	Phase II Trial of the Effects of Interferon Alfa-2b on the Immunogenicity of a Polyvalent Melanoma Antigen Vaccine in Patients With Stage III Malignant Melanoma Detailed Description: OBJECTIVES: I. Determine the effect of interferon alfa-2b on the potentiation of antimelanoma antibodies and cellular immune responses induced by immunization to a polyvalent melanoma vaccine and interleukin-2 in patients with stage III malignant melanoma. II. Determine the optimal dose of interferon that will maximally stimulate these responses in these patients. III. Determine the toxicity of this regimen in these patients. OUTLINE: This is a randomized study. Patients are randomized into a vaccine treated control arm or to receive one of two doses of interferon alfa-2b plus vaccine. All patients receive polyvalent melanoma vaccine incorporated into interleukin-2 liposomes. The vaccine is administered intradermally every 2 weeks for 8 weeks, monthly for 3 months, and then every 3 months for a total of 2 years or until disease progression. Patients assigned to arms II or III also receive interferon alfa-2b subcutaneously, at one of two doses, three times a week for 2 years. Patients are followed for survival. PROJECTED ACCRUAL: A total of 32 patients will be accrued for this study within 18 months. Histologically proven, surgically resected stage III melanoma Clinically positive nodes AND/OR At least 2 histologically positive nodes**HLA-A2, A3, A11, or A26** positive Intact cellular immunity as evidenced by at least 5 mm reaction at 48 hours to at least 1 of the following recall antigens: PPD Mumps Candida Streptokinase streptodornase OR able to be sensitized to dinitrochlorobenzene
Completed	Vaccine Therapy in Treating Patients With Metastatic Melanoma of the Eye Conditions: Extraocular Extension Melanoma; Recurrent Intraocular Melanoma 2007 Drug: gp100 antigen; Drug: interleukin-2; Drug: MART-1 antigen; Drug: Montanide ISA-51
	Phase II Study of gp100:209-217 (210M) Antigen and MART-1:26-35 (27L) Antigen Emulsified in Montanide ISA-51 in Patients With Metastatic Ocular Melanoma Detailed Description: OBJECTIVES: I. Determine the clinical response in patients with metastatic ocular melanoma treated with gp100:209-217 (210M) antigen and MART-1:26-35 (27L) antigen emulsified in Montanide ISA-51. II. Determine the clinical benefit of interleukin-2 in combination with this vaccine in these patients. PROTOCOL OUTLINE: Patients receive vaccine subcutaneously once weekly. Treatment repeats every 4 weeks for a total of 6 courses in the absence of disease progression or unacceptable toxicity. Patients with progressive disease may receive vaccine SC on day 1 followed by interleukin-2 IV over 15 minutes every 8 hours for a maximum of 12 doses. Treatment repeats every 3 weeks for at least 4 courses in the absence of disease progression or unacceptable toxicity. PROJECTED ACCRUAL: A total of 15-25 patients will be accrued for this study within 1 year. Diagnosis of metastatic ocular melanoma Progressive disease Measurable disease HLA-A*201 positive --Prior/Concurrent Therapy-- Biologic therapy: At least 3 weeks since prior biologic therapy Chemotherapy: At least 3 weeks since prior chemotherapy Endocrine therapy: At least 3 weeks since prior endocrine therapy No concurrent steroid therapy Radiotherapy: At least 3 weeks since prior radiotherapy Surgery
Completed	Fludarabine Followed by Vaccine Therapy and White Blood Cell Infusions in Treating Patients With Unresectable or Metastatic Condition: Melanoma (Skin) 2004-2010 Interventions: Biological: gp100 antigen; Biological: incomplete Freund's adjuvant; Biological: keyhole limpet hemocyanin; Drug: fludarabine phosphate; Procedure: peripheral blood stem cell transplantation

