Randomized Phase II Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma (MPM) After Completion of Combined Modality Therapy
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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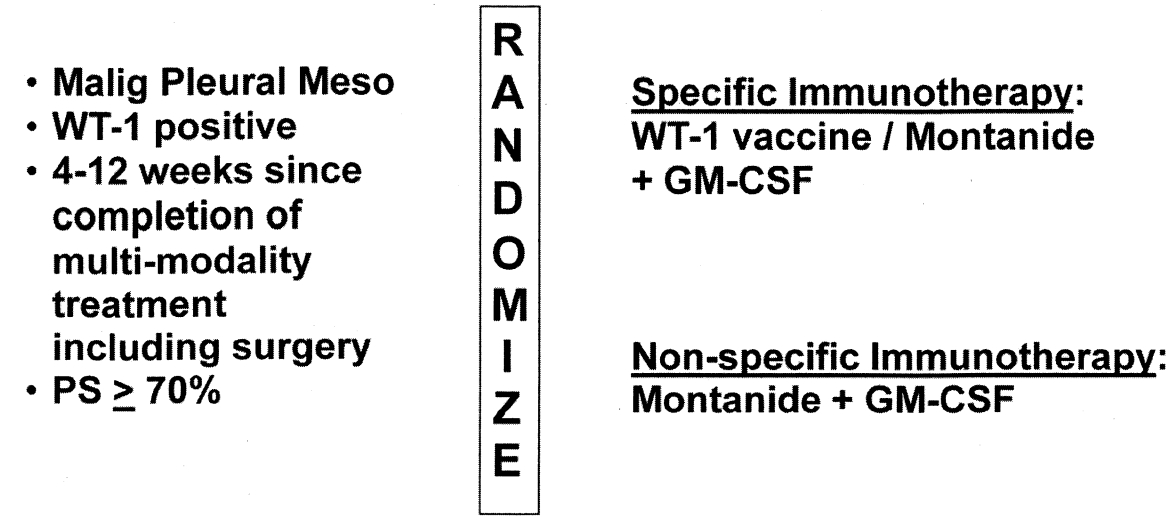
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a double-blinded, randomized trial comparing adjuvant treatment with the WT-1 analog peptide vaccine plus Montanide adjuvant + GM-CSF to treatment with Montanide + GM-CSF in patients with malignant pleural mesothelioma (MPM) who have completed combined modality therapy. Thirty-nine patients will be enrolled in each arm. The primary endpoint is the 1-year progression-free survival rate in each of the two arms.



Primary endpoint: 1-year PFS
Aim to increase from 50% to 70%
N=78 patients (39 per arm)

As specified in the statistical section in the protocol, an interim analysis took place to assess for futility. At the time of this analysis >=10 out of the first 20 patients had experienced progression within 1 year. As a result of these findings, enrollment to the control arm (GM-CSF + Montanide) was recommended to be closed, while enrollment to the study arm continues pending further follow up data. This amendment (6/2015) addresses this change in trial design.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To assess the 1-year progression free survival in patients treated with WT-1 analog peptide vaccine + GM-CSF or Montanide + GM-CSF after completion of combined modality therapy for MPM.

Secondary Objectives:

1) To confirm the immunogenicity of the WT-1 analog peptide vaccine in patients with MPM after completion of combined modality therapy.

2) To assess the utility of using the serum marker, soluble mesothelin related protein (SMRP), in monitoring patients with MPM for disease progression.

3) To assess the overall survival of patients treated with WT-1 analog peptide vaccine + GM-CSF or Montanide + GM-CSF after completion of combined modality therapy for MPM.

3.0 BACKGROUND AND RATIONALE

Malignant Pleural Mesothelioma (MPM) – There are between 2000 and 3000 new cases of MPM diagnosed annually in the United States. Its epidemiology has been linked to asbestos with a latency period of 25 years or more between exposure and disease onset, though only about two-thirds of patients report a clear history of asbestos exposure. MPM is notoriously difficult to treat. Only one chemotherapy regimen has been FDA approved for the treatment of mesothelioma (pemetrexed and cisplatin). This approval was based on the results of a phase III trial demonstrating that treatment with the combination of pemetrexed and cisplatin improved survival over treatment with cisplatin alone, but the benefit was small. The overall median survival improved from 9.3 months to 12.1 months (p=0.20) and the 1-year survival improved from 38% to 50%.[1]

For patients with early stage mesothelioma, surgical resection by pleurectomy/decortication or extrapleural pneumonectomy may be considered. Since the tumor essentially encases the entire lung and often invades the chest wall or mediastinum, even radical surgical resection typically leaves disease behind. For that reason, multimodality therapy is usually advised, adding radiation and chemotherapy to the treatment plan. In retrospective data series, multimodality therapy offers higher survival rates than surgery alone.[2] Treating the pleura with radiation offers a major challenge in delivering adequate doses without damaging the underlying lung. However, hemithoracic radiation after extrapleural pneumonectomy is safe and decreases the risk of local control.[3] Chemotherapy is used in an effort to decrease systemic relapse. In a multicenter study led by our institution, 77 patients received induction pemetrexed/cisplatin, and if no progression, extrapleural pneumonectomy, and hemithoracic radiation.[4] The overall median survival was only 17 months. For the 40 patients who completed all therapy, the median survival was a more promising 30 months. Nearly all patients recurred. Additional, less toxic therapies that could control residual disease after this aggressive treatment program are needed.

Wilms' tumor 1 (WT-1) – The Wilms' tumor suppressor gene, WT1, was first identified in childhood renal tumors, but WT1 is also highly expressed in multiple other hematologic malignancies and solid tumors, and, in particular, mesothelioma [5 6]. WT1 was originally identified by cDNA mapping to a region of chromosome 11p13. The WT1 cDNA encodes a protein containing four Kruppel zinc fingers and contains a complex pattern of alternative splicing resulting in four different transcription factors. Each WT1 isoform has different DNA binding and transcriptional activities [7], and can positively or negatively regulate various genes involved in cellular proliferation, differentiation, apoptosis, organ development and sex determination. WT1 is normally expressed in tissues of the mesodermal origin during embryogenesis including the kidney, gonads, heart, mesothelium and spleen [8]. In normal adult tissues, WT1 expression is limited to low levels in the nuclei of normal CD34+ hematopoietic stem cells, myoepithelial progenitor cells, renal podocytes and some cells in the testis and ovary [9]. WT1 is highly homologous in mice and humans (96% at the amino acid level) and has similar tissue distribution and function [10,11]. Although originally described as a tumor suppressor gene, the WT1 proteins appear to be involved in tumorigenesis.

The strong expression of WT-1 protein in mesothelioma makes it a rationale target for therapeutics. The expression is so high, that pathologists routinely use immunohistochemical stains for WT-1 to help distinguish epithelial mesothelioma from pulmonary adenocarcinoma. In three different pathology series, the rate of WT-1 nuclear staining ranged from 72% to 93% [12-14].

Development of a WT-1 peptide vaccine: Although WT-1 is a nuclear protein, it is processed and presented on the cell surface. For this reason, WT-1 is an attractive target for immunotherapy [5]. WT1 protein is a self-antigen, and, as a result, breaking tolerance is a potential problem for effective vaccination. One strategy to circumvent the poor immunogenicity of tumor-associated peptides at the surface of target cells is to design synthetic analogue peptides that will be more immunogenic. Such peptide analogues could generate an immune response that not only recognizes the immunizing epitopes, but also cross-reacts with the original native peptides; this is known as a heteroclitic response. By using computer prediction analysis, we designed a large number of synthetic peptides derived from WT-1 protein sequences in which single or double amino acid substitutions were introduced into the peptides at key HLA A0201 binding positions. Peptides predicted to bind with high affinity to HLA A0201 molecules were directly assayed for their ability to stabilize MHC class I A0201 molecules on the surface of TAP negative T2 cell line. The new peptides could stabilize MHC class I A0201 molecules better than native sequences. Avidly binding peptides were then assayed in an antigen specific T-cell expansion in vitro system for ability to elicit HLA restricted, peptide specific CTL responses using purified T cells from healthy donors. Two synthetic analogue peptides generated more effective immune responses than the native peptides. In addition, CD8+ T cells stimulated with the new synthetic peptides displayed heteroclitic features and cross-reacted with the native WT-1 peptides and also were able to mediate peptide specific cytotoxicity. Importantly, T cells stimulated with the new synthetic peptides cross-reacted with the native WT1 peptide sequence and were able to kill HLA matched CML blasts.[15]

Peptides capable of stimulating CD4+ response are necessary for inducing T-cell memory. WT1 analog peptides are capable of stimulating a peptide-specific CD4+ response that can recognize WT1+ tumor cells in multiple HLA-DRB1 settings. Using cross priming experiments, it was shown that WT1 peptide is presented on the surface of mesothelioma tumor cells and could be recognized by the T cells stimulated by the individual WT1DR peptides. Human T cells stimulated with the analog WT1A1 can kill WT1+ mesothelioma cell lines.[16]

In conclusion, analog heteroclitic WT1 peptides with increased immunogenicity can be synthesized and are potential vaccine candidates. To these peptides we have added 2 longer WT1 sequences that are capable of inducing CD4 responses in vitro. The 4 peptides with an immunological adjuvant constitute our vaccine.

