Melacine® Vaccine Briefing Document

February 27, 2002

Table of Contents

List of Tables

List of Figures

List of Appendices

1. INTRODUCTION

Greater than 30% of patients with intermediate-thickness, node-negative malignant melanoma will relapse within 5 years. As yet there is no approved adjuvant therapy for these patients. The Southwest Oncology Group conducted a randomized Phase 3 trial (SWOG-9035) of Melacine® vaccine (a vaccine composed of lysate from two melanoma cell lines plus adjuvant) versus observation in patients with Stage II melanoma, designated as intermediate-thickness (1.5 to 4.0 mm or Clark's level IV if thickness unknown), clinically or pathologically node-negative melanoma (T3N0M0).

SWOG-9035 accrued 689 patients over 4½ years. This represents one of the largest randomized, controlled trials of adjuvant vaccine therapy in human cancer reported to date. Intent-to-treat analysis showed a benefit in prolonging relapse-free survival time, although the difference was not statistically significant. However, there was a highly significant benefit for adjuvant vaccine therapy in patients who expressed HLA-A2 and/or HLA-C3 genes. The significant benefit included not only relapse-free survival ($p=0.005$) but also overall survival ($p=0.003$). Of note, expression of either HLA-A2 or HLA-C3 in the absence of vaccine was of no clinical benefit, indicating that simple expression of particular HLA molecules is not a prognostic factor for positive outcome in this group of patients. HLA genes, often called immune response genes, are known to be responsible for many of the differences observed in immune responses between individuals. The results are particularly intriguing in regard to entering the post-genomic era where responses to therapies can be tailored to the patient's genetic capabilities to respond to such treatments.

In discussions with FDA, market approval for Melacine vaccine as adjunctive immunotherapy in patients with Stage II melanoma and who express HLA-A2 and/or HLA-C3 genes will require another Phase 3 study. Since Accelerated Approval is not an option and a second Phase 3 trial will require approximately eight years to complete, Corixa would like to address key issues regarding the patient population and to assure adequacy of the trial to fulfill regulatory approval. Corixa has proposed a second randomized Phase 3 pivotal trial of Melacine vaccine versus observation designed to reproduce the SWOG-9035 trial in patients expressing HLA-A2 and/or HLA-C3. However, since SWOG-9035 was initiated in 1992, there have been three pertinent changes in standard practice that confound attempts to precisely repeat SWOG-9035, including (1) the approval and demonstrated efficacy of Interferon alfa-2b in "high-risk" adjuvant patients, (2) a new AJCC Staging System with a different categorization of risk factors, and (3) the common use of sentinel node biopsies.

The purpose of this document is to summarize and discuss:

- Overview of Melacine vaccine and clinical studies
- The results of SWOG-9035
- Issues for further development of Melacine vaccine as adjuvant therapy for Stage II melanoma
- A proposed second randomized pivotal trial of Melacine vaccine as adjuvant therapy for Stage II melanoma
- Issues for ODAC and the FDA

2. OVERVIEW OF MELACINE VACCINE AND CLINICAL STUDIES

Melacine vaccine (referred to in this document as "Melacine" or "the vaccine") is a melanoma cell line–derived vaccine for the immunotherapy of melanoma. The vaccine consists of two components: Melanoma Lysate and Detox™. Melanoma Lysate is a homogenate prepared from two allogeneic human melanoma cell lines (Mel-D and Mel-S). This lysate contains multiple melanoma-associated antigens, including tyrosinase, gp100, Melan-A/MART-1, TRP-1, S-100, GD2, GD3, MAGE-1, -2, and -3, and HMW-MