Information for outpatients from foreign countries
Kurume University Cancer Vaccine Center

- ✧ All patients need appointment in advance. Please make your appointment according to the below directions.
- ✧ Interpretation service and introduction of interpreters are not provided. Please contact us through a good speaker of Japanese and come to the clinic with an interpreter.
- ✧ Cancer vaccine therapy is unapproved, thus, provided as a clinical study. The aim of the study is an evaluation and assessment of clinical effects and adverse events of the vaccine. There are several requirements to enroll the study. Please see the below description.
- ✧ You are responsible for all the cost of the vaccine therapy.

Please read the following description to understand the cancer vaccine therapy.

I. What is immunity?

Immune system discriminates self (your cells) and non-self (such as pathogens) and eliminates non-self from your body. Cancer cells are unregulated growing cells originated from normal cells with several gene damages. Immune system recognizes altered parts of cancer cells.

Some cellular components of immune system, such as macrophages, natural killer (NK) cells, NKT cells, helper T-cells, and cytotoxic T-lymphocytes (CTL, also called killer T-cells), recognize cancer cells and contribute to cancer cell exclusion. The CTLs are the most evolved and specialized type for such function because only CTLs can both learn about target cells (immunological memory) and directly destroy cancer cells. If altered or different parts of cancer cells from normal cells, also called cancer antigens, are administered as cancer vaccine, it activates the CTLs recognizing cancer cells, inducing more powerful anti-cancer effects.

II. What is immunotherapy?

"Cancer immunotherapy" fights against cancer through enhancing your immunity to the cancer cells. The above cells together with dendritic cells and B cells contribute immune system and cancer immunotherapy activates some of them. There are two types of cancer immunotherapy, antigen-specific and –nonspecific therapies. Nonspecific immunotherapy includes "cell therapy" in which patient's lymphocytes are activated ex vivo and back to the patient through infusion. Our vaccine therapy use peptides, fragments of protein, as antigens to expand and activate CTLs in patients. These CTLs are expected to suppress tumor growth, expansion, and/or recurrence, therefor belong to antigen-specific immunotherapy.

III. Peptide vaccine for cancer.

Our vaccine components are synthetic peptides (9 to 10 amino acids in length). Aim of the vaccine therapy is suppression of tumor growth, expansion, and/or recurrence through activation of patient's immunity against cancer cells by the injection of peptide vaccine. Vaccine-activated CTLs recognize cancer antigens expressed on the cancer cells and destroy the cancer cells, but not normal cells. Therefore, the vaccine therapy is

safer than other anti-cancer therapies with low adverse effects (side effects). Vaccine peptides are optimized for each patient, thus, our vaccine therapy is a personalized medicine.

1. Clinical effects: Clinical studies of the peptide vaccines for lung cancer, colorectal cancer, and gynecologic cancer were started since 1999. Subsequently, clinical studies of the personalized peptide vaccines for prostate cancer, gastric cancer, pancreatic cancer, liver cancer, malignant brain tumor, and the other cancers were started since 2001. Peptide-specific immunity was increased in more than half (66%) of patients in these clinical studies, however, decrease of tumor-mass, frequently observed in chemotherapy, was not observed in the majority (90%) of patients. The studies also indicated that life span of the patients with immune responder group was longer than non-responder group.

Our studies indicate that complete regression of tumor mass, as well as partial regression to the same extent in patients with standard cancer therapies, are not expected in the most patients treated with our vaccine. Therefore, our vaccine therapy is not alternative to standard chemotherapy and/or radiation therapy. Although, our vaccine therapy is a promising new modality for cancer treatment, since prolongation of life span is expected; the vaccine treatment is done in the outpatient clinic; it does not change the quality of life (QOL) due to rare severe side effects.

2. Possible adverse effects (side effects)

Vaccine-related adverse events observed in 500 cases are shown below.

Mild events	Frequency (%)
Inflammation at injection site (e.g., warmth, erythema, itching)	70
Fever	4.4
Herpes zoster	1.9
Urticaria	0.6
Lymphedema	0.3
Worsening of asthma, wheezing	0.3

Severe events	Frequency (%)
Herpes zoster	1.0
Inflammation surrounding tumor, rectal bleeding and bladder-vaginal fistula in patient with cervical cancer)	0.3
Colitis, rectal bleeding	0.3
Anaphylaxis like syndrome	0.3

IV. Patient's eligibility for the study enrollment

Please talk with your doctor regarding the eligibility. 9)-11) will be examined by our clinic.