The vaccine includes 3 peptides designed to stimulate common HLA-DR expressing cells in addition to 1 peptide for HLA-A0201 cells. Therefore, the relevant HLA alleles include HLA-DR B- 1, 4, 7, 11, and 15 (and possibly others), which together with A0201 should cover most patients. Assuming the peptides are immunogenic to one of these HLA types, immunologic responses should be seen in a large fraction of the cohort.

Immune Adjuvants: Montanide ISA 51 VG is an immune adjuvant that contains a natural metabolizable oil and a refined emulsifier similar to mannide monooleate. We have selected Montanide ISA 51 VG due to its established efficacy as an adjuvant and its lack of toxicity. It has proven safe and relatively nontoxic at the dose level proposed and highly effective at augmenting immunogenicity in several clinical trials of cancer vaccines [17,18]. Several melanoma vaccines containing various protein antigens plus Montanide induce cytotoxic T cells against target cells expressing these antigens, and some clinical responses were seen [17-19]. Side effects have been mild, and mainly characterized by grade 1-2 discomfort at the injection sites.

Recombinant Sargramostim (GM-CSF) is a human protein grown in a yeast (S. cerevisiae) vector. Sargramostim (GM-CSF) promotes clonal expansion and differentiation of hematopoietic progenitor cells, antigen presenting cells, and dendritic cells. Partially committed progenitor cells divide and differentiate in the granulocyte/macrophage pathway. In addition to having extensive clinical application in promoting granulocyte recovery after cytotoxic chemotherapy, Sargramostim (GM-CSF) has been found to promote activation of T cells and dendritic cells making it an attractive immune adjuvant. It has been used in conjunction with other adjuvants or alone in several clinical vaccine trials which demonstrated immune as well as clinical responses [17,18,20-22].

Pilot Trial with WT-1 Vaccine in Patients with Thoracic and Hematologic Malignancies: At MSKCC, we conducted a pilot trial to determine the immunogenicity and safety of vaccination with our WT1 heteroclitic peptides in humans (IRB 06-085).[23] As described above, in order to broaden the immune response in the setting of varied HLA subtypes, four different peptides were included in the vaccine. Peptides were suspended in Montanide adjuvant, and GM-CSF was administered at the injection site.

In one arm of the study, we enrolled primarily patients with mesothelioma. These patients had unresectable or relapsed disease and had received no more than one prior pemetrexed containing chemotherapy regimen. Patients with NSCLC, either stage III or IV after completion of initial treatment with surgery and/or chemotherapy and/or radiation therapy, were also eligible. Patients were required to have tumors that showed immunohistochemical staining for WT1 in greater than 10% of cells. At least 4 weeks must have elapsed between the patient's last chemotherapy or radiation treatment and the first vaccination. All HLA subtypes were eligible, though the HLA subtype was determined for the purposes of measuring immune response.

Therapy consisted of six vaccinations of the WT1 peptide (200 mcg per peptide, 800 mcg total combined with Montaninde to a total volume of 1.0 mL) administered weeks 0, 4, 6, 8, 10, and 12. All vaccinations were administered subcutaneously with vaccination sites rotating between extremities. Injection sites were pre-stimulated with Sargramostim (GM-CSF) (70mcg) injected subcutaneously on days -2 and 0. Patients who had a clinical, molecular, or immunologic response and did not have disease progression were able to continue with up to 6 more vaccinations administered approximately every month. Immune responses were measured by T-cell proliferative response and delayed type hypersensitivity (DTH) against WT-1 peptides. In patients with adequate samples, T-cell gamma interferon release as measured by ELISPOT was performed as well.

Nine patients with mesothelioma were enrolled, and 8 were evaluable for immune response. This included 5 patients who relapsed after multimodality therapy and 4 who had unresectable disease and were previously treated with chemotherapy. All had epithelioid histology. One patient had disease progression after just two injections and was not evaluable for immune response.

Three patients with NSCLC were enrolled all of whom had stage III disease treated with combined modality therapy. One patient withdrew consent after one vaccination, so two patients were evaluable for immune response.

This table summarizes the patient characteristics:

Patient #	Age	Gender	Dx	Histology	Stage	Prior rx	# vaccinations
1	62	M	MPM	Epithelioid	IV (Recurrence)	Chemo, EPP, RT	12
2	74	M	MPM	Epithelioid	IV (Recurrence)	Chemo, EPP, RT	3
3	76	M	MPM	Epithelioid	IV (Recurrence)	EPP, RT	6
4	77	F	MPM	Epithelioid	III	Pem, carbo	2
5	84	M	MPM	Epithelioid	III	Pem, carbo	6
6	65	M	MPM	Epithelioid	II	Untreated	8
7	75	M	MPM	Epithelioid	IV (Recurrence)	Chemo, EPP, RT	5
8	85	M	MPM	Epithelioid	IV	Pem, carbo	8
9	45	M	MPM	Epithelioid	IV (Recurrence)	Chemo, EPP, RT	6
10	59	F	NSCLC	Adenocarcinoma	IIIA	Chemo, surgery	10
11	55	F	NSCLC	NOS	IIIB	Chemo/RT	1
12	53	M	NSCLC	Squamous	IIIB	Chemo/RT	12

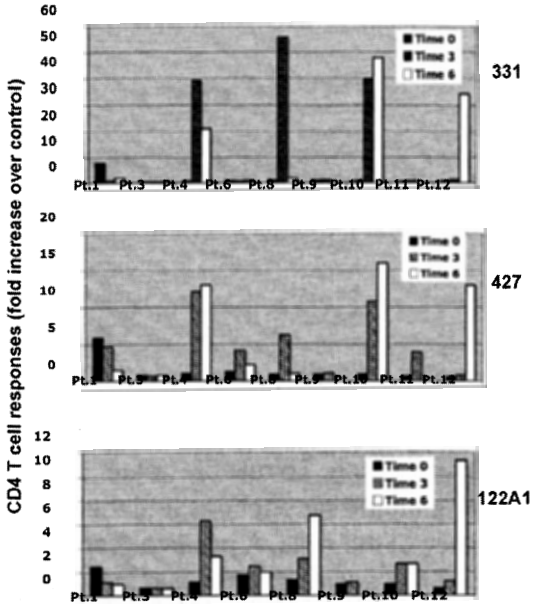
Immune response data:

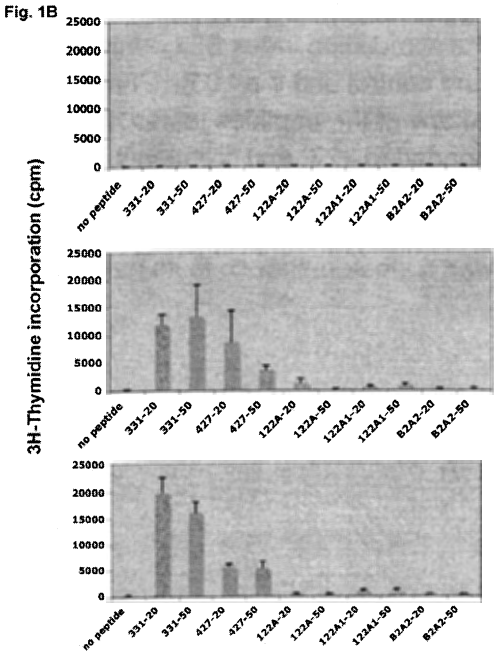
DTH: Two of the six MPM patients tested for DTH developed a response. The 3 other patients were unable to be DTH tested. One of the two NSCLC patients had a DTH reaction.

