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A Randomized Phase II Trial of Adjuvant Galinpepimut-S, WT-1 Analog Peptide Vaccine, after Multimodality Therapy for Patients with Malignant Pleural Mesothelioma

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Abstract

Purpose—Determine the 1-year progression-free survival (PFS) among patients with malignant pleural mesothelioma (MPM) receiving the WT1 peptide vaccine galinpepimut-S after multimodality therapy vs those receiving control adjuvants.

Patients and Methods—This double-blind, controlled, two center phase II trial randomized MPM patients after surgery and another treatment modality to galinpepimut-S with GM-CSF and Montanide or GM-CSF and Montanide alone. An improvement in 1-year PFS from 50% to 70% was the predefined efficacy threshold, and 78 patients total were planned. The study was not powered for comparison between the two arms.

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Prior presentations: A preliminary analysis of this trial was presented at the International Mesothelioma Interest Group meeting in Birmingham, UK. Updated data were presented at the ASCO Annual Meeting 2016.

Results—41 patients were randomized. Treatment related adverse events were mild, self-limited, and not clinically significant. Based on a stringent prespecified futility analysis (futility = ≥ 10 of 20 patients on one arm experiencing progression < 1 year), the control arm closed early. The treatment arm was subsequently closed because of the resultant unblinding. The PFS rate at 1 year from beginning study treatment was 33% and 45% in the control and vaccine arms, respectively. Median PFS was 7.4 months vs 10.1 months and median OS was 18.3 months vs 22.8 months in the control and vaccine arms, respectively.

Conclusion—The favorable safety profile was confirmed. PFS and OS were greater in those who received vaccine but the trial was neither designed nor powered for comparison between the arms. Based on these promising results, the investigators are planning a larger randomized trial with greater statistical power to define the optimal use and benefit of galinpepimut-S in the treatment of MPM.

Introduction

Malignant pleural mesothelioma (MPM) remains difficult to treat with only one FDA approved chemotherapy regimen (cisplatin and pemetrexed)[1] for patients with advanced disease. For patients with early stage disease, multimodality therapy is a preferred approach which includes cytoreductive surgery (such as extended pleurectomy/decortication), pemetrexed-based chemotherapy, and, in some cases, thoracic radiation.[2] However, even with this aggressive approach to early stage disease, the majority of patients experience recurrence due to persistent microscopic disease. Therefore, it is imperative that efforts continue to further improve outcomes.

One promising avenue involves exploiting the Wilms tumor-1 protein in MPM. In normal adult tissues, WT1 expression is limited, but WT1 is highly overexpressed in MPM as well as several other hematologic and solid tumors,[3] making it an ideal candidate for a tumor selective cancer vaccine in WT1 expressing malignancies. Although WT1 is a nuclear and cytoplasmic protein that functions as a transcription factor regulating genes involved in cellular proliferation, differentiation, apoptosis, organ development, and sex determination, the protein is processed by the proteasome and the derived peptides are presented on the cell surface making it an attractive target for immunotherapy.[4-8] WT1 was ranked as the top cancer antigen by a working group organized by the National Cancer Institute in 2009.[9]

Because WT1 is a self-antigen, overcoming immune tolerance is challenging and a potential obstacle in vaccine development. To address this, we enhanced the immunogenicity of WT1 by designing synthetic immunogenic peptide analogs that generate cross-reactivity to native peptides, known as a heteroclitic response. Single amino acid substitutions were introduced to improve HLA-A*02:01 major histocompatibility complex binding affinity of two of the vaccine peptides. These new peptides had improved stability, elicited WT1 specific T cell recognition and cytotoxic T cell lymphocytes, and stimulated T cells to react with native WT1.[10] To provide immunogenicity over a broader range of HLA subtypes, and to elicit CD4 as well as CD8 responses, four WT1 peptides ranging in length from 9 to 22 amino acids (Supplementary Table 1) were combined into a vaccine, galinpepimut-S. All four peptides were shown to be immunogenic in preclinical studies and in pilot human trials.[11,12]

Immunologic adjuvants (Montanide and GM-CSF) were co-administered as part of the vaccination regimen to retain the peptides at the injection site and to induce local inflammation near the peptide.

A prior pilot study to assess the safety, activity, and immunogenicity of galinpepimut-S included nine patients with MPM and 3 with NSCLC.[11] No severe toxicity was associated with treatment and immune responses occurred in a high proportion of patients. These results were the rationale for the subsequent randomized phase II trial of galinpepimut-S in MPM described herein. Of note, a similar pilot study in 9 patients with acute myeloid leukemia yielded similar safety and immunologic data.[13] Based on the data from these first two trials, we chose to evaluate galinpepimut-S in patients who have minimal disease burden after completion of multimodality therapy but remain at exceedingly high risk for recurrence.

