
	（□ 重篤な有害事象に関する報告書　（西暦　年　月　日　付臨床様式9-1、9-2号　写））		
	□ 安全性情報等		
	（□ 安全性情報等に関する報告書　（西暦　年　月　日　付臨床様式10号写））		
	□ 臨床研究に関する変更		
	（臨床研究に関する変更申請書　（西暦　年　月　日　付臨床様式7号写））		
	□ 緊急の危険を回避するための臨床研究実施計画書からの逸脱		
	（緊急の危険を回避するための臨床研究実施計画書からの逸脱に関する報告書　（西暦　年　月　日　付臨床様式6号写））		
	□ 継続審査		
	（臨床研究実施状況報告書　（西暦　年　月　日　付臨床様式8号写））		
	□ その他（　）		
審査区分	■	委員会審査（審査日　：西暦　2014年7月15日　）	
	□	迅速審査（審査終了日　：西暦　年　月　日　）	
審査結果	■ 承認　□ 修正の上で承認　□ 却下　□ 既承認事項の取り消し　□ 保留		
「承認」以外の場合の理由等			
備考			

西暦　2014年7月15日

診療科長　三好 新一郎　殿
研究責任者　豊岡 伸一　殿

依頼のあった臨床研究に関する審査事項について上記のとおり決定しましたので通知いたします。

岡山大学病院長
岡山大学大学院医歯薬学総合研究科長

臨研様式5号

整理番号	mi2005

西暦　2014年7月15日

臨床研究審査委員専門会委員出欠リスト

氏名	職業、資格及び所属	委員区分	出欠	備考
深　松　紘　子	皮膚科・助教	④	○	内規第4条第1号
佃　　和　憲	低侵襲治療センター・講師	④	○	内規第4条第1号
石　原　嘉　人	矯正歯科・助教	④	×	内規第4条第1号
前　田　嘉　信	血液，腫瘍内科・講師/医局長	④	○	内規第4条第2号
元　木　崇　之	消化管外科・助教/医局長	④	○	内規第4条第2号
尾　崎　敏　文	検査部・部長	④	○	内規第4条第3号
柳　井　広　之	病理部・副部長	④	○	内規第4条第4号
北　村　佳　久	薬剤部・副薬剤部長	④	×	内規第4条第5号
三　村　　瞳	看護部・副看護部長	④	×	内規第4条第6号
西　堀　正　洋	大学院医歯薬学総合研究科・教授	④	×	内規第4条第7号
桐　田　泰　三	研究推進産学官連携機構産学官連携コーディネーター	④	※－	内規第4条第8号
近　藤　真紀子	大学院保健学研究科・准教授	④	×	内規第4条第9号
津　田　敏　秀	大学院環境生命科学研究科・教授	④	×	内規第4条第10号
吉　岡　文　夫	大学院社会文化科学研究科・教授	①	○	内規第4条第11号
山　崎　英　男	医事課・総括主査	①	○	内規第4条第11号
芳　井　増　稔	元福山市立市民病院看護部長	②，③	○	内規第4条第12号
古　野　勝　志	元医療法人長光会長島病院薬局長	②，③	○	内規第4条第12号
坂　口　幸　司	弁護士・坂口法律事務所	②，③	○	内規第4条第12号
犬　飼　茂　子	元岡山市立京山中学校校長	②，③	○	内規第4条第12号

注）委員区分については以下の区分により番号で記載する。

①非専門委員
②実施医療機関と利害関係を有しない委員（①に定める委員を除く）
③臨床研究審査専門委員会の設置者と利害関係を有しない委員（①に定める委員を除く）
④①～③以外の委員

また、出欠については以下の区分により記号で記載する。

○（出席し、かつ当該試験に関与しない委員）
－（出席したが、当該試験に関与するため審議及び採決に不参加の委員）
×（欠席した委員）
※（本臨床研究審査専門委員会内規にて医療機器に関する審議事項がない場合は、成立要件に含まないため不参加（欠席）の委員）
※－（出席したが、本臨床研究審査専門委員会内規で医療機器審査のみ審議および採決に参加の為、医薬品審議及び採決に不参加の委員）

本臨床研究審査専門委員会は、本委員会の標準業務手順書に従って組織され、活動していることを確認し、保証いたします。

臨研様式4号

整理番号	m12005
区分	■ 医薬品 □ 医療機器

西暦　2014年5月26日

臨床研究分担者・臨床研究協力者リスト　（ ■ 新規 □ 変更

岡山大学病院長　殿

岡山大学大学院医歯薬学総合研究科長　殿

臨床研究責任者

（診療科名）　呼吸器外科

（氏名）　豊岡 伸一

下記の研究において、下に示す者を臨床研究分担者・臨床研究協力者として業務を分担したく提出いたします。

記

試験薬の化学名又は識別記号	メトホルミン	臨床研究実施計画書番号	
研究課題名	悪性腫瘍患者におけるメトホルミンの免疫機能への影響の検討		

臨床研究分担者の氏名、所属又は職名及び分担業務の内容（10名を上回る場合別紙に記載）

氏名	所属又は職名	分担業務の内容				利益相反の有無
鵜殿　平一郎	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 腫瘍制御学講座 免疫学分野・教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
三好　新一郎	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 腫瘍制御学講座 呼吸器・乳腺内分泌外科学分野 教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
土井原　博義	岡山大学病院 乳腺・内分泌外科 教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
那須　保友	岡山大学病院新医療研究開発センター 教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
木浦　勝行	岡山大学病院 呼吸器・アレルギー内科 教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
藤原　俊義	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 腫瘍制御学講座 消化器外科学分野 教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
樋之津　史郎	岡山大学病院新医療研究開発センター 教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
和田　淳	岡山大学大学院医歯薬学総合研究科 病態制御科学専攻 病態機構学講座 腎・免疫・内分泌代謝内科学分野 准教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
平田　泰三	岡山大学病院新医療研究開発センター 准教授	■	臨床研究業務全般	□	（　）	□ 有 ■ 無
宗　淳一	岡山大学病院 呼吸器外科 講師	■	臨床研究業務全般	□	（　）	□ 有 ■ 無