CD4 T cell response: CD4 T cell response to immunizing WT1 peptides 331, 427 and 122A1 and the native peptide 122A was directly assessed by unprimed CD4+T cell proliferation. Seven patients were tested after 3 and 6 vaccinations and two patients were tested after 3, 6, 9 and 12 vaccinations (Summary data, Figure 1A; detailed data from a representative patient, Figure 1B). Prior to vaccination, none of patients showed any peptide-specific responses. The small response to 331, 427 or 122A1 seen in patient 1 on time 0 was not significant statistically ($p = 0.24$, 0.28 or 0.16, respectively). Following vaccinations, six

patients (# 4, 6, 8, 10, 11 and 12) showed increased proliferation to the immunizing peptides (defined as an increase of more than twice the stimulation index SI: counts per minute in the test sample divided by counts per minute in the control and a $p<.05$). Three patients (# 1, 3 and 9) did not have measurable responses to any of the peptides tested. Four patients responded to peptide 331, four patients responded to 427, and 5 patients responded to 122A1 peptides. Among the peptides tested, WT1-331 seemed to be the most immunogenic, as shown by 4 out of 6 patients who had strong responses to the peptide. Two of five patients who responded to 122A1 also showed a weak response to its native peptide 122A (data not shown).

Fig.1 A

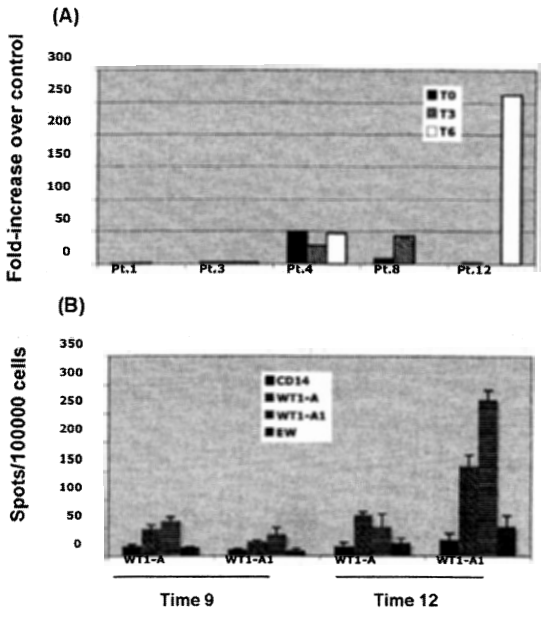




CD8 T cell responses: Five out of seven patients who are HLA-A0201 positive were tested for their CD8 T cell response to HLA-A0201-restricted peptide WT1-A1 and WT1-A by IFN-γ ELISPOT assay and WT1-A-specific tetramer staining. To reliably detect the peptide-specific response, CD3+T cells were stimulated with immunizing peptides and their native sequences *in vitro* for two rounds to expand the frequency of the cells. A positive response to the vaccine was defined as a 2-fold increase in IFN-γ-secreting cells and in frequencies of CD8+WT1-A tetramer+ cells, over the controls (irrelevant peptides), with at least 30 spots and $p < 0.05$.

T cell responses specific for WT1-A native and heteroclitic sequences were characterized (Figure 2). Prior to vaccination, only one patient (#4) showed significant IFN-γ secretion by CD3 T cells and WT1-A/A0201 tetramer positive cells, after *in vitro* stimulation. Four other patients did not show WT1-A specific responses. Following vaccination, all 5 patients showed significant increase in the numbers of IFN-γ-secreting cells at different time points. IFN-γ secretion increased twice for patient 3 after 6 vaccinations, 43-fold for patient 8 after 3 vaccinations, and 262-fold for patient 12 after 6 vaccinations (Figure 2A). A similar response was also seen in the cultures when T cells were stimulated with WT1-A peptide (data not shown). No increase was seen in patient 1 after 3 and 6 vaccinations (data not shown), but after 9 vaccinations, the response to WT1-A native sequence increased 3.1 and 2.5-fold in WT1-A and WT1-A1 stimulation, respectively (Figure 2B). Similarly, a 3.1 fold increase in IFN-γ secretion was observed in both WT1-A and WT1-A1 stimulation, after 12 vaccinations.

Fig.2



The frequency of WT1-A/HLA-A0201 tetramer positive CD8 T cells increased as early as after 3 vaccinations in 3 patients (Figure 3A). No increase in tetramer positive populations was detected in patients 1, 3 and 11 (not shown.) Representative data of WT1-A/HLA-A0201 tetramer staining from patient 4 is illustrated (Figure 3B.) CD3 T cells were stimulated with peptide WT1-A1, 122A1 or their native peptides WT1-A and WT1-122A. Percentages of WT1-A/HLA-A0201 tetramer positive CD8 T cells from pre-, and after 3 and 6 vaccinations are shown as T0, T3 and T6. Prior to vaccination, WT1-specifc T cells comprised 1.17% of CD8 T cells, in response to WT1-A peptide stimulation. The percentage of the tetramer positive cells in this culture is much higher than the stimulation with other peptides WT1-A1, 122A and 122A1, suggesting that the WT1-specifc precursor CD8 T cells existed and expanded efficiently when the native peptide was used for the stimulation. Following vaccination, a robust increase in WT1-A specific CD8 T cells was seen in all cultures with indicated peptide stimulations. Of note is that with WT1-A1 analog peptide stimulation, the percentage of WT1-A-specifc CD8 T cells steadily increased from 0.11% to 2.47% and 4.36%, after 3 and 6 vaccinations. This result demonstrated vaccination of patients with analog peptide WT1-A1 elicited an efficient CD8 T cell response against the native sequence (i.e. a heteroclitic response). Interestingly, stimulating cells with 122A1 class II analog peptide induced WT1-specific CD8 T cell responses, in a similar magnitude as did class I analog peptide WT1-A1, demonstrating efficient processing, presentation of, and cross reactivity to the WT1-A epitope in vitro.

Fig.3 A

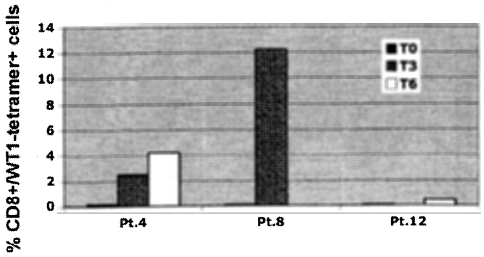
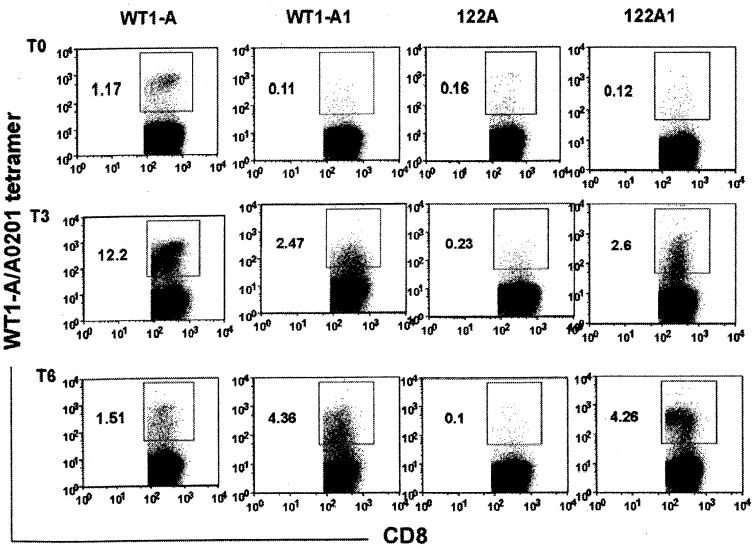
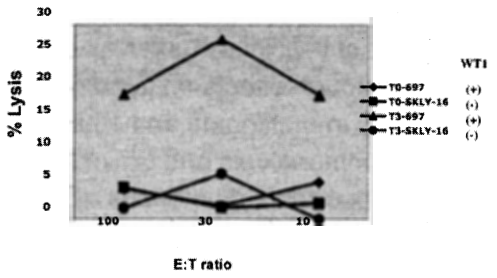


Fig. 3B



In addition, we measured the cytotoxicity in patients who had sufficient CD3 T cells. T cells were defrosted and re-stimulated with autologous DCs, CD14+ cells, or CD40L-activated B cells (20) and cytotoxicity was measured against the WT1 positive cell line, 697, or WT1-negative cell line, SKLY-16. Both cell lines were HLA-A0201- positive and have been well defined in our previous studies as suitable to test HLA-A0201-restricted, WT-1-specific killing by stimulated T cells (13, 14.) Cytotoxicity was not observed with cells obtained before vaccination, but after 3 vaccinations, CD3 T cells stimulated with WT1-A peptide were able to kill 697 cells, but not SKLY-16 cells (Figure 4, patient 8). We also detected the similar WT1-specific cytotoxicity in patient 3 (after 3 and 6 vaccinations) and patient 4 (after 9 vaccinations; other time points were not tested) (data not shown). These results demonstrated that vaccination were able to elicit a WT1-specific, cytotoxic CD8 T cells.