Criteria:

1）Patients must be diagnosed as cancer.

2）Patients can lead a daily life without help and have no problem for traveling.

3）Patients must be more 18 year-old

4）Patients can provide written consent. If patient cannot provide written consent according to his/her neural disorder, legally authorized representative can provide the written consent. If patients are under age of 20 year-old, legally authorized representative can provide the written consent.

5）Patients must have adequate hematologic, renal, hepatic, cardiac, and respiratory functions.

6）Patients do not have a history of severe allergic reactions.

7）Patients without pregnancy or nursing. Patients not desiring future fertility (for female). Patients must accept contraception from the 1st vaccination until 70 days after the last vaccination (for male).

8）Patients do not have a history of inoculation of peptide(s) same as any component of our vaccine.

9）Patient's laboratory data must satisfy the followings:

WBC is more than 2,500/mm^3
Lymphocyte is more than 900/mm^3
Hb is more than 8.0g/dL
Platelet is more than 80,000/mm^3 (>50,000/mm^3 for liver cancer)
Serum Creatinine is less than 2x upper limit of normal (ULN)
Total bilirubin is less than 2x ULN

10） Patients have a positive status for HLA-A2, -A3, -A11, -A24, -A26, -A31, or -A33.

11） Patients showed positive IgG responses to at least 2 of the HLA-class I-matched vaccine candidate peptides.

12） Patients can pay all the cost of the vaccine therapy.

13） Patients whose doctor agrees cancer vaccine treatment.

Our doctor will concern and decide your eligibility for the study enrollment after you visit our outpatient clinic and all laboratory data coming. Please accept our doctor's decision, whether you can or cannot participate in our study.

V. The schedule of the clinical study

■ One cycle/course

day 0	1st visit	Doctor explains the study and performs a medical examination. After receiving your consent, we take your blood for lab tests. Vaccine treatment does not start yet.
day 7	Notification of the enrollment to the study	We contact you or your representative (good speaker of Japanese) by phone or-e-mail whether you can participate in the study or not.
Any one day during day 14-28	2nd visit 1st vaccination	Two to four vaccine preparations, depends on lab test results, are subcutaneously inject at outpatient clinic. Each preparation inject to two sites.
28 days after the 1st vaccination.	3rd visit 2nd vaccination	We check the adverse effects of prier vaccination. The 2nd vaccination is performed if you have no problems.
28 days after the 2nd vaccination	4th visit 3rd vaccination	We check the adverse effects of prier vaccination and continue the study if you have no problems.
28 days after the 3rd vaccination	5th visit 4th vaccination	We check the adverse effects of prier vaccination and continue the study if you have no problems. We take your blood for lab tests to evaluate the immunological effects.
7 days after the 4th vaccination	Explanation of the effects after one cycle	We contact you or your representative to explain the results of lab tests and ask you make a decision to continue the study or not when you are able to do so. Please discuss the further vaccination schedule with our doctor.

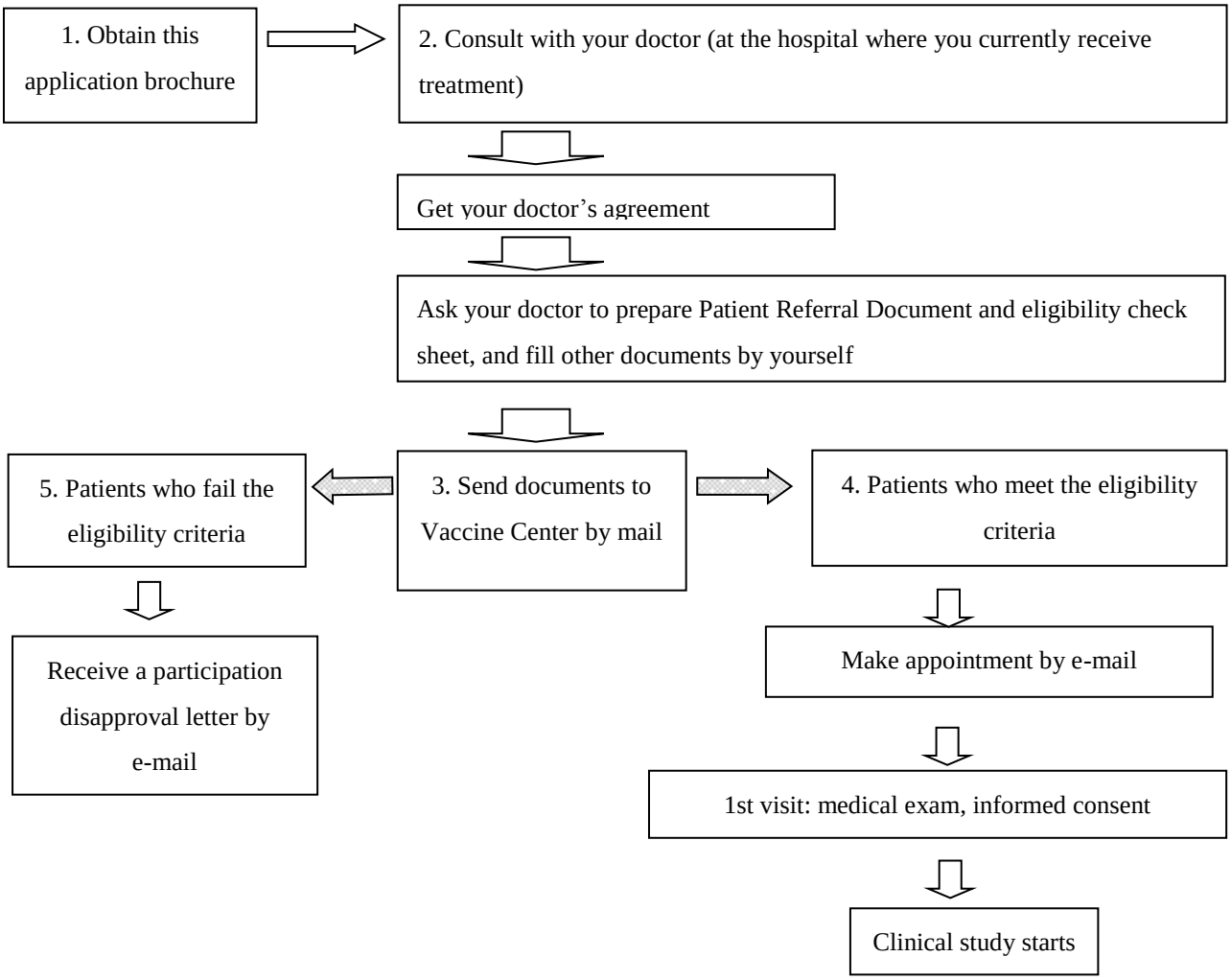
VI. Medical cost

(1) 1 cycle: about 900,000 Japanese Yen (including first medical examination, 4 doses of vaccination, and lab tests)

(2) Following credit cards are accepted for the payment.

MUFG CARD, DC, UFJ CARD, VISA, JCB, NICOS, MASTER CARD, AMEX, DINERS CLUB

VII. Outline for making appointment



(1) Obtain the application brochure

This brochure contains the following documents.

① Information for outpatients from foreign countries, pages 1-7

② Application form of out-patient's consultation for cancer vaccine, page 8

③ 「Letter to his/her attending doctor」 pages 9-11

④ 「Eligibility check sheet」 page 12-13

(2) Consult with your attending doctor

Please hand the documents ③ and ④ to your doctor.

With your doctor's agreement, you obtain the following documents form your doctor: Patient Referral Document, eligibility check sheet, lab test report, and send these documents to Kurume University Vaccine Center by mail. Caution: Do not open the documents from your doctor if the documents are sealed.

(3) Send documents

We would like you to check the documents in the envelope to see if everything is fine before sending them.

We manage the documents with an appointment number in order of arrival.

Our doctor evaluates your documents for eligibility criteria.

(4) Necessary documents to be enclosed

① Application form for participant of cancer vaccine study (page 8)

Please fill inside the bold line of the application form.

② Patient Referral Document from your doctor

③ Eligibility check sheet (page 12-13) filled by your doctor

④ Other documents, such as detailed blood examination report

(5) Patients who meet the eligibility criteria

We contact you about an appointment for the first visit/first consultation day.

(6) Patients who fail to meet the eligibility criteria

We e-mail you the report describing the reason(s) of participation disapproval.

We appreciate your understanding that we do not return the documents you send.

VIII. Guide of the first consultation day

(1) Procedures for the first consultation

Hospital: Kurume University Medical Center/Kurume University Cancer Vaccine Center

*The center is differently located from Kurume University Hospital (at Asahi-machi)

Address: 155-1 Kokubu-machi, Kurume, Fukuoka 839-0863 Japan

Please see other materials for the access methods.

At the first-time patient reception desk (general reception desk ⑥), you mention your visit to the cancer vaccine department and show your Passport.

※Please bring your Passport required for identity verification and the registration.

※We inform you the flow of the first consultation day in detail in advance.

After you finish registration, please come to the waiting room of the cancer vaccine center.

(2) Medical examination and blood sampling

Doctor explains peptide vaccine therapy and confirms your consent for the clinical study participation.

We carry out lab tests to confirm that you meet the participation criteria.

You are asked to stay for 1-1.5 hr after seeing a doctor until the results of some tests come out.

We inform you of the results of the HLA-typing and immunological tests one week or so after your first visit.

∗ You might need to wait longer than you had expected before seeing a doctor. Therefore, please plan your visiting schedule capable of managing such a case.

IX. Closing remarks – toward drug approval

I would appreciate you reading throughout this brochure to understand personalized peptide vaccines and clinical trials. All staffs spend their days and nights in the effort for the drug approval of this cancer vaccine as soon as possible. We started aforementioned clinical study helpful to obtain the drug approval of cancer vaccines. We are, however, most regrettable that not all patients who hope for the cancer vaccine are able to enroll the study and to receive the cancer vaccine therapy. Therefore, we make further efforts to achieve our goal – drug approval of the cancer vaccine available to everyone soon. We would appreciate your understanding of the current situation for the cancer vaccine.

Kyogo Itoh MD, PhD

The director of Kurume University Cancer Vaccine Center

Application form for participant of cancer vaccine study

Please describe the type of the cancer (example: prostate cancer, breast cancer)

Type of cancer

Please fill only inside the bold line

Name	**Gender** Male, Female	**Date of birth** (mm/dd/yyyy), **age** / / ,
Information of a contact person, who can communicate in Japanese **Name:** **Address:** **E-mail Address:** **Telephone (daytime)**		
Documents from your attending doctor ※Eligibility check sheet, Patient Referral Document, lab test report **Please check either box □enclosed □sent separately**		

The following contents only for our staff.

受付日 ／ ／	事務局受付番号	がん種	
診療科	主治医	備考	
書類の受理 □受診申込書 □適格基準チェックシート □診療情報提供書 □返信用封筒 □血液検査詳細情報 □その他添付資料 （ ）検査報告書 枚、他 枚		確認日 ／	確認者
適格基準 （ 可 ・ 不可 ）	確認日 ／	確認者	
返信 （ 未 ・ 済 ）	確認日 ／	確認者	
予約 （ 未 ・ 済 ）	確認日 ／	確認者	
予約日 ／ （ ） : ・本登録	初診場所確認 （ 未・済 ） ・久留米大学医療センター	備考	

Dear his/her attending doctor,

We are writing to introduce our studies of "the personalized peptide vaccines for advanced cancer patients". Although your patient is interested in the currently conducting phase II clinical trial (treatment not covered by health insurance) at Kurume University (Japan), there are some inclusion criteria as well as exclusion criteria to enroll in this study. Therefore, on behalf of your patient, we would appreciate if you could fill the form of eligibility check sheet, and mail it to us or hand it over to your patient together with Patient Referral Document.

1. Personalized peptide vaccines for advanced cancers

Personalized peptide vaccine is one of specific immunotherapies, which induce tumor-specific cytotoxic T-lymphocytes (CTLs) by subcutaneous injection of synthetic antigen peptides (9 to 10 amino acids in length). These peptides are similar to the peptides bound to the human leukocyte antigen (HLA) on the surface of cancer cells. Vaccine-activated CTLs recognize cancer antigens expressed on the cancer cells and destroy the cancer cells, but not normal cells. Therefore, the vaccine therapy is safer than other anti-cancer therapies with low adverse effects (side effects). Vaccine peptides are optimized for each patient, thus, our vaccine therapy is a kind of personalized medicine. The vaccine peptides are selected and administered from a panel of 31 candidate peptides based on the HLA-types and pre-vaccination IgG levels to each peptide.