Materials and Methods

This randomized, double-blinded, controlled phase II study of galinpepimut-S in patients with MPM after multimodality treatment (NCT 01265433) was reviewed and approved by the Institutional Review Boards at Memorial Sloan Kettering Cancer Center (MSK) and MD Anderson Cancer Center (MDACC) as well as the Human Research Protection Office of the U.S. Army Medical Research and Material Command. The study was conducted in accordance with good clinical practice and followed the guiding principles of the Declaration of Helsinki, as well as local laws and regulations. Eligibility criteria were as follows: pathologically confirmed MPM, IHC positive for WT1 (clone WT49) in greater than 10% of cells, completion of multimodality therapy (including surgical resection by either pleurectomy/decortication or extrapleural pneumonectomy and chemotherapy or radiation therapy or both), 4 to 12 weeks elapsed since completion of multimodality therapy, age ≥18 years, Karnofsky Performance Status ≥ 70%, and adequate hematologic, renal, and hepatic function (ANC ≥ 1000/μL, platelets > 50 K/μL, total bilirubin ≤ 2.0 mg/dl, creatinine ≤ 2.0 mg/dl, and AST and ALT ≤2.5 × upper limits of normal). Exclusion criteria were pregnancy, active infection requiring systemic treatment, use of systemic corticosteroids, known immunodeficiency syndrome, other serious unstable medical illness, or another active cancer.

Treatment Plan

After obtaining written informed consent and confirmation of eligibility, patients were stratified by surgery type (extrapleural pneumonectomy vs pleurectomy/decortication) and clinical stage (I/II vs III/IV) and randomized to receive granulocyte-macrophage colony-stimulating factor (GM-CSF) 70 μg, Montanide 500 μg, and galinpepimut-S 800 μg (total weight; 200 μg of each of the 4 peptides within the mixture) versus the adjuvants only (GM-CSF 70 μg and Montanide 500 μg). Patients, caregivers, and investigators were blinded as to treatment arm. After injection teaching, GM-CSF 70 μg was self-administered 2 days prior and the day of each vaccine treatment in the site of prospective vaccination on a limb. A series of 6 vaccines were given every 14 days (weeks 0, 2, 4, 6, 8, and 10, +/- 3 days). On treatment days, depending on randomization, nurses administered Montanide, GM-CSF and

galinpepimut-S or Montanide and GM-CSF alone to the same anatomical site where the GM-CSF was administered 2 days prior. Patients were assessed at baseline, weeks 2, 6, and 12 and every 3 months for up to 2 years or until disease progression with history and physical examination. CT scans of the chest were performed at baseline, week 12, and every 3 months for 2 years or until disease progression and assessed using the modified RECIST for mesothelioma with reference study radiologists.[14] Toxicities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

Galinpepimut-S Formulation

Galinpepimut-S contains 4 peptides (Supplementary Table 1) that stimulate both CD4 and CD8.[10,12] For this study, galinpepimut-S was manufactured at AmbioPharm, Inc. and provided in a sterile solution with phosphate buffered saline. Each vial contained a final injectable dose of 200 μg of each peptide in a volume of 0.5 ml vial, overfill was 40%. Vialing under Good Manufacturing Practice conditions and sterility testing was performed by University of Iowa Pharmaceuticals. For administration, the 0.5 ml of vaccine was mixed with Montanide ISA 51 VG (Seppic Pharmaceuticals, Fairfield, NJ) in a 1:1 ratio and then vortexed in a Fisher Scientific vortex machine >3000 rpm for 12 minutes with the use of an attachment.

T-cell Immune Response Assays

Peripheral blood was collected for T cell immune proliferation assessment as well as gamma-interferon release as measured by ELISPOT at baseline and at week 12. All measurements were done in quadruplicate at each time point. A response was considered positive for reactivity with the test peptides if the result was at least 2-fold higher for the test peptides as compared to the control peptides, statistically significant with $p<0.05$, and a minimum number of spots were measured (>200 for CD4 and >30 for CD8).

Statistical Analysis

The primary endpoint of this trial was 1-year progression free survival (PFS) rate. PFS was calculated from the date of randomization to the date of progression, death, or last follow-up. Extrapolating from prior multicenter trials of neoadjuvant chemotherapy followed by extrapleural pneumonectomy and hemithoracic radiation (Supplementary Table 2), the 1-year PFS after multimodality therapy was expected to be 50%. An improvement in 1-year PFS to 70% was considered to be of interest in the vaccine arm. Thus, two parallel arms of single-stage design were employed to assess PFS at 1-year in each arm separately. For each arm, a 50% PFS rate at 12 months was defined as not promising and a 70% PFS rate at 12 months was considered promising. The probabilities of a type I and type II error were set at 0.10 and 0.10, respectively. Based on this, thirty-nine patients were planned for accrual to each arm. All patients who received at least one vaccination were considered evaluable in an intent-to-treat analysis. All patients were followed for a minimum of 12 months.

A stopping rule for futility was implemented such that accrual to an arm was to be stopped for futility if: ≥ 7 of the first 10, ≥10 of the first 20, or ≥ 14 of the first 30 patients accrued experience progression within 1 year. Overall survival was calculated from the date of

randomization to the date of death or last follow-up. Survival distributions for each arm were estimated using Kaplan-Meier methodology. Exploratory comparisons between treatment arms were assessed using the logrank test.

Results

Patient Characteristics

Forty-six patients were consented to this protocol between May 2011 and August 2015. MD Anderson Cancer Center (MDACC) joined in May 2013. Three patients were unable to proceed with vaccine therapy due the development of radiation pneumonitis and the need for treatment with systemic corticosteroids. Two patients elected to withdraw consent prior to receipt of any study interventions. Forty-one patients were randomized to receive at least one dose of galinpepimut-S or control and were considered evaluable (Figure 1).

The characteristics of the 41 evaluable patients are listed in Table 1. Baseline characteristics were similar in the two arms, and typical for this patient population. The median age at enrollment was 68 (range 34 to 84) and the median KPS at enrollment was 80% (range 70 to 100%). As expected based on the eligibility requirement for WT1 expression, no sarcomatoid patients were included. Ninety-five percent of patients had purely epithelioid tumors, while 5% had tumors with mixed histology. All patients underwent some type of surgery: 7% extrapleural pneumonectomy; 15% extended pleurectomy decortication; 34% pleurectomy-decortication (removal of all gross tumor with a parietal and visceral pleurectomy but without diaphragmatic or pericardial resection); and 44% partial pleurectomy decortication (partial removal of parietal and/or visceral and/or cases with residual gross tumor).[15] Forty-nine percent achieved a macroscopic complete resection (MCR defined as R0 or R1 resection). All but one patient received chemotherapy and all regimens contained pemetrexed and platinum. The vast majority of patients, 76%, received intensity modulated pleural radiation therapy (IMPRINT)[2,16] with 7% receiving a different type of radiation and 17% receiving no radiation prior to enrollment. Twenty patients were randomized to galinpepimut-S and 21 to the control arm. There were, on average, 61 days (range 29-181) between last treatment and beginning injections on this study. This time interval was not statistically different between vaccine and control groups or between types of surgery.

Progression-free and Overall Survival

Based on the protocol specified futility analysis and the recommendation of the Data Safety Monitoring Board, the control arm closed to accrual in May 2015. Subsequently, the vaccine arm was closed in November 2015 because there was no way to maintain blinding as both investigators and patients would know that the new enrolled participants were getting the active vaccine treatment. After all patients were on study for 1 year, the database was locked, patients were unblinded, and progression-free and overall survival were calculated. The progression-free survival (PFS) rate at 1 year from start of galinpepimut-S was 33% and 45% in the control arm and vaccine arm, respectively. Among the control patients, median PFS was 7.4 months (95% CI 2.8-14.6 months) and median overall survival (OS) was 18.3 months (95% CI 10.2-28 months). For the patients randomized to galinpepimut-S, median

PFS was 10.1 months (95% CI 5.5—20.8 months) and median OS was 22.8 months (95% CI 9.1-37.6 months). Although the study was not powered for comparison between the treatment arms, these exploratory analyses were performed (Figures 2 and 3) and revealed a hazard ratio for PFS of 0.78 (95% CI 0.4-1.5, p=0.46) and a hazard ratio for OS of 0.79 (95% CI 0.4-1.7, p=0.54). A subset analysis was performed for PFS and OS among the 20 patients who had a macroscopic complete resection (MCR), R0/1, (Figures 4A and B). Among the control patients with MCR, median PFS was 5.7 months (95% CI 0.69-14 months) and median OS was 16.6 months (95% CI 2.3-24.5 months). For patients randomized to galinpepimut-S with MCR, median PFS was 8.3 months (95% CI 2.3-24.5 months) and median OS was 22.8 months (95% CI 7.1-37.6 months).

Toxicities

Treatment related adverse events were mild and self-limited (Table 2). Injection site reactions were more common among those receiving vaccine compared to those receiving control injections with GM-CSF and Montanide alone, 85% versus 43%, all grade 1. Fatigue was comparable in both arms at 50% with galinpepimut-S and 48% with control injections. Interestingly, fever and arthralgias occurred only among those treated with control injections, while nausea occurred in 10% of those receiving galinpepimut-S. The two cases of lymphopenia were considered possibly related and, while grade 3, resolved without any intervention and there were no negative sequelae of this laboratory abnormality.

Immune Response

Data were available from 22 (11 in each arm) of the 41 patients for immunologic assessment (Table 3, Supplementary Figures 1A, 1B, and 2 include illustrative response data from patient 10). There were technical issues in maintaining fully viable cells arriving from MDACC at MSK which precluded reliable analysis and therefore these samples are not included in the analyses. In the vaccine arm, 2 of 3 HLA-A*02:01 patients showed positive responses in an ELISPOT assay and in an MHC tetramer assay to the RMF (WT1A) peptide or the longer 122A peptide with the imbedded HLA-A*02:01 epitope (the latter being able to evoke both CD4 and CD8 immune responses by design). Four of 8 patients tested positive in a CD4 proliferation assay in response to 1 or more of the longer peptides. In the control arm, 0 of 4 HLA-A02 patients showed a response in the ELISPOT assay or the tetramer assay. One of 8 tested patients showed increased CD4 responses after vaccination. One patient was positive before vaccination and after vaccination had a reduced response. One other patient was positive before vaccination and after vaccination had no response. A fraction of patients have been reported to mount IgG and T cell responses to WT1 epitopes without vaccination.[17] In addition, the CD8 test involves repeated stimulation ex vivo and the WT1 peptides are self-peptides to which T cells may have been exposed and repeated stimulations can generate responses even in unvaccinated donors.[10,12]

As an exploratory analysis, the PFS and OS were examined in various subgroups related to their immune response (IR) to interrogate possible prognostic trends and to see if the patients in whom IR data were available differed from the group as a whole, thereby introducing bias. Patients who had enough cells to perform the IR tests tended to have longer median PFS, but not OS. Patients who were vaccinated and made a positive IR or patients

who got vaccine and mounted no IR did not differ in their outcomes appreciably from the larger cohorts.