	A Pilot Trial of Therapeutic Vaccination With a Modified gp100 Melanoma Peptide (gp100:209-217(210M)), Montanide ISA 51, and KLH With Reconstitution After Chemotherapy to Induce Lymphopenia in Patients With Metastatic Melanoma **Primary** 1) Toxicity by clinical and laboratory observation at 1 month. 2) Antigen-specific T-cell responses by tetramer analysis, ELISPOT, and cytokine flow cytometry periodically **Secondary**: 1) Compare 2 different dosing schedules of fludarabine in terms of lymphocyte recovery using a complete blood count periodically 2) Tumor regression by standard imaging at study completion **Primary 1)** etermine the toxicity and immune effects of vaccination comprising modified gp100 peptide (gp100:209-217[210M]), Montanide ISA-51, and keyhole limpet hemocyanin followed by peripheral blood mononuclear cell reinfusion after treatment-induced lymphopenia with fludarabine in patients with unresectable or metastatic melanoma. 2) Determine the induction of antigen-specific T-cell responses in patients treated with this regimen. 3) Determine the kinetics and duration of immune response in patients treated with this regimen. 4) Compare the immunologic effects of this regimen in these patients with historical results. **Secondary 1)** ompare 2 different dosing schedules of fludarabine, in terms of induction of lymphopenia and granulocytopenia and on the induction of a specific immune response to this vaccine, in these patients. **OUTLINE:** This is a pilot, randomized study. Patients are randomized to 1 of 2 treatment arms. Within 2 weeks before the start of fludarabine, all patients undergo leukapheresis over 4-6 hours for the collection of peripheral blood mononuclear cells (PBMCs). •**Arm I:** Patients receive fludarabine IV over 30 minutes on days 1-5. •**Arm II:** Patients receive fludarabine as in arm I on days 1, 3, and 5. In both arms, patients receive autologous PBMCs IV over approximately 30 minutes on day 8 and vaccination comprising gp100:209-217(210M) peptide, Montanide ISA-51, and keyhole limpet hemocyanin subcutaneously on days 8, 22, 36, 50, and 64. Patients with stable or responding disease continue to receive vaccination on day 78 and then every 28-31 days for up to 1 year. Patients are followed every 3 months. PROJECTED ACCRUAL: A total of 20 patients (10 per treatment arm) will be accrued for this study within 2 years.	
Completed	Vaccine Therapy With or Without Interleukin-2 in Treating Patients With Metastatic Melanoma Conditions: Stage IV Melanoma; Recurrent Melanoma 2007 Interventions: Drug: gp100 antigen; Drug: interleukin-2	gene therapy
	Phase II Study of DNA Encoding the gp100 Antigen Alone or in Combination With Interleukin-2 in Patients With Recurrent Metastatic Melanoma	
Completed	Vaccine Therapy in Treating Patients With Metastatic Melanoma Who Are Undergoing Surgery for Lymph Node and Tumor Condition: Melanoma (Skin) 1999-2011 Interventions: Biological: aldesleukin; Biological: gp100 antigen; Biological: tyrosinase peptide	

	A Phase I-II Trial of Antigen-Pulsed Autologous Dendritic Cells for Induction of Anti-Tumor Immunity in Patients Completing Lymphadenectomy for Metastatic Melanoma OBJECTIVES: I. Determine the safety and toxicity of intravenous injections of autologous cultured dendritic cells pulsed with either gp100 and tyrosinase peptides or autologous melanoma tumor cell lysates in patients with metastatic melanoma. II. Determine whether treatment with melanoma tumor antigen pulsed autologous dendritic cells results in increased in vitro tumor specific cytotoxic T-cell responses. III. Determine whether this treatment can induce positive skin test responses to tumor antigens. IV. Evaluate the disease free and overall survival of these patients. OUTLINE: This is a randomized, dose escalation study. Approximately 1-2 weeks following surgical lymphadenectomy, patients undergo leukapheresis to collect dendritic cells and are then divided into 3 groups. Group A consists of patients without adequate tumor for preparation of tumor lysate and who have tumors that express tyrosinase or gp100 with types HLA-A1, A2, or A3. Group B consists of the patients who have adequate tumor for lysate preparation but who do not type for HLA-A1, A2, or A3 (required for the peptide pulsed protocol). Group C are the patients with adequate tumor who are eligible for the peptide pulsed protocol. Group A patients receive autologous dendritic cells pulsed with appropriate peptide antigens. Group B patients are treated with autologous dendritic cells pulsed with autologous tumor cell lysates. Group C patients are randomized to receive dendritic cells pulsed with either peptide antigens or tumor lysate. All patients are administered intravenous active immunotherapy for 4 monthly intervals. The dose of the immunizations is escalated for each cohort of three patients that is accrued in each of the groups mentioned above. Each immunization at each dose level is followed by three days of interleukin-2 administered subcutaneously twice daily. Patients are followed at least 5 years for survival. PROJECTED ACCRUAL: There will be 100 patients accrued in this study over 2 years. There will be 50, 20, and 30 patients in groups A, B, and C, respectively. Histologically confirmed metastatic melanoma involving cervical, axillary, inguinal, groin, or iliac lymph nodes All gross disease is resected at the time of surgical lymphadenectomy No distant metastases
Recruiting	Vaccine Therapy With or Without Cyclophosphamide in Treating Patients With Recurrent or Refractory Multiple Myeloma Condition: Multiple Myeloma and Plasma Cell Neoplasm 2007-2012 Interventions: Biological: oncolytic measles virus encoding thyroidal sodium iodide symporter; Drug: cyclophosphamide; Genetic: reverse transcriptase-polymerase chain reaction; Other: flow cytometry; Other: immunologic technique; Other: laboratory biomarker analysis; Procedure: biopsy

	Phase I Trial of Systemic Administration of Edmonston Strain of Measles Virus, Genetically Engineered to Express NIS, With or Without Cyclophosphamide, in Patients With Recurrent or Refractory Multiple Myeloma **Primary: 1)** Toxicity. 2) Maximum tolerated dose [Designated as safety issue: Yes] **Secondary**: 1) Hematologic response (complete response, very good partial response, minimal response). 2) Viral replication and shedding. 3) Biodistribution and kinetics of viral spread and NIS gene expression. 4)Tolerability [Designated as safety issue: Yes] **Biological: MV-NIS** Dose escalation theme. Start at 10^7 TCID50 increase by a factor of 3 to a final dose of 81x10^7 TCID50. Other Name: oncolytic measles virus encoding thyroidal sodium iodide symporter. Other: I-123 prior MV-NIS 5 mCi Oral Any time pre-MV-NIS (for baseline I-123 scan) Other: I-123 post MV-NIS 5 mCi Oral at Days 3, 8, and 15 (two additional doses may be given for imaging based on imaging results) Other Name: 5 mCi Oral at Days 3, 8, and 15 (two additional doses may be given for imaging based on imaging results) Drug: Liothyronine 0.025 mg - 1 oral tablet three times daily. Starting 4 days prior to MV-NIS administration through day of last 123I scan (no longer than Day 29) Other Name: Cytomel **Biological: MV-NIS** **D**ose escalation theme. Start at 10^7 TCID50 increase by a factor of 3 to a final dose of 81x10^7 TCID50. Other Name: oncolytic measles virus encoding thyroidal sodium iodide symporter Drug: cyclophosphamide 10mg/kg Other: I-123 prior MV-NIS 5 mCi Oral Any time pre-MV-NIS (for baseline I-123 scan) Other: I-123 post MV-NIS 5 mCi Oral at Days 3, 8, and 15 (two additional doses may be given for imaging based on imaging results) Other Name: 5 mCi Oral at Days 3, 8, and 15 (two additional doses may be given for imaging based on imaging results) Drug: Liothyronine 0.025 mg - 1 oral tablet three times daily. Starting 4 days prior to MV-NIS administration through day of last 123I scan (no longer than Day 29) ther Name: Cytomel

	Primary: •Determine the safety and toxicity of Edmonston vaccine strain oncolytic measles virus encoding thyroidal sodium iodide symporter (MV-NIS) when administered with or without cyclophosphamide in patients with relapsed or refractory multiple myeloma. •Determine the maximum tolerated dose of MV-NIS when administered with or without cyclophosphamide in these patients. **Secondary:** •Determine the time course of viral gene expression and viral elimination, and the biodistribution of virally infected cells at various time points after treatment with these regimens using iodine I 123 gamma camera imaging. •Assess viral replication, viremia, viral shedding in urine and respiratory secretions, and viral persistence after treatment with these regimens. •Monitor humoral responses to MV-NIS in these patients. •Explore the antimyeloma efficacy (i.e., clinical response rate, time to progression, progression-free survival, duration of response) of the virus using standard myeloma response criteria as well as immunoglobulin free light chain measurements. OUTLINE: This is a dose-escalation study of oncolytic measles virus encoding thyroidal sodium iodide symporter (MV-NIS). Patients are stratified according to receipt of cyclophosphamide during study treatment (yes vs no). Patients are initially accrued to part 1. Once the maximum tolerated dose (MTD) of MV-NIS alone is determined, subsequent patients are accrued to part 2. •Part 1 (MV-NIS alone : Patients receive MV-NIS IV over 30 minutes on day 1. Cohorts of 3-6 patients receive escalating doses of MV-NIS until the MTD is determined. The MTD is defined as the dose preceding that at which 2 of 6 patients experience dose-limiting toxicity. •Part 2 (MV-NIS and cyclophosphamide): Patients receive cyclophosphamide IV over 30 minutes on day -1 and MV-NIS IV over 30 minutes on day 1. Cohorts of 3-6 patients receive escalating doses of MV-NIS* in combination with cyclophosphamide until the MTD is determined. The MTD of MV-NIS is defined as in part 1. NOTE: *Starting dose of MV-NIS is the MTD determined in part 1. Blood and bone marrow samples are obtained for research studies, including flow cytometry, at baseline and at week 6. Serial measurements of viral RNA in mononuclear cells are conducted in samples of blood, saliva, and urine on days 3, 8, and 15 and are tested for viral replication by quantitative reverse transcriptase-polymerase chain reaction. Measles virus-specific immunity is evaluated at baseline and on day 42. After the completion of study treatment, patients are followed periodically for 1 year.PROJECTED CCRUAL: A total of 54 patients will be accrued for this study.
Recruiting	Safety Study of Cancer Specific Epitope Peptides Cocktail and Cyclophosphamide for Advanced or Relapsed Solid Tumors Condition: Metastatic Solid Tumors 2008 九大 Intervention: Biological: 5 peptide vaccines of KOC1, TTK, CO16, DEPDC1, MPHOSPH1

	Phase I Study of Tumor Specific Potentiated Vaccine Therapy Using Cyclophosphamide Combined Epitope Peptide Cocktail for Progressive/Relapsed Solid Tumors(GI/Lung/Cervical Cancer) **Primary:** •safety of the cyclophosphamide combined tumor specific epitope peptide cocktail [Time Frame: 2 years] [Designated as safety issue: Yes] **Secondary**: •immunological efficacies and clinical efficacies of the cyclophosphamide combined tumor specific epitope peptides cocktail [Time Frame: 2.5 years] [KOC1, TTK, CO16(URLC10), DEPDC1, MPHOSPH1 have been identified using genome-wide expression profile analysis by the use of cDNA microarray in the previous studies. The investigators have determined the HLA-A*2402 restricted epitope peptides respectively derived from KOC1, TTK, CO16(URLC10), DEPDC1, and MPHOSPH1 showed strong INF-gamma production when stimulated with the appropriate targets expressing the appropriate protein and HLA-A*2402. Furthermore, when vaccinated these peptides, specific CTLs were determined after the vaccination. Therefore the investigators focused on the prevention of further expansion of the solid tumors highly expressing these 5 proteins using these 5 peptides.
Completed	Carcinoembryonic Antigen-loaded Dendritic Cells in Advanced Colorectal Cancer Patients Conditions: Colorectal Cancer; Liver Metastases 2005-2010 Intervention: Biological: CEA-loaded dendritic cell vaccine
	Dendritic cells (DCs) are the professional antigen-presenting cells of the immune system. As such they are currently used in clinical vaccination protocols in cancer patients. We evaluate the ability of mature DCs pulsed with carcinoembryonic antigen (CEA)-peptide (arm A) or electroporated with CEA-mRNA (arm B) to induce CEA-specific T cell responses in patients with resectable liver metastases from colorectal cancer. To evaluate immune responses, CEA-specific T cell reactivity is monitored in peripheral blood, resected abdominal lymph nodes, tumor tissue and biopsies of vaccination sites and post-treatment DTH skin tests. Patients are vaccinated intradermally and intravenously with CEA-peptide pulsed mature DCs three times prior to resection of liver metastases. In 2007 a side-study has been added (arm C), in which patients with stage III or high-risk stage II colorectal cancer that are amenable for standard adjuvant oxaliplatin/capecitabine therapy are vaccinated with CEApeptide-pulsed DCs. Also in this group, safety and immune responses in peripheral blood and the DTH-skin test are the primary endpoints. Results are compared with the results obtained in arm A. Biological: CEA-loaded dendritic cell vaccine: Carcinoembryonic antigen (either peptide or mRNA) loaded dendritic cells. Biological: CEA-loaded dendritic cell vaccine: Carcinoembryonic antigen (either peptide or mRNA) loaded dendritic cells. Biological: CEA-loaded dendritic cell vaccine: Carcinoembryonic antigen (either peptide or mRNA) loaded dendritic cells. Primary: •immunological response against carcinoembryonic antigen and the control protein KLH. •Toxicity
Completed	Evaluate the Immunogenicity & Safety of GSK Biologicals' HPV Vaccine in Female Subjects Aged 10-14 Years Conditions: Human Papillomavirus (HPV) Infection; Cervical Neoplasia Intervention: Biological: HPV-16/18 L1/AS04
Completed	Vaccine Therapy Plus GM-CSF in Treating Patients With Multiple Myeloma Undergoing Bone Marrow or Peripheral Stem Cell

Condition:	Multiple Myeloma and Plasma Cell Neoplasm
Interventions:	Biological: keyhole limpet hemocyanin; Biological: sargramostim

Phase I Trial of Post Transplant Immunization With Autologous Myeloma Idiotype-KLH/GM-CSF In Myeloma Patients Following Autologous or Allogeneic Marrow or Stem Cell Transplantation

Primary: •Toxicities graded using the National Cancer Institute (NCI) Common Toxicity Criteria [Time Frame: Up to 2 years]

Descriptive statistics will be used to summarize changes from baseline in clinical laboratory parameters for each cohort.

•Immune response [Up to 2 years] Descriptive statistics will be used to summarize changes from baseline in clinical laboratory parameters for each cohort.

PRIMARY OBJECTIVES:

I. To determine the safety of multiple subcutaneous vaccinations with myeloma Id-KLH (idiotype-keyhole limpet hemocyanin) with GM-CSF (sargramostim) in post allogeneic transplant myeloma patients, or with GM-CSF +/- interleukin (IL)-2 (aldesleukin) in post autologous transplant myeloma patients.

II. To evaluate patients pre and post bone marrow transplantation (BMT) for evidence of endogenous idiotype specific immune response.

III. To characterize the time course, specificity and persistence of antibody and T cell immune response to myeloma idiotype and to KLH induced by myeloma Ig (Id) immunization.

IV. To clone, expand and characterize T cells specific for the tumor idiotype. V. Monitor myeloma involvement in bone marrow and serum paraprotein level following vaccination.

VI. Use stored patient samples to clone, expand, and characterize T cells specific for myeloma antigens other than idiotype and identify the antigens they recognize so that they can be used in future studies.

OUTLINE: Patients receive autologous immunoglobulin idiotype-KLH conjugate vaccine combined with sargramostim subcutaneously (SC) in weeks 0, 2, 6, and 10 and sargramostim SC once daily (QD) for three days following each vaccine injection. Some patients also receive aldesleukin SC daily from weeks 2-14.

After completion of study treatment, patients are followed up every 3 months for 1 year and then every 6 months for 1 year.

資料２　案１

治療用がんワクチンの評価における考慮事項に関するガイドライン（案）

目次（2013.8.23 改訂案）

資料２　案１

治療用がんワクチンの臨床評価等における考慮事項に関するガイドライン（素案）

1.はじめに

本ガイドラインはがんワクチンの臨床試験の開始に当たっての留意点について考察したものである。また、がんワクチンはがん細胞に特異的に発現するがん抗原に対する特異的な免疫反応の誘導や増幅を目指したものであり、本文章では主としてがん抗原特異的ペプチド、ペプチドとキャリアータンパク質との融合タンパク質、及びがん抗原タンパク質等を対象としたがんワクチンの臨床開発における評価事項について言及する。

1.1 背景

活性化リンパ球療法、及び非特異的な免疫活性化療法といった、がんに対する免疫反応の亢進を利用したがん治療の試みは古くから行われていた。しかしながら、これらの非特異的な免疫の活性化による治療の試み法は多くの場合期待された効果は認められず、臨床開発が失敗に終わっている。一方で、ゲノム解析及びがん抗原タンパク質等の網羅的な解析により、がん細胞に特異的に発現するがん抗原の理解が急速に進んでおり、多くのモノクローナル抗体医薬品の開発に貢献している。抗腫瘍抗体医薬品に加え、がん抗原に対する患者の免疫反応を亢進させることによるがん治療の試みが行われている。このがん特異的な獲得免疫の誘導及び増幅を行う治療法として開発されている製品群は多岐にわたっており、がん抗原ペプチド、がん抗原タンパク質、及びがん抗原ペプチド(単鎖ペプチドと長鎖ペプチド)と免疫活性化能の高いタンパク質との融合製品等を始めとして、がん抗原処理した抗原提示細胞としての樹状細胞やがん抗原を導入した患者がん細胞等の細胞治療薬、がん抗原遺伝子を導入したウイルスベクターなどの遺伝子治療薬等が開発されつつある。また、がんに対する免疫の活性化を目的として、免疫賦活化作用のある顆粒球マクロファージコロニー刺激因子（GM-CSF）等のサイトカイン又はアジュバントとがんワクチンの併用投与も試みられている。

がんワクチンの開発にあたり、留意点として例えば以下のような点が挙げられる。

- 目的とするがん抗原が特定されている場合とされていない場合で、免疫応答性の評価方法が変わりうること
- 従来の細胞毒性型の抗悪性腫瘍薬の免疫抑制作用等を有する場合、がんワクチンの期待される作用と相反する臨床効果を持つ場合もあること
- 抗悪性腫瘍薬剤投与後に免疫抑制が惹起される可能性があること

1.2 がんワクチンの作用メカニズム

多くのがんワクチンで想定されている作用メカニズムは、患者の体内又は体外においてがん抗原等が抗原提示細胞に暴露することにより引き起こされる、生体免疫反応の誘導に依存している。すなわち、抗原提示細胞中でプロセッシングを受けたがん抗原が抗原提示細胞の細胞膜表面で抗原提示され、当該がん抗原に特異的なT細胞応答を誘導する、あるいは既に患者が持っている抗原特異的なT細胞応答性をペプチド等の刺激により増幅させるというものである。このT細胞応答には、がん抗原特異的な細胞傷害活性を持つ細胞傷害性T細胞の誘導及びがん抗原特異的な免疫反応の促進作用をもつヘルパーT細胞の誘導等が含まれる。特にがん細胞に対する傷害作用では、抗原特異的な細胞傷害性T細胞の増幅が薬効の発現に重要とされる。

がんワクチンは、抗原提示細胞を介して誘導されるがん抗原に対する応答性を誘導するものである。これらの抗原提示細胞はヒト白血球抗原（HLA）拘束性にT細胞へ抗原決定基を提示し、提示を受けた細胞傷害性T細胞は同じ抗原決定基を発現している腫瘍細胞を攻撃できるようになると考えられている。ヘルパーT細胞はがん抗原特異的な抗体産生能を持つB細胞応答を補助することもでき、B細胞が産生した抗体による腫瘍細胞死のメカニズムも想定されている。

抗原提示及びそのプロセッシング、リンパ球の活性化、腫瘍細胞死といった宿主免疫系による活性化されがん細胞を攻撃する臨床効果を発揮するまでには、従来の抗がん剤と比べ生体内でかなりの時間を要すると考えられている。したがって、がんワクチンの開発には従来のバイオ医薬品及び化学合成による抗悪性腫瘍薬とは異なり、遅発性の臨床効果を評価できるような試験計画を立案する必要があると考えられる。

1.3 適用範囲

本ガイドラインは治療用がんワクチンを対象とし、がんの予防に用いるワクチンや感染症を対象としたワクチンは対象としない。また、がん細胞を直接攻撃して治療効果を発揮するとされるT細胞やNK細胞を利用した適応免疫製剤についても対象外とする。

なお、上記以外の細胞医薬品や遺伝子治療用医薬品等のがんワクチンについては対象としないが、臨床評価等に当たっては適用できる部分もあると考えられるので、適時参照することが望ましい。

2. ペプチドやタンパク質からなるがんワクチンの品質