2. Clinical outcome of personalized peptide vaccines

Most common adverse event is mild inflammation at injection site (e.g., warmth, erythema, itching) and severe adverse events were rarely observed. Vaccine-related mild adverse events are as follows: inflammation at injection site (70%), fever (4.4%), herpes zoster (1.9%), urticaria (0.6%), lymphedema (0.3%), worsening of asthma, wheezing (o.3%). Vaccine-related severe adverse events are as follows: herpes zoster (1%), inflammation surrounding tumor e.g., rectal bleeding and bladder-vaginal fistula in patient with cervical cancer (0.3%), colitis and rectal bleeding (0.3%), anaphylaxis like syndrome (0.3%).

Peptide-specific immunity was increased in more than half (66%) of patients in the previous clinical studies, however, decrease of tumor-mass, frequently observed in chemotherapy, was not observed in the majority (90%) of patients. The studies also indicated that life span of the patients with immune responder group was longer than non-responder group. Our studies indicates that complete regression of tumor mass, as well as partial regression to the same extent in patients with standard cancer therapies, are not expected in the most patients treated with our vaccine. Therefore, our

vaccine therapy is not alternative to standard chemotherapy and/or radiation therapy. Although, our vaccine therapy is a promising new modality for cancer treatment, since prolongation of life span is expected; the vaccine treatment is done in the outpatient clinic; it does not change the quality of life (QOL) due to rare severe side effects.

We recommend a personalized peptide vaccine combined with usual chemotherapy or radiation therapy since this immunotherapy alone has limited clinical benefits. Therefore, even if your patient enrolls in this clinical trial, you don't need to stop treating your patient, but we might ask you the cooperation to suspend your treatment temporarily for some types of tumors.

3. Types and stages of tumors for this phase II clinical trial

We don't limit the types and stages of tumors for this trial, but might stop accepting application temporarily when participants reach the planned number.

4. Application for personalized peptide vaccine clinical trial

As mentioned above, since there are some inclusion and exclusion criteria to enroll in this trial, we would like you to fill the eligibility check sheet of qualification, and mail it to us or hand it over to your patient, enclosed together with a report of medical certificate and history as well as the latest complete blood test result.

Medical certificate and history report need to include the followings:

1. Diagnosis
2. Stages of disease
3. Diagnosed Date
4. Treatment history since diagnosed
5. Current treatment

The above is the summary of our personalized peptide vaccine and its clinical trial.
We would appreciate your understanding and support to cure your patient.

Sincerely yours,

Kyogo Itoh, M.D., Ph.D.
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Eligibility Check Sheet

Patient's name: _____ Date: (MM/DD/YYYY) ___/___/____

Doctor's name: _____

Hospital/Institution: _____

＊Please check "YES" or "NO" for the following questions about the patient's medical condition.

1	Has the patient been diagnosed as cancer/malignant tumor? Type of cancer (e.g., colon cancer, non-small cell lung cancer) [ ]	□YES □NO
2	What is your patient's ECOG performance status and does he belong to the criteria "PS:0"? PS: 0 – Fully active, able to carry on all pre-disease performance without restriction. PS: 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. PS: 2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. PS: 3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. PS: 4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	□YES □NO PS [ ]
3	Does the patient meet the following requirements? Please provide all requested data. It is critical in order to qualify the patient. If this form is not complete, the patient may not participate our clinical study. ① WBC ≥ 2,500/mm^3 ② Lymphocytes ≥ 900/mm^3 ③ Hemoglobin ≥ 8.0g/dL ④ Platelet ≥ 80,000/mm^3 ⑤ Creatinine ≤ 2 times of upper standard level in your hospital/institution ⑥ Total Bilirubin ≤ 2 times of upper standard level in your hospital/institution	□YES □NO Please fill in the patient's most recent blood data from the past month. WBC ( ) Lymphocyte( ) Hb ( ) Plt ( ) Creatinine ( ) Total-Bilirubin( )
4	Is the patient 18 years or older?	□YES □NO
5	Does the patient have a life expectancy of at least 12 weeks?	□YES □NO
6	Does the patient have a history of severe allergic symptom(s)?	□YES □NO
7	Is the patient pregnant, nursing, or desiring future fertility? (for female) Does the patient accept contraception from the 1st vaccination until 70 days after the last vaccination? (for male)	□YES □NO The patient is □ male □ female
8	Does the patient exhibit the following severe diseases?	□YES □NO

	<Examples> Active severe infection, cardiovascular disorder, respiratory disorder, kidney disorder, immune-deficient diseases, blood-coagulation disorder.	
9	Can you provide us the medical information such as X-ray image, progress, and medical history for the patient when he/she is qualified to enroll this trial?	□YES □NO