Fig.4



Clinical outcomes: Among the nine patients with mesothelioma, 8 developed disease progression ranging from 1 to 6 months after starting the vaccinations. However, one patient remains without progression 18 months after finishing all 12 planned vaccinations. The median survival (measured from the date of the first vaccinations) is 11 months with five patients still alive. Though patient selection certainly biases this result, the long survival times for several of these patients with advanced and previously treated MPM is encouraging.

Experience with other WT1 vaccines in humans -- The use of WT1-derived peptides for vaccination of AML and certain carcinomas have also been reported in Japan and Germany.[19,24]

Oka and colleagues in Japan conducted a Phase I clinical study of immunotherapy targeting the WT1 protein in patients with leukemia, MDS, lung cancer, or breast cancer.[19] Patients were intradermally injected with an HLA-A*2402-restricted, natural, or modified 9-mer WT1 peptide emulsified with Montanide ISA51 VG UFCH adjuvant at 0.3, 1.0, or 3.0 mg per body at 2-week intervals, with toxicity and clinical and immunological responses as the principal endpoints. Twenty-six patients received one or more WT1 vaccinations, and 18 of the 26 patients completed WT1 vaccination protocol with three or more injections of WT1 peptides. Toxicity consisted only of local erythema at the WT1 vaccine injection sites in patients with breast or lung cancer or acute myeloid leukemia with adequate normal hematopoiesis. Severe leukocytopenia occurred in patients with myelodysplastic syndrome with abnormal hematopoiesis derived from WT1-expressing, transformed hematopoietic stem cells. Twelve of the 20 patients for whom the efficacy of WT1 vaccination could be assessed showed clinical responses such as reduction in leukemic blast cells or tumor sizes and/or tumor markers. A clear correlation was observed between an increase in the frequencies of WT1-specific cytotoxic T lymphocytes after WT1 vaccination and clinical responses. It was therefore demonstrated that WT1 vaccination could induce WT1-specific cytotoxic T lymphocytes and result in cancer regression without damage to normal tissues in the clinical setting.

Letsch and colleagues in Germany reported the preliminary findings from their study vaccinating 14 patients with AML or MDS with an HLA-A2 restricted WT1 peptide with KLH and GM-GSF adjuvants. Interestingly, they detected IgM and IgG responses to WT-1 in about 15% of patients before treatment. The vaccine augmented IgM responses in 6 of 6 patients at week 26 or 30, though no CD4 T-cell or IgG responses were noted.

A search of www.clinicaltrials.gov identifies ongoing studies of WT-1 immune-directed therapy that are being conducted by Duke University, Glaxo-Smith Kline, and the NIH.

GM-CSF: GM-CSF has been used in a number of vaccines studies as an immunologic adjuvant with the presumed benefit mediated through effects on dendritic and other antigen-presenting cells. Several human vaccine studies in melanoma and other human malignancies have reported both encouraging immunologic and clinical results. More recently, two melanoma vaccine studies have reported a deleterious effect of GM-CSF when used as a vaccine adjuvant.[25,26] While it is important to be cognizant of such a potential negative effect, this study uses a different vaccine with a different dose of GM-CSF in a different disease. Other peptide vaccines studies have used GM-CSF as an adjuvant without negative results. [27,28]

Rationale for study design: We have chosen to test the efficacy of our WT-1 peptide vaccine in MPM patients who have minimal disease burden after completion of multimodality therapy, but remain at exceedingly high risk for recurrence. Designing a clinical trial to show a benefit from a cancer vaccine is notoriously challenging. Single arm studies showing prolonged time to progression or survival are fraught with patient selection bias. The only way to avoid this bias and show that a vaccine has provided a benefit is by conducting a randomized trial. In this case, we chose to study treatment with Montanide and GM-CSF in one arm. Some immunologists would argue that the use of immune stimulants, such as GM-CSF, could provide a non-specific immune response resulting in some anti-tumor effects. Indeed, this has been observed in studies in prostate cancer and melanoma [29,30]. The other arm will receive treatment with GM-CSF plus more targeted immunotherapy with WT-1 vax/Montanide. Although the size of this randomized phase II trial precludes direct comparison of the two arms, it will provide valuable information regarding the utility of immunotherapy in the adjuvant setting for this disease. If this study yields promising results, a larger randomized phase III trial would be warranted for confirmation of benefit from WT-1 vax.

Serum markers: In this study, patients will receive the WT-1 vaccine at the time of minimal residual disease after completion of multimodality therapy. We are using standard imaging studies (ie CT scans) to document the time of recurrence. However, imaging of MPM is notoriously challenging due to the pattern of spread along the pleura or the peritoneum. This could be particularly true in this setting due to post-operative changes or radiation effects. Thus, this study provides an optimal clinical scenario to assess the utility of novel serum markers which have the potential to be more sensitive for monitoring disease status.

Mesothelin, a cell surface protein, is shed into the serum of patients with mesothelioma and is a promising tumor marker. It can be measured using a commercially available test kit as soluble mesothelin-related peptide (SMRP).[31] Elevated SMRP levels can also occur in metastatic adenocarcinomas, especially ovarian and pancreatic. SMRP levels may reflect tumor load and disease progression. The role of SMRP in predicting mesothelioma development in subjects exposed to asbestos has raised significant interest in using SMRP as a tumor marker. [32]

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The study will be a randomized phase II trial to determine the 1-year progression free survival after treatment with WT-1 analog peptide vaccine in patients with MPM after completion of combined modality therapy. Seventy-eight will be enrolled (39 in each arm). One group will receive a preparation of WT-1-derived native and synthetic peptides plus immunologic adjuvant Montanide ISA 51 VG (Seppic Pharmaceuticals, Fairfield, NJ.) and Sargramostim (GM-CSF). The other group with receive Montanide adjuvant + GM-CSF.

4.2 Intervention

Patients will receive 6 injections over 12 weeks. Routine toxicity assessments will continue throughout the trial. Immune responses will be evaluated at baseline and at week 12 by CD4 T cell proliferation, CD4 and CD8 T-cell interferon release. If patient is removed from study prior to week 12 they will have their immunologic blood work checked at the time of study removal. A CT scan of the chest will be performed at baseline, week 12 and then every 3 months thereafter for up to two years until disease progression. The serum tumor marker, SMRP, will be obtained at baseline, at weeks 6 and 12 and then every 3 months thereafter for up to two years until disease progression.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5. 1 WT-1 Vaccine: The vaccine contains four separate WT1 peptides:

- WT1-A1: HLA class I peptide with a mutated amino acid R126Y to stimulate $CD8^+$ responses.
- WT1-122A1 long: HLA class II peptide containing an embedded WT1-A1 heteroclitic sequence within the longer peptide to stimulate both $CD4^+$ and $CD8^+$ responses according to data from preclinical and phase 1 studies.
- WT1-427 long and WT1-331 long: HLA class II peptides inducing $CD4^+$ responses that could provide help for long lasting $CD8^+$ T cell responses.

Name: ***WT-1 Vax***

Structural Formula: The amino acid sequences are:

Name of Peptide	Sequence
WT1-A1	YMFPNAPYL
WT1-122A1long	SGQAYMFPNAPYLPSCLES
WT1-427long	RSDELVRHHNMHQRNMTKL
WT1-331long	PGCNKRYFKLSHLQMHSRKHTG

Drug Product: WT-1 Vax was manufactured at AmbioPharm, Inc. The four peptides are provided in a sterile solution with phosphate buffered saline to produce the vaccine product. Each vial contains 280 μg of each peptide in a total volume of 0.7 ml (0.4 mg/ml of each peptide, overfill of 40%). Vialing under GMP conditions and sterility testing was performed by University of Iowa Pharmaceuticals. It will be shipped directly to individual sites at -70 to -90° C. The vaccine emulsion will be individually prepared prior to use. This will require mixture of the peptide solution with the immunologic adjuvant Montanide ISA 51 VG.

Formulation: WT-1 Vax is emulsified with Montanide ISA 51 VG by pharmacists in response to a physician order to treat a protocol patient. The peptide vaccine product and Montanide ISA 51 VG are provided in separate vials. The vaccine product containing 4 WT1 peptides (280 µg each, total 1120 µg) is mixed at a 1:1 (v:v) ratio with Montanide ISA 51 VG as an emulsion in Phosphate buffered saline to a total volume of 1.4 ml. The peptide and Montanide mixture is then vortexed in a Fisher Scientific vortex machine running at highest speed (>3000rpm) for 12 minutes with the use of an attachment. This preparation will take place in the Investigational Pharmacy. The emulsified solution should be administered to the patient within 2 hours of preparation. The dose, 1ml of the emulsion containing 200 µg of each peptide, will be drawn up into a 1-3 ml syringe using an 18 gauge needle. The dose will then be injected into the patient subcutaneously using a 25 gauge needle.

Dose: The 200 mcg dose for each peptide was chosen because it is within the range of safe and active doses used by others. Peptide vaccines have generated immune and clinical responses within a wide range of doses (100-2000 mcg injected) without clear evidence of dose- response relationships. Higher doses have the theoretical possibility of stimulating lower affinity TCRs on T cells and making a reduced response. [1]

Route: Subcutaneous

Storage: Vials of WT1 Vax should be stored at or below -70° C until use.

IND: This vaccine will be administered under an IND held by Memorial Sloan Kettering Cancer Center. MD Anderson will separately apply for an IND to administer the identical vaccine at their center using an identical protocol. Data will be combined for analysis.

5.2 Montanide ISA 51 VG: An water-in-oil (w/o) emulsion with immunoadjuvant activity. Montanide ISA 51 VG appears to act by enhancing the immune system's cytotoxic T-lymphocyte (CTL) response against antigen(s) in vaccines. The surfactant mannide monooleate in Montanide ISA 51 VG contains vegetable-grade (VG) oleic acid derived from olive oil. The adjuvant is stored between 4°C and 40°C, preferably 15°-20°C. Current shelf life in ampule is 5 years. See above for instructions on its use in this study.

5.3 Sargramostim (GM-CSF): Please refer to the package insert in Appendix 4. Sargramostim (GM-CSF) will be administered at a dose 70 mcg (0.14mL) as a subcutaneous injection at the site of vaccination on day -2 and day 0. Sargramostim (GM-CSF) is available in both a lyophilized and a liquid form and is manufactured by Bayer Healthcare Pharmaceuticals. Lyophilized Sargramostim is a sterile white, preservative free powder (250 mcg) that requires reconstitution with 1 mL sterile water for injection, USP or 1 mL bacteriostatic water for injection, USP. Liquid Sargramostim is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500mcg/ml) in a vial. The liquid may be stored for up to 20 days at 2-8° degrees C once the vial has been entered. After 20 days the remaining solution in the vial should be discarded. Refer to the "Preparation of Leukine" section in the package insert in Appendix 4 for storage of lyophilized Sargramostim following reconstitution with either sterile water for injection, USP or bacteriostatic water for injection, USP. If required, other prescribing information for Sargramostim (GM-CSF) can be found on the MSKCC formulary intranet website.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Pathologic diagnosis of malignant pleural mesothelioma (MPM) confirmed at participating institution.
- Positive immunohistochemical staining for WT-1 (greater than 10% of cells).
- Completion of multimodality therapy. This must include surgical resection by either pleurectomy/decortication or extrapleural pneumonectomy. The surgery should be performed with the intent of complete resection, though patients with an R1 resection will still be eligible. Patients should have also received treatment with chemotherapy and/or radiation. Patients with an R2 resection are also eligible as long as the site of residual disease is treated post-operatively with radiotherapy.
- 4-12 weeks since completion of combined modality therapy.
- Age $\geq$ 18 years
- Karnofsky performance status $\geq$ 70%
- Hematologic parameters: Absolute neutrophil count $\geq$ 1000/mcL, Platelets > 50 K/mcL.
- Biochemical parameters: Total bilirubin $\leq$ 2.0 mg/dl, AST and ALT $\leq$ 2.5 x upper limits of normal, Creatinine $\leq$ 2.0 mg/dl.

6.2 Subject Exclusion Criteria

- Pregnant or lactating women.
- Patients with active infection requiring systemic antibiotics, antiviral, or antifungal treatments.
- Patients with a serious unstable medical illness or another active cancer.
- Patients taking systemic corticosteroids.
- Patients with an immunodeficiency syndrome.

7.0 RECRUITMENT PLAN

This trial initially was designed to enroll a total of 78 patients (39 in each arm). With the early closure of the control arm, the total number of patients will be reduced to 60. This will take approximately 6 years to complete. Every effort will be made to include women and minorities in the research study.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at the participating institution. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

8.0 PRETREATMENT EVALUATION

Within 2 weeks of the first vaccination, patients will have the following:

- History and physical examination.
- CBC with differential.
- Comprehensive panel.
- Soluble mesothelin related protein (SMRP) level
- Serum B-hCG for women with reproductive potential.
- HLA typing (a specific HLA type is not required for participation).

Within 4 weeks of the first vaccination:

- CT scan of the chest.

9.0 TREATMENT/INTERVENTION PLAN

- Patients will be treated as outpatients.
- Treatment will be administered on weeks 0, 2, 4, 6, 8, and 10.
- All injections will be administered subcutaneously with sites rotated among extremities.
- Patients will be randomized to receive either non-specific immune therapy (Montanide adjuvant + GM-CSF) or GM-CSF plus the WT-1 peptide vaccine with Montanide adjuvant:

  All patients will receive Sargramostim (GM-CSF) (70 mcg) injected subcutaneously on days 0 and -2 of each vaccination. Patients may self administer the Sargramostim (GM-CSF) on day -2 if they have been appropriately instructed on SQ injection administration. Patients will be informed of the expected reactions such as irritation at the injection site. Patients will keep a logbook noting the time and placement of the injection.

  Patients will also receive 1.0 ml of emulsion with Montanide alone or with WT-1 peptides plus Montanide. It will be administered by a nurse (it may not be self-administered) subcutaneously to the same anatomical site as

the GM-CSF. This site will be marked by the patient or treating healthcare professional by a permanent marker pen.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

T-cell Immune Response Assays

Peripheral blood 100 ml will be drawn immediately before vaccinations at baseline and on week 12. At each time point, 12 green top tubes and 1 red top tube of blood will be obtained. These samples will be delivered on the day of acquisition. All samples will be delivered to:

Tao Dao, Ph.D.
Memorial Sloan-Kettering Cancer Center
Mortimer B. Zuckerman Research Center: Z1945
415 E 68th St.
New York, NY 10065

The blood samples obtained at baseline and week 12 will be tested for CD4 T cell proliferation, CD4 and CD8 T cell interferon release. See Appendix I for details on the techniques. The immunologic correlative blood samples described above may be collected at alternate time points if patients are required to come off study due to disease progression.

Clinical course: Refer to schema below:

	Baseline[1]	Week						
		0	2	4	6	8	10	12	Q 3 month[4]
Informed consent	X								
History, medications, and adverse events recording	X		X		X			X	X
Physical exam	X		X		X			X	X
CBC	X				X			X	X
Comprehensive panel	X				X			X	X
Beta-hCG[a]	X								
HLA typing	X								
CT scan of chest	X							X[2]	X[2]
Immunology bloods	X							X[3]	
SMRP level	X				X			X	X
WT-1 Vax/ Montanide + GM-CSF[b]		X	X	X	X	X	X		

[a] For women with reproductive potential.
[b] Sargramostim (GM-CSF) will be injected subcutaneously on day -2 and day 0 for each time point.

[1] Baseline implies within two weeks of the first vaccination except imaging studies which will be within 4 weeks. HLA typing could have been performed anytime.
[2]May be performed earlier if clinically indicated.
[3] If a patient is removed from study prior to week 12 they will have their immunology blood work at the time of study removal.
[4] For two years or until disease progression

- History and physical examination at baseline, at weeks 2, 6, and 12 and every 3 months thereafter for up to 2 years or until disease progression.

- CBC and comprehensive panel will be drawn at baseline, at weeks 6 and 12, and every 3 months thereafter for up to 2 years or until disease progression.

- CT scan of the chest will be performed at baseline and at week 12. Follow up CT scans will be performed every 3 months for two years or until disease progression.

- Note that all study procedures may be conducted within a +/- 3 day window in the first 12 weeks and within a +/- 7 day window in the subsequent weeks without being considered a study violation.

11.0 TOXICITIES/SIDE EFFECTS

Expected Toxicities

The expected toxicity with these doses of Montanide includes mild inflammation at injection sites and occasional fever. In rare patients, allergic reactions have been observed. The toxicities of Sargramostim (GM-CSF) at standard doses of 250ucg/m^2 /day for 5 to 14 days include inflammation at injection sites, edema, fluid retention, headache, myalgia, arthralgia, dyspnea, and allergic reactions. Patients with pre-existing renal and/or hepatic disorders may demonstrate elevations in serum creatinine or bilirubin/transaminases respectively. In this trial, a total of 140 micrograms will be injected with each vaccination cycle.

Potential Risks

Autoimmune or hypersensitivity reactions to components of the vaccine are theoretical possibilities, though unlikely. There have been no autoimmune or hypersensitivity reactions in patients vaccinated with other WT-1 peptides.

Criteria for Toxicity

Toxicity will be graded in accordance with the Common Toxicity Criteria, version 4.0 (CTCAE4.0) developed by the National Cancer Institute. http://ctep.cancer.gov.

Criteria for Treatment Cessation

Expected adverse events from the vaccine include local erythema, edema and itching. These are usually mild and may be observed after each administration of the vaccine. These symptoms will be treated symptomatically and will not require treatment interruptions or discontinuation.

In patients who develop a grade 2 allergic reaction consisting of generalized urticaria or evidence of systemic allergic reaction, vaccination will be discontinued and the patient will be taken off study.

Patients who develop Grade 3 or 4, toxicity that is considered possibly or probably related to the vaccine or any of its components will be taken off study.

Patients who develop evidence of autoimmune disorders or anaphylactic reaction considered to be possibly related to the vaccine will be taken off study.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Immune response: Immune responses will be measured by T cell proliferative response against WT-1 peptides. In patients with adequate samples, T cell gamma interferon release as measured by ELISPOT will be performed as well.

T cell responses ex vivo: Heparinized peripheral blood (100 ml) will be drawn prior to treatment and at week 12 during treatment as indicated in Section 10.0. If the patient is removed from study prior to week 12 they will have their blood sampled at the time of study removal. Peripheral blood lymphocytes (PBLs) will be tested for proliferation and gamma-interferon release by ELISPOT as described in Appendix I.

T cell proliferative and interferon release responses will be measured ex vivo in quadruplicate at each timepoint after challenge with the vaccinating peptide, an irrelevant control peptide, or no peptide. A response will be called positive for reactivity with the test peptides if the result is at least 2 fold higher for the test peptides as compared to the control peptides and statistically significant. While comparisons of positivity between timepoints in an individual patient will be attempted, expected differences in baselines (ie control responses) between timepoints may preclude conclusions about the magnitude of response as a result of vaccination. For assays preformed in Dr. Scheinberg's lab, immune data will be reviewed by an independent group of 2 or 3 investigators led by Jedd Wolchok, M.D.

Radiographic assessment: In this study, patients will be receiving the WT-1 vaccine after completion of surgery plus chemotherapy and/or radiation. As a result, patients may not have evidence of disease at the time of enrollment, they may have residual pleural scarring from radiation, or they may have some residual disease if the resection was incomplete. Response is not one of the parameters that will be assessed. Patients will have periodic CT scans, however, to monitor for disease progression which is the primary endpoint of the trial. The Modified Response Evaluation Criteria in Solid Tumors Group (Modified RECIST) criteria will be used, if needed, for measurements.[33] Progressive disease would include an increase in the sum of measurements over 20% if some residual disease is evident at the time of enrollment, or the development of new sites of disease.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Conditions that may define early death include patients that have died without documentation of disease progression and before it was time to conduct the first tumor reassessment. Inevaluable patients have received protocol treatment and did not have any follow-up assessment completed before initiation of alternative treatment.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study.

If at any time the patient refuses to comply with study procedures or withdraws informed consent, he/she will be taken off study.

If at any time the patient develops unacceptable toxicity he/she will be removed from study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

This is a double-blinded, randomized phase II trial assessing the efficacy of vaccination with the WT-1 vaccine plus the immunologic adjuvant Montanide ISA 51 VG plus GM-CSF (Arm A) to non-specific immune stimulation with Montanide and GM-CSF alone as a control (Arm B) in patients who have completed multimodality therapy including surgery (plus at least one of chemotherapy and radiation) for malignant pleural mesothelioma. . There is no intended comparison between the two arms. The literature lacks solid historical control data in this population. One of the reasons for accruing patients to the control arm is to further define the progression rate in a control population.

The primary endpoint is 1-year progression free survival (PFS) rate from start of WT-1 vaccine. Patients will be randomized according to the randomization procedure in Section 15.2 at the time of enrollment on the vaccine study which is after completion of multimodality therapy. PFS will be calculated from the time of randomization to first evidence of disease recurrence or death of any cause. Based on prior multicenter trials of neoadjuvant chemotherapy followed by extrapleural pneumonectomy and hemithoracic radiation (see table below), the 1-year PFS after completion of multimodality therapy is expected to be 50%. An improvement in 1-year PFS to 70% would be of interest for the vaccine arm (Arm A).

Author	Country	Year	Study type	N	Med time to recurrence (mo)
Weder [34]	Switzerland	2004	Prospective	19	16.5
Rea[35]	Italy	2007	Prospective	21	16.3
Weder[36]	Switzerland	2007	Prospective	61	13.5
Batirel[37]	Turkey	2008	Prospective	20	10
Bolukbas[38]	Germany	2009	Prospective	35	15.8
Krug[4]	US	2009	Prospective	77	10.1

Van Schil[39]	EORTC	2009	Prospective	59	13.9
Hasani[40]	Australia	2009	Retrospective	36	12.5

Therefore a two parallel single-stage design will be employed to assess the primary endpoint of PFS at 1-year in each arm separately. For each arm, a 50% progression-free rate at 12 months is considered not promising, a 70% progression-free rate at 12 months is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. Thirty-nine patients will be accrued to each arm. All patients who receive at least one vaccination will be considered evaluable in an intent-to-treat analysis. All patients will be followed for a minimum of twelve months. At the end of the trial, if 24 or more patients are progression-free at one year out of a total of 39 patients then that treatment arm will be considered worthy of further investigation. If 23 or fewer patients are progression-free at one year in a given treatment arm then that treatment arm will be declared negative. This design yields at least a 0.90 probability of a positive result if the true progression-free survival is at least 70% and yields a 0.90 probability of a negative result if the true progression-free survival is 50%.

We have included a stopping rule for futility into the trial design (each arm can stop separately). Accrual to an arm will be stopped for futilitfor futility if:

>= 7 of the first 10 patients accrued experience progression within 1 year

>= 10 out of first 20 patients accrued experience progression within 1 year

>= 14 out of first 30 patients accrued experience progression within 1 year

The trial will not be halted between stopping rule assessments. Accrual to date has been slow (5 patients in one year at MSKCC). The benefit of the stopping rule outweighs the potential for over-accruing patients in between these interim assessments. This design has 7% chance of stopping if true PFS rate is 70% and 75% if true PFS rate is 50%.

A planned interim analysis took place to assess for futility. At the time of this analysis >=10 out of the first 20 patients had experienced progression within 1 year. As a result of these findings, enrollment to the control arm (GM-CSF + Montanide) was recommended to be closed, while enrollment to the study arm continues pending further follow up data. This amendment (6/2015) addresses this change in trial design.

Toxicities will be tabulated according to the NCI Common Toxicity (version 4.0). Immunologic response will be assessed for all patients. Immune responses will be evaluated at baseline and at week 12 by CD4 T cell proliferation, CD4 and CD8 T-cell interferon release. A response will be called positive for reactivity with the test peptides if the result is at least 2 fold higher for the test peptides as compared to the control peptides. Overall survival will be calculated from date of randomization to date of death or last follow-up. Progression free survival will be calculated from date of randomization to date of progression, death or last

follow-up. Survival distributions for each arm will be estimated using Kaplan-Meier methodology.

Measurement of the tumor marker, SMRP, is an exploratory aspect of this study to determine whether elevating levels on serial measurements correlates with recurrence as determined using traditional CT scan imaging.

Originally, a total of 78 patients were planned for accrual to this study. Due to the interim analysis that led to early closure of the control arm, total sample size was lowered to 60 patients. Enrollment is anticipated to take 6 years. Additional centers will enroll patients on an identical protocol under their own IND, and the data will be pooled with those from MSKCC for the final analysis.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

15.2 Randomization

After eligibility is established, patients will be randomized with stratification for surgery type (extrapleural pneumonectomy or pleurectomy/decortication) and clinical stage (stages I/II or stages III/IV) by the PPR office.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database, CRDB) at Memorial Sloan-Kettering Cancer Center. Source documentation will be available to support the computerized patient record.

The protocol will be conducted as a single research study effort and data from each site will be included in the analysis of results. The PI at each site will be responsible for the conduct of the study/the monitoring of the progress and will review all data at their site. In case of an

FDA audit, the FDA will audit MSKCC and other sites independently as each site will hold their own IND. Each center is responsible for having all source documents, research records, all IRB approval documents, Drug Accountability Record forms, patient registration lists, response assessments scans, etc. available for audit.

The trial supporter, U.S. Army Medical Research & Materiel Command (USAMRMC), may request review of clinical data from MSKCC for interim monitoring, and/or prior to final reporting of data.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

All SAE reports will be distributed within 7 days to the principal investigators and medical monitors at institutions conducting trials with WT1 vax. If necessary, risk profiles will be updated in the informed consent documents at all sites. If early stopping rules in this study

are met, all institutions conducting trials with WT1 vax will be notified within 72 hours. Regularly scheduled conference calls and email correspondence will facilitate communication and transmission of updates on the study drug.

17.0 PROTECTION OF HUMAN SUBJECTS

Risks: The standard of care for patients eligible for this study is generally surveillance for disease progression. Administration of the WT-1 vaccine has the potential of causing toxicities that would not occur if no treatment was administered.

Benefits: Administration of the WT-1 vaccine will potentially improve relapse rates or time to progression when compared to observation.

Possible toxicities/side effects: The potential toxicities are surmised from the prior pilot trial with this vaccine and from other similar vaccine studies. Toxicities may result from the WT-1 peptides themselves, from the Montanide adjuvant, or from Sargramostim (GM-CSF). The most likely toxicity is redness or swelling at the site of the injection. Other possible toxicities include bone or muscle aches, fever, headache, swelling in the feet. Less common but potentially serious toxicities include allergic reactions, elevated liver function blood tests, elevated kidney function blood tests, or shortness of breath.

Costs: Patients will be charged for physician visits, routine laboratory, radiologic, and pathologic studies required for monitoring their condition. Patients will not be billed for GM-CSF or the vaccine. Patients will not be charged for immunologic testing.

Alternatives: Alternative treatment options include observation, or participation in other investigational studies

Inclusion of Children in Research: This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Unblinding

Should a patient develop a Serious Adverse Event felt at least possibly due to the study drug, the medical monitor will be notified. The role of the medical monitor is described in Appendix 5. Furthermore, PPR will be notified and the patient will be unblinded to determine if s/he was receiving WT1 vax. The treating physician and the principal investigator will be informed. The treatment arm assignment will be included in the SAE report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: T-Cell Assays

Appendix 2: A-15872 Site-Specific Protocol Addendum

Appendix 3: Abbreviations

Appendix 4: Sargramostim package insert

Appendix 5: HRPO Protocol Addendum

Appendix 6: GM-CSF Administration Log

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

Randomized Phase II Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma (MPM) After Completion of Combined Modality Therapy

You have been asked to participate in a research study. In order to decide whether or not you should agree to be part of this research study, you should know enough about its risks and benefits in order to make a sound judgment. This process is known as informed consent.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your healthcare team. If you have any questions, you can ask your study doctor for more explanation.

This consent form gives you detailed information about the research study. Once you understand the study, its risks, and its benefits, you will be asked to sign the form if you wish to take part. You will be given a copy to keep.

You are being asked to take part in this study because you have malignant pleural mesothelioma that has been removed by surgery and has also been treated with chemotherapy and/or radiation therapy.

Why is this study being done?

We are testing a Wilms Tumor-1 (WT1) vaccine to see if it delays or prevents the mesothelioma from growing back after surgery. WT1 is a protein in cancer cells that regulates gene expression and causes cell growth. Mesothelioma tumors generally have high levels of WT1.

This study was originally designed to have two treatment groups. One group received non-specific immunotherapy with medications called Montanide and Sargramostim (Granulocyte Macrophage Colony Stimulating Factor, GM-CSF). Enrollment to this group has stopped. The other group, which continues, receives more specific immunotherapy with the WT1 vaccine plus Montanide and GM-CSF. Both Montanide and GM-CSF are commonly given along with vaccines because they have a general effect in boosting the immune response. Some researchers believe that this general increase in the immune system may have some effect in treating cancer. Some studies using GM-CSF with melanoma vaccines have suggested that it could lessen the effects of the vaccine. The addition of the WT1 proteins makes this therapy more directed to mesothelioma. The combination of WT1 vaccine with Montanide and GM-CSF has been tested in a prior trial including 9 patients with advanced mesothelioma. In that trial, the vaccine was safe and caused an immune response.

Is there a potential conflict of interest for this study?

You should be aware that Memorial Sloan –Kettering Cancer Center (MSKCC) has both a scientific and financial interest in the investigational drug WT-1 analog vaccine. One of the scientists at MSKCC is the inventor of WT-1 analog vaccine. There is a patent on WT-1 analog vaccine which is owned by MSKCC and licensed to Sellas Life Sciences Group. This means that MSKCC and the inventor would receive a part of the revenue from any future sales of WT-1 analog vaccine.

The cost of this study is being supported by a grant from the Department of Defense.

If you are interested in details about the steps MSKCC has taken to protect your best interests on this trial, please speak to our patient representative, Jorge Capote, RN at 212-639-8254.

How many people will take part in the study?

About 39 people will take part in this study at MSKCC. In total, about 60 patients will be enrolled across all sites.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam
- Blood work including complete blood counts and comprehensive panel which includes electrolytes, liver and kidney function.
- Pregnancy testing if appropriate
- CT scan of the chest
- Tumor marker blood test called SMRP

In addition, you have immunology blood tests and Human Leukocyte Antigen (HLA) typing (a blood test that determines your tissue type) to help us assess your immune response to the vaccine.

During the study…

Sargramostim will be given by two injections two days apart every two weeks. You may be taught to do the Sargramostim (GM-CSF) injection yourself in which case you will be given a log sheet to record the injection time and location. The Montanide is given as an injection under the skin on the same day as the second Sargramostim injection and will be given at the same spot which will be marked with a pen. Each vaccine is given at a different location under the skin in the arm or the leg. You will receive 6 injections of Sargramostim.

The WT-1 vaccine is given together with the Montanide. You will receive 6 injections of the WT-1 vaccine.

To monitor your health while receiving the vaccine, you will need the following tests and procedures. They are part of regular cancer care.

- History and physical exam in weeks 2, 6, and 12.
- Blood work including complete blood counts and comprehensive panel which includes electrolytes, liver and kidney function at weeks 6 and 12.
- CT scan of the chest at week 12.
- Tumor marker blood test called Soluble Mesothelin Related Peptide (SMRP) at weeks 6 and 12.

When I am finished taking the therapy…

All patients will have the following tests and procedures every 3 months for up to 2 years:

- History and physical exam
- Blood work including complete blood counts and comprehensive panel which includes electrolytes, liver and kidney function.
- CT scan of the chest.
- Tumor marker blood test called SMRP.

	Baseline	Week							
		0	2	4	6	8	10	12	Every 3 months for up to 2 years
History and physical exam	X		X		X			X	X
CBC	X				X			X	X
Comprehensive panel	X				X			X	X
Pregnancy test (if appropriate)	X								
HLA typing	X								
CT scan of chest	X							X	X
Immunology bloods	X							X	
SMRP level	X				X			X	X
WT-1 Vaccine/ Montanide + GM-CSF		X	X	X	X	X	X		

How long will I be in the study?

You will be asked to take the WT1 vaccine/Montanide + GM-CSF every 2 weeks for a total of 12 weeks. After you are finished taking the treatment, the study doctor will ask you to visit the office for follow-up exams as described above every 3 months for up to 2 years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the WT1 vaccine can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the WT1 vaccine. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Montanide with the **WT1 vaccine** include those which are:

Likely

- Redness, swelling, or itching at the site of the injection

Less Likely

- Bone or muscle aches
- Fever
- Headache
- Swelling in the feet

Rare but serious

- Allergic reactions-patients may have hives or other rash
- Shortness of breath

Risks and side effects related to **GM-CSF** include those which are:

Likely

- Redness, swelling, or itching at the site of the injection

Less Likely

- Bone or muscle aches
- Headache
- Swelling in the feet

Rare but serious

- Allergic reactions-patients may have hives or other rash, or shortness of breath
- Elevated liver function blood tests
- Elevated kidney function blood tests

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn more about WT1 vaccine as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Every effort will be made to keep your study records private. It is the responsibility of the research staff at Memorial Hospital to make sure that your records are managed to protect your privacy. If information from this study is used in any reports or publications, your name and anything else that could identify you will not be used. Trained staff at Memorial Hospital may review your records if necessary. Access to your medical information will be limited to those listed in the Research Authorization Form, which is a part of the informed consent process.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

There will be no charge for:

- WT-1 vaccine
- Montanide
- Sargramostim (GM-CSF)
- Blood tests to monitor your immune response
- HLA typing

You or your insurance company will be responsible for all other charges such as doctor visits, CT scans and routine blood work. You or your insurance carrier will be charged for the administration of the drug even though the drug is free of charge. You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

You will get medical treatment if you are injured as a result of taking part in the study.

If you think you have been injured as a result of taking part in this research study, you must tell your study doctor or the person in charge of this research study as soon as possible. The name and phone number of the person in charge of this research are listed on this consent form.

We will offer you treatment for research injuries as a result of your taking part in this study. You and/or your health plan will be charged for this treatment. Medical services will be offered at the usual charge. You will be responsible for any costs not covered by your health plan/insurance.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor Marjorie G. Zauderer, M.D. at 646-888-4656.

Any hospital that does research on people has an institutional review board (IRB). This board reviews all new studies to make sure that the patient's rights and welfare are protected. The IRB at MSKCC has reviewed this study.

For a non-physician whom you may call for more information about the consent process, research patients' rights, or research related injury is Jorge Capote, RN, Patient Representative, telephone number: (212) 639-8254.

Randomized Phase II Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma (MPM) After Completion of Combined Modality Therapy

RESEARCH AUTHORIZATION

Randomized Phase II Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma (MPM) After Completion of Combined Modality Therapy

Research Participant Name: _____

Research Participant MRN :_____

We understand that information about you and your health is personal. We are committed to protecting the privacy of your information. Because of this commitment, we must obtain approval from you before we can use your protected health information for research purposes. This form provides that authorization. This form also helps us make sure that you are informed of how this information will be used or disclosed in the future. Please read the information below carefully before signing this form.

USE AND DISCLOSURE COVERED BY THIS AUTHORIZATION

A representative of Memorial Sloan-Kettering Cancer Center must answer these questions completely before providing this authorization form to you. *PLEASE DO NOT SIGN A BLANK FORM.* ***You or your personal representative should read the descriptions below before signing this form.***

Who will have access to and/or use your health information?

The following individuals and/or organization(s) may have access to use, disclose or receive some information about you. They may only share the information to the individuals/parties indicated on this list. This information must be shared with you, the research subject and/or your personal representative, as required by law.

- ☑ Every research site for this study, including Memorial Sloan Kettering Cancer Center and the research support staff (for example, research study assistant) and medical staff at each location
- ☑ Every health care personnel who provides services to you in connection with this study
- ☑ Any laboratories, other individuals/organizations that analyze your health information in connection with this study as defined by protocol
- ☑ The following research sponsors: Memorial Sloan Kettering Cancer Center
- ☑ The National Cancer Institute and/or the National Institute of Health
- ☑ The United States Food and Drug Administration and other regulatory agencies responsible for oversight.
- ☑ The members and staff of the hospital's Institutional Review Board and Privacy Board

☑ Principal Investigator and Co-Principal Investigator(s): *Marjorie G. Zauderer, M.D. and Valerie Rusch, M.D.*

☑ Members of the Research Team including the participating investigators, research assistants, clinical nurses, fellows/residents, and clerical support staff.

☑Members and staff of the hospital's Office of Clinical Research, Computing Resource Group that manages research databases, and the research management and support staff in the clinical departments

☑ Members of the Hospital's Data Safety Monitoring Board/Committee and Quality Assurance Committee

- Others:Representatives of the U.S. Army Medical Research & Material Command Human Research Protections Office

☑ Sellas Life Sciences Group

What information will be used or disclosed?

The boxes checked below should provide you with enough detail so that you can understand what information may be used or disclosed.

☒ Your entire research record
☒ Any part of your medical records held by the hospital

☒ HIV-related information. This includes any information indicating that you have had an HIV-related test, or have HIV infection, HIV-related illness or AIDS, or any information which could indicate that you have been potentially exposed to HIV. (New York State requires us to obtain special consent)

☒ The following information:

- Blood
- Injection diaries

SPECIFIC UNDERSTANDINGS

By signing this form, you give permission for the sharing of your protected health information noted above. The purpose for the use and disclosure of your information is to conduct the research study explained to you during the informed consent process. This form also ensures that the information relating to the research is available to everyone who may need it. Your protected health information may also be used for your research treatment, to collect payment for your treatment while on the study (when applicable), and to run the business operations of the hospital.

Once we have shared your information with the individuals and organizations listed on this form, they may be able to share your information again, if they are not subject to laws that protect your privacy.

It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in the research study. You will not receive the research treatment that was described to you. Your health care outside the study will not be affected. The payment for your health care or your health care benefits will not be affected.

If you sign this authorization form, you will have the right to withdraw it at any time. To withdraw the authorization will prohibit further use or disclosure of your health information. If the hospital has already used your health information approved by your authorization or needs the information to fulfill an obligation or analyze the data, the use or disclosure can not be stopped. This authorization form will not expire unless you withdraw it. If you want to withdraw this authorization, please write to Dr. Marjorie G. Zauderer, Department of Medicine, at the hospital.

You have a right to see and copy your health information described in this authorization form in accordance with the hospital's policies. You also have a right to receive a copy of this form after you have signed it.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that the individuals/organizations are prohibited from sharing any HIV-related information without your approval unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (800) 523-2437 or (212) 480-2493 or the New York City Commission of Human Rights at (212) 306-7450 or (212) 306-7500. These agencies are responsible for protecting your rights.

PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

Randomized Phase II Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma (MPM) After Completion of Combined Modality Therapy

Statement of professional obtaining consent

I have fully explained this clinical research study to the participant or his/her Legally Authorized Representative (**LAR**). In my judgment and the participant's or that of his/her Legally Authorized Representative, there was sufficient access to information, including risks and benefits to make an informed decision. The consent discussion will be documented in the participant's EMR.

Consenting Professional Must Personally Sign & Date		
Assent (Minor between the ages of 7 and less than 18): If the participant is a minor, I have obtained his/her assent to participate in the study to the best of their ability to understand. ☐ **YES** ☐ **NO** ☐ **N/A (Adult or Child <7)**		
Consenting Professional's Signature		**Date:**
Consenting Professional's Name (Print)		

Participant's (or Legally Authorized Representative's (LAR)) statement

I have read this form with the description of the clinical research study. I have also talked it over with the consenting professional to my satisfaction. By signing below, I am agreeing to the following: (1) to voluntarily be a participant in this clinical research study (2) authorizing for the use and disclosure of my/their protected health information (data about myself) and (3) that I received a signed copy of this consent form.

Participant/LAR Must Personally Sign & Date		
Participant/LAR Signature		**Date:**
Participant/LAR Name (Print)		
LAR Relationship to Participant		

Witness Signature (If Required)

☐ **Non-English Speaking Participant Witness and/or Interpreter:** I declare that I am fluent in both English and participant's (or LAR) language and confirm that the consent discussion was appropriately translated for the participant (or LAR).

☐ **Other:** I confirm that the consent discussion was appropriate for the participant's (or LAR's) understanding of the study.

Name of Witness: _____

Signature of Witness: _____ Date: _____

(If witness is used for consent discussion, their name must be documented in the EMR.)

The Participant/Legally Authorized Representative Must Be Provided With A Signed Copy Of This Form