臨床研究協力者の氏名、所属又は職名及び分担業務の内容（10名を上回る場合別紙に記載）

氏名	所属又は職名	分担業務の内容			
		□	臨床研究業務全般	□	
		□	臨床研究業務全般	□	
		□	臨床研究業務全般	□	
		□	臨床研究業務全般	□	

西暦　2014年7月15日

上記の研究において、臨床研究分担者及び臨床研究協力者のリストを了承いたします。

岡山大学病院長

岡山大学大学院医歯薬学総合研究科長

臨床研究分担者の氏名、所属又は職名及び分担業務の内容(10名を上回る分)

氏名	所属又は職名	分担業務の内容	利益相反の有無
山本 寛斉	岡山大学病院 呼吸器外科 助教	■ 臨床研究業務全般 □ ( )	□ 有 ■ 無
牧 佑歩	岡山大学病院 呼吸器外科 助教	■ 臨床研究業務全般 □ ( )	□ 有 ■ 無
榮川 伸吾	岡山大学大学院医歯薬学総合研究科病態制御科学専攻腫瘍制御学講座免疫学分野 助教	■ 臨床研究業務全般 □ ( )	□ 有 ■ 無
渡邉 元嗣	岡山大学大学院医歯薬学総合研究科病態制御科学専攻腫瘍制御学講座呼吸器・乳腺内分泌外科学分野 大学院生	■ 臨床研究業務全般 □ ( )	□ 有 ■ 無

ORIGINAL ARTICLE

Cognitive and affective functions in diabetic patients associated with diabetes-related factors, white matter abnormality and aging

N. Hishikawa[a], T.Yamashita[a], K. Deguchi[a], J. Wada[b], K. Shikata[b], H. Makino[b] and K. Abe[a]

[a]*Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama; and* [b]*Department of Medicine and Clinical Science, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan*

Keywords:
cognitive and affective functions, diabetes mellitus, HbA1c, insulin resistance, MRI

Received 26 March 2014
Accepted 1 August 2014

European Journal of Neurology 2015, **22:** 313–321

doi:10.1111/ene.12568

Background and purpose: Diabetes mellitus (DM) is associated with a decline in cognitive and affective functions.

Methods: In all, 182 outpatients with DM were investigated for associations of cognitive and affective functions with diabetes-related factors and cerebral white matter abnormalities. In addition, the difference in cognitive decline of age-matched late elderly normal subjects and DM patients was investigated.

Results: The present study revealed that cognitive and affective functions declined in some DM patients. Furthermore, the decline in these functions was unrelated to fasting blood sugar level but was related to glycosylated hemoglobin (HbA1c) and insulin resistance. Poor HbA1c control was associated with a significant decline in the 'calculation' subscale and insulin resistance for 'naming', 'read list of letters' and 'delayed recall' Montreal Cognitive Assessment (MoCA) subscale scores. Magnetic resonance imaging scans showed that both periventricular hyperintensity (PVH) and deep white matter hyperintensity were associated with Mini Mental State Examination (MMSE) and MoCA scores, but only PVH was related to homeostasis model assessment of insulin resistance scores. Compared with age-matched late elderly normal subjects, 'orientation to time' and 'registration' MMSE subscales declined in late elderly DM patients.

Conclusions: These results suggest that cognitive and affective decline in DM patients was mostly related to glucose control and insulin resistance, whilst amongst late elderly subjects the impairment of 'attention' and 'orientation' were characteristic features of DM patients.

Introduction

As a rapidly aging country, Japan is facing increases in patients with both dementia and diabetes mellitus (DM). DM is an important vascular risk factor (VRF) not only for cardiovascular and cerebrovascular diseases but also for cognitive and affective impairments such as vascular dementia [1]. VFRs are also associated with the occurrence and progression of Alzheimer's disease (AD). However, treatment of VRFs is effective for preventing cognitive decline in AD patients [2,3]. It is presumed that in DM patients chronic hyperglycemia, arteriosclerosis, insidious ischaemia and insulin resistance could lead to generalized atrophy, cerebral white matter changes, accumulation of advanced glycation end-products, and metabolic disturbance of amyloid-β and tau, which probably leads to vascular dementia, AD and acceleration of 'aging' [4].

Cognitive impairment of DM patients is correlated with glucose control, postprandial hyperglycemia, severe hypoglycemia, acute glucose fluctuation, hyperinsulinemia and insulin resistance [5–11]. A close relationship has been shown between poor glucose control and cognitive decline [6], and between oral

Correspondence: K. Abe, Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikatacho Kitaku, Okayama 700-8558, Japan (tel.: +81-86-235-7365; fax: +81-86-235-7368; e-mail: nozomi-hishikawa@okayama-u.ac.jp).