Discussion

Treatment options for patients with MPM remain limited and, despite aggressive multimodality therapy for early stage disease, MPM remains highly lethal. This randomized, double-blinded, controlled phase II trial evaluated the use of the analog WT1 peptide vaccine, galinpepimut-S, in patients who completed multimodality therapy to improve outcomes for MPM. The results confirmed earlier pilot trials in MPM and leukemia that administration of galinpepimut-S is safe, well-tolerated and feasible in the outpatient setting. Importantly, the data demonstrated that vaccine administration was associated with a non-statistically significant increase in PFS and OS (PFS HR 0.78 95% CI 0.4-1.5 p=0.46 and OS HR 0.79 95% CI 0.4-1.7 p=0.54). Median PFS and OS were 36% longer and 25% longer, respectively, in the galinpepimut-S arm as compared to the placebo arm. This pattern was also noted among patients who had a MCR prior to study enrollment. Importantly, the control group was well-matched, and received the same Montanide and GM-CSF doses, and had the same adverse effects from them, contributing to complete blinding of the patients and investigators, thereby minimizing possible alternative effects from investigator bias contributing to the PFS outcomes.

However, this pilot trial was not powered for comparison between the two treatment arms with the planned accrual of 78 patients and, due to the early closure, accrued only 53% of the planned sample. Additionally, because this is an understudied population with complex and variable initial therapies, the selection of 1 year PFS-rate was challenging and, in retrospect, the initially prespecified 50% threshold at 1 year from randomization was too high. Notably, survival in the historical controls (Supplementary Table 2) was calculated from the date of surgery. In contrast, the futility threshold in this study was based on the date of randomization which occurred, on average, 5 months after surgery. Thus, when the expectations for 12-month PFS from the historical controls were applied to the initial design of this trial, the median lapse of 5 months between surgery and randomization on the clinical trial was not taken into account.

The interpretation of IR in this cohort was limited as half of patients did not have adequate samples suitable for IR analysis. Additionally, any association between IR and outcomes may be confounded by patient selection, in that those who had enough cells to perform the IR testings remained alive and healthy and without recurrence or subsequent therapy that could adversely impact IR analysis. Because the vaccinated patients did well regardless of whether an IR was capable of being measured, this suggests that the assays used were not sensitive enough to predict clinical response in this small sample or that technical issues precluded a significant analysis. It is also possible that patients mounted an immune response and lost it over the 12 weeks before they were retested.

In summary, PFS and OS were greater among MPM patients who received galinpepimut-S vaccination, among all patients and in particular among those who had a MCR. Because of the tolerance and excellent safety profile of galinpepimut-S, the immune response data in

this and previous trials, and the observed survival patterns, the investigators have concluded that these results warrant additional randomized studies to help define the optimal use and benefit of galinpepimut-S in the treatment of MPM. A randomized phase II/III study of galinpepimut-S after multimodality therapy is planned.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Translational Relevance

The development of novel therapeutic strategies in malignant pleural mesothelioma (MPM) is dependent on exploiting its molecular aberrations. The high expression of WT-1 in most MPM and its absence in normal adult tissues make it a promising target for new treatments and, in particular, for a tumor selective vaccine. Here, we report the results of a randomized phase II evaluating a multivalent WT-1 peptide vaccine, galinpepimut-S, in the treatment of MPM after multimodality therapy. In addition to demonstrating a signal for efficacy, we show that the vaccine stimulates immune responses in certain individuals and an immune response was associated with improved survival, although this did not reach statistical significance. Based on these promising results, a large randomized phase III trial is planned for patients with WT-1 expressing mesothelioma.

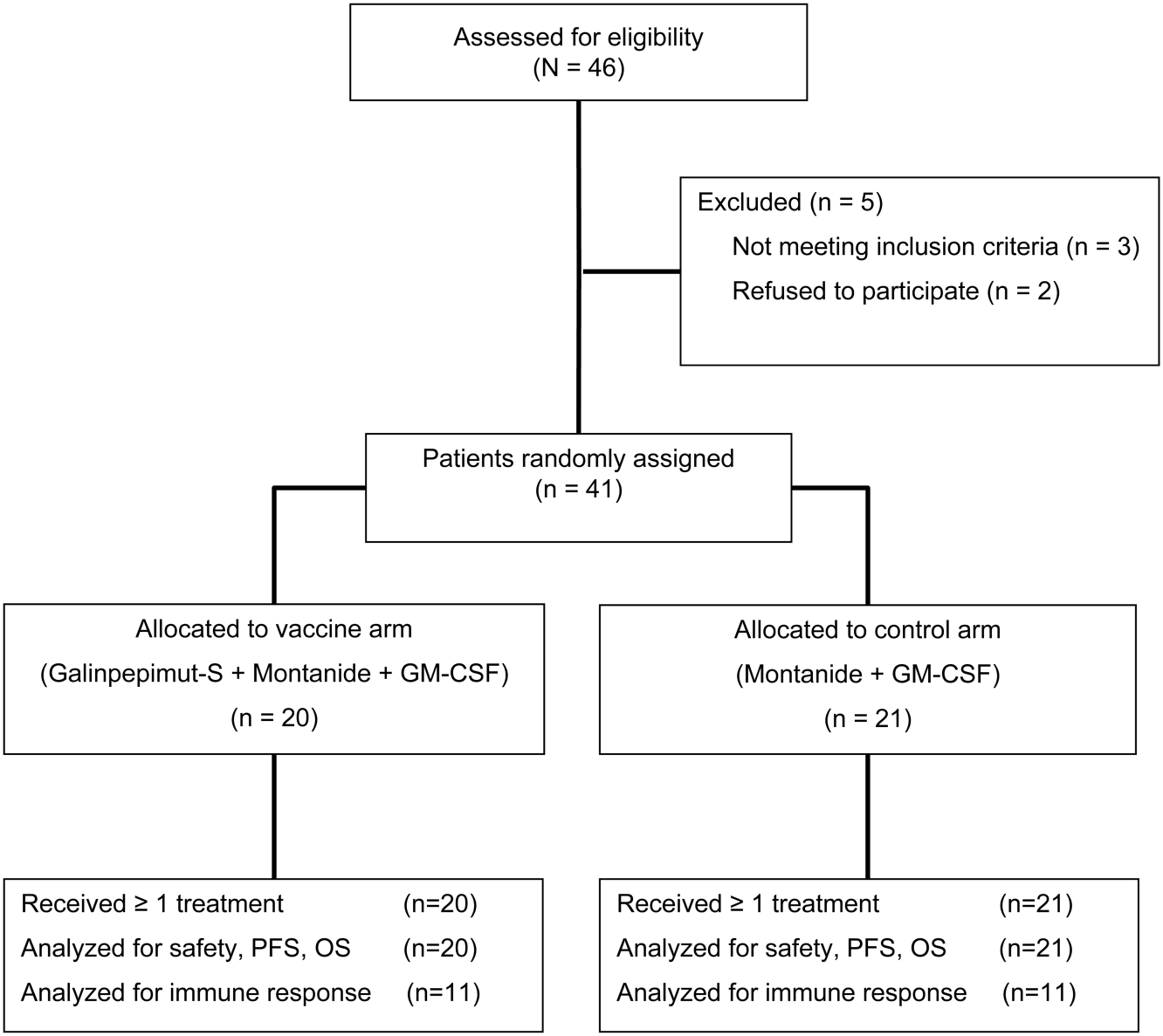

Figure 1. Consort Diagram of the Phase II Randomized Study
Disposition of consented patients.

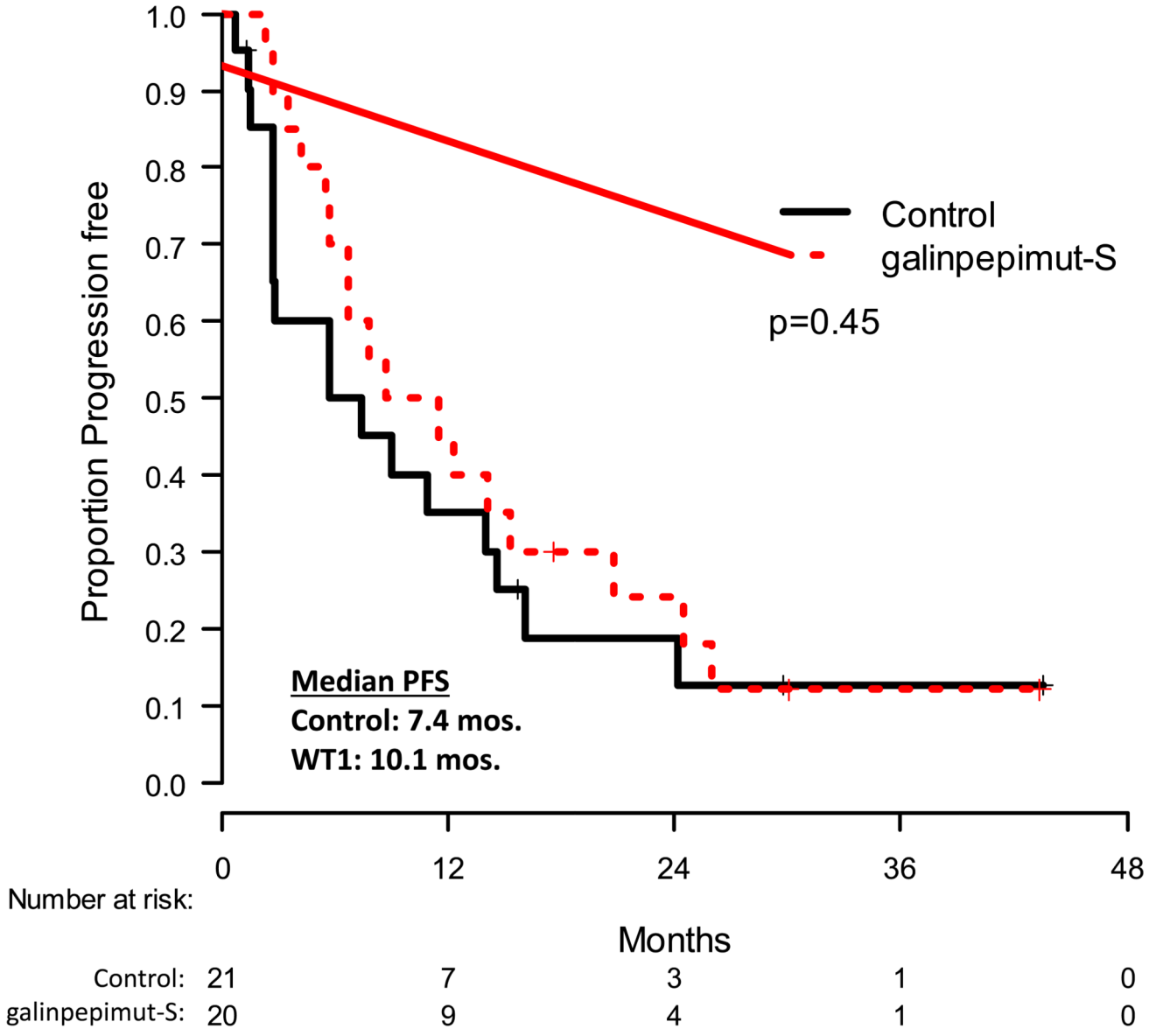

Figure 2. Progression-Free Survival

Kaplan-Meier plot of progression-free survival by treatment arm calculated from the time of randomization to progression, death, or censor date.

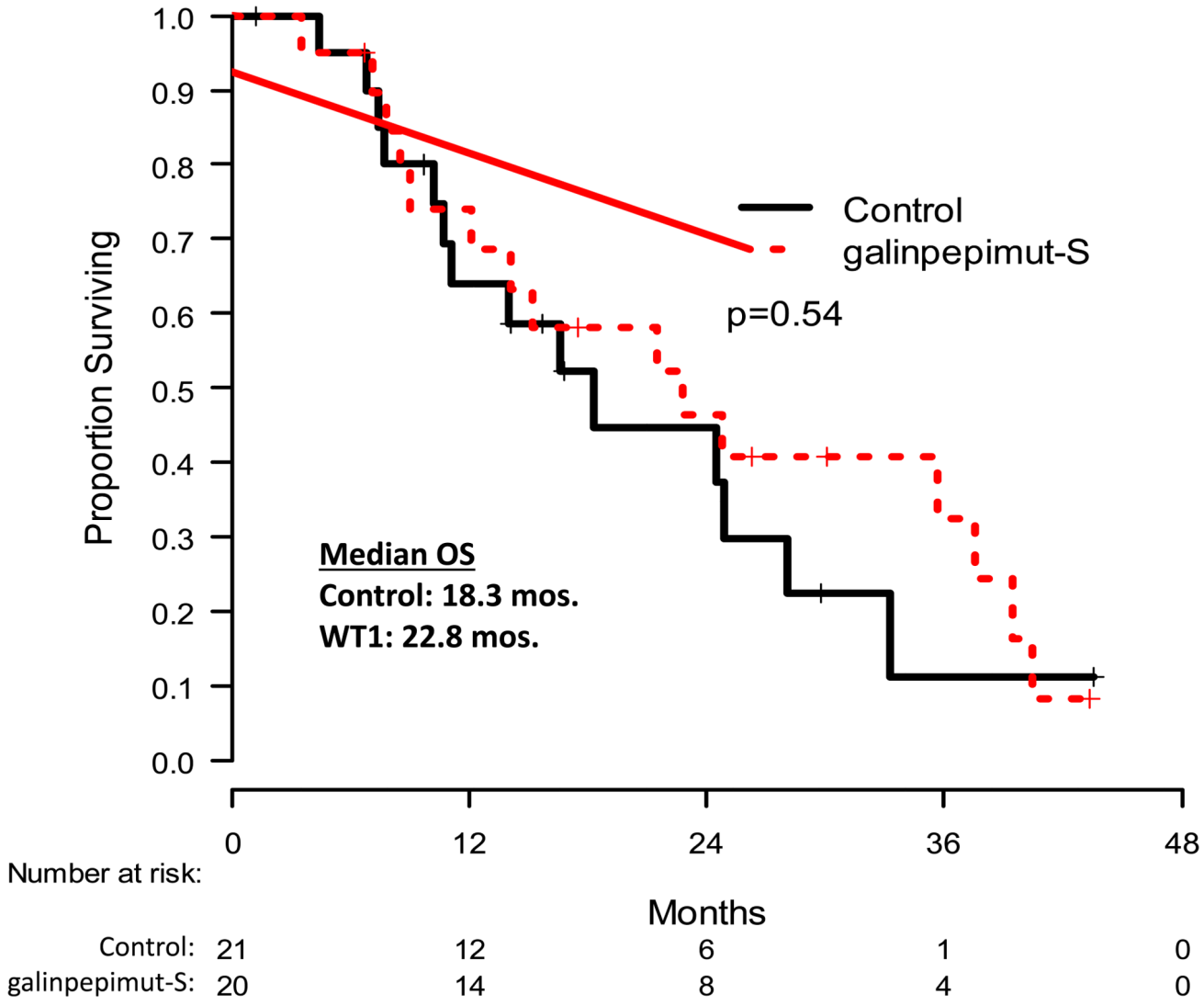

Figure 3. Overall Survival

Kaplan-Meier plot of overall survival by treatment arm calculated from the time of randomization to progression, death, or censor date.

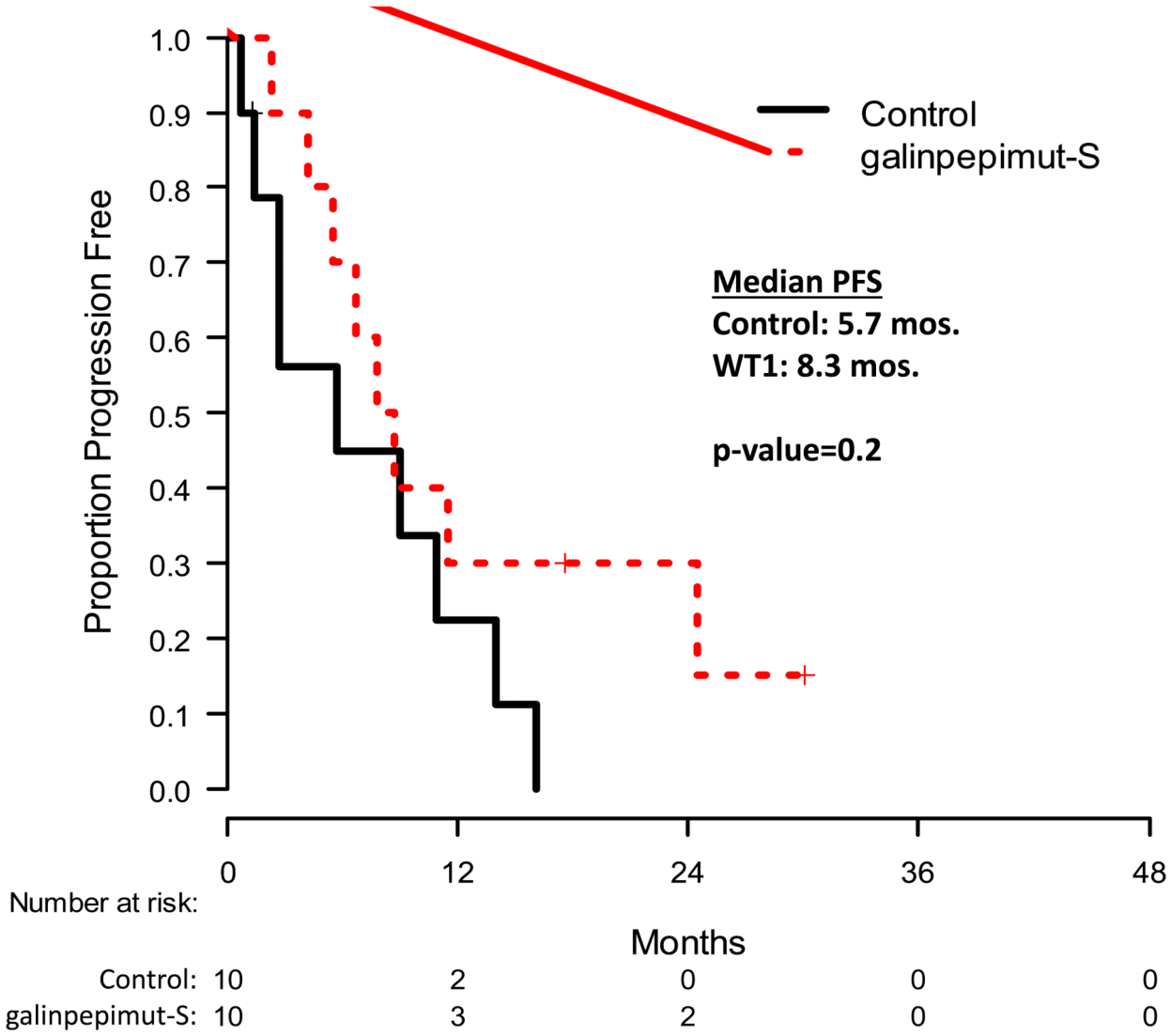

Figure 4A. Progression-free survival among patients with macroscopic complete resection

Kaplan-Meier plot of progression-free survival by treatment arm among patients with macroscopic complete resections calculated from the time of randomization to progression, death, or censor date.

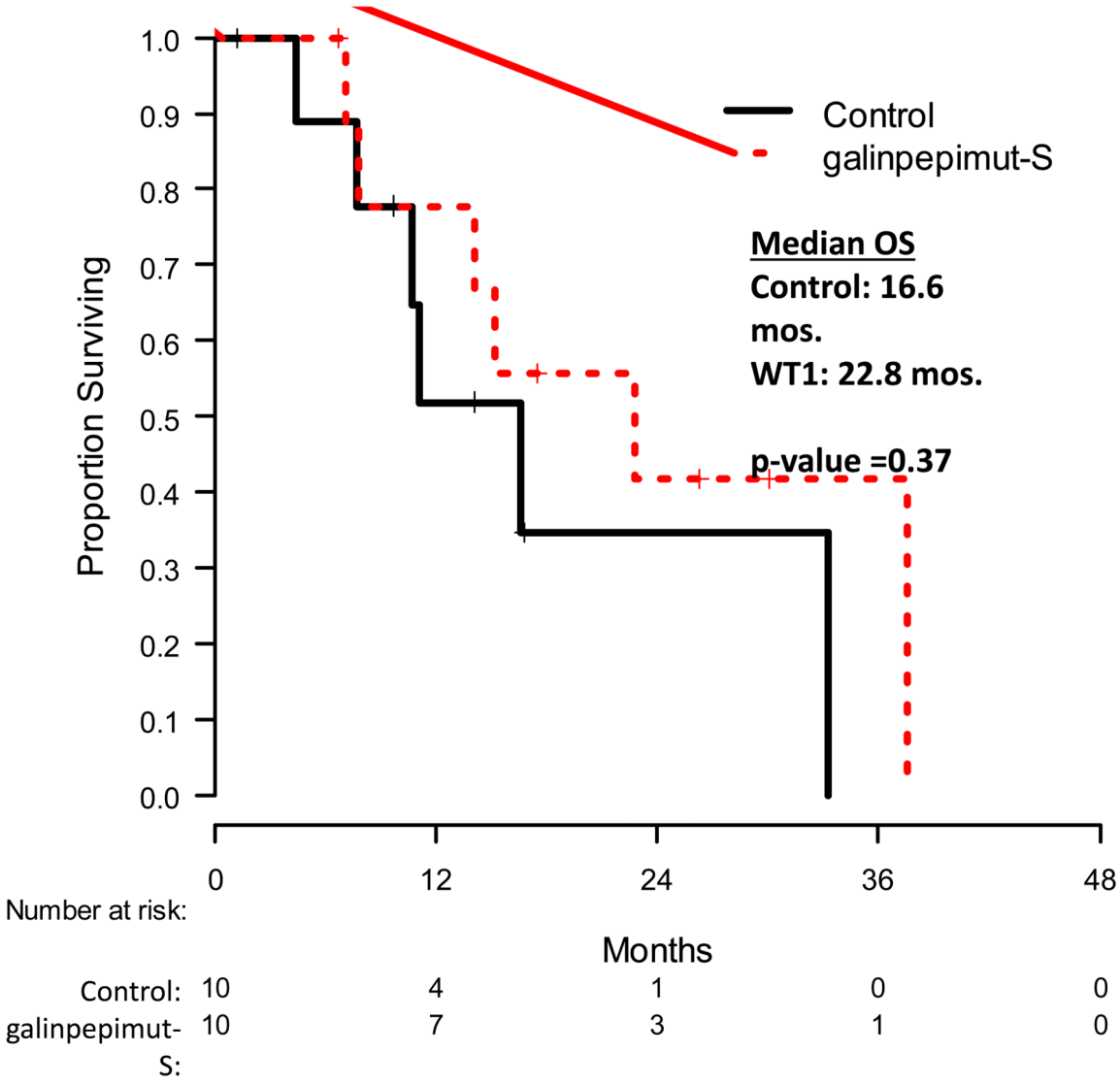

Figure 4B. Overall survival among patients with macroscopic complete resection

Kaplan-Meier plot of overall survival by treatment arm among patients with macroscopic complete resections calculated from the time of randomization to progression, death, or censor date.

Table 1

Patient, Disease, and Prior Treatment Characteristics

	All (N=41)		Galinpepimut-S (N=20)		Control (N=21)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
Age, years **Median (range)**	68 (34-84)		70 (34-84)		67 (48-79)	
Gender						
Male	35	85	17	85	18	86
Female	6	15	3	15	3	14
KPS at enrollment						
70%	4	10	1	5	3	14
80%	19	46	7	35	12	57
90%	17	41	11	55	6	29
100%	1	2	1	5	0	0
Smoking status						
Former	25	61	12	60	13	62
Current	0	0	0	0	0	0
Never	16	39	8	40	8	38
Histology						
Epithelioid	39	95	18	90	21	100
Mixed	2	5	2	10	0	0
Sarcomatoid	0	0	0	0	0	0
Surgery						
EPP	3	7	1	5	2	10
EPD	6	15	3	15	3	14
P/D	14	34	7	35	7	33
Partial PD	18	44	9	45	9	43

	All (N=41)		Galinpepimut-S (N=20)		Control (N=21)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
MCR						
Yes	20	49	10	50	10	48
No	21	51	10	50	11	52
Chemotherapy						
Pem/platinum	40	98	19	95	21	100
Other	0	0	0	0	0	0
None	1	2	1	5	0	0
Radiation						
Pleural IMRT	31	76	14	70	17	81
Other	3	7	2	10	1	5
None	7	17	4	20	3	14

KPS = Karnofsky performance status; EPP = extrapleural pneumonectomy; EPD = extended pleurectomy decortication; P/D = pleurectomy decortication (removal of all gross tumor with a parietal and visceral pleurectomy but without diaphragmatic or pericardial resection); partial PD = partial pleurectomy decortication (partial removal of parietal and/or visceral and/or cases with residual gross tumor)

Table 2

Treatment-Related Adverse Events

Event	Galinpepimut-S (N=20)		Control (N=21)	
	Any grade (%)	≥grade 3 (%)	Any grade (%)	≥grade 3 (%)
Injection site reaction	17 (85)	0 (0)	9 (43)	0 (0)
Fatigue	10 (50)	0 (0)	10 (48)	0 (0)
Fever	0 (0)	0 (0)	4 (19)	0 (0)
Arthralgias	0 (0)	0 (0)	2 (10)	0 (0)
Nausea	2 (10)	0 (0)	0 (0)	0 (0)
Rash, maculopapular	1 (5)	0 (0)	1 (5)	0 (0)
Lymphopenia	1 (5)	1 (5)	1 (5)	1 (5)

Table 3

Immune Response Data

	Vaccine N=10 (%)	Control N=12 (%)
CD4 ELISPOT		
***Positive**	4 (40)	1 (8)
***Negative**	4 (40)	8 (67)
***Not tested**	2 (20)	3 (25)
CD8 ELISPOT		
***Positive**	1 (10)	1 (8)
***Negative**	1 (10)	3 (25)
***Not tested**	8 (80)	8 (67)
Tetramer assay		
***Positive**	1 (10)	2 (17)
***Negative**	0 (0)	3 (25)
***Not tested**	9 (90)	7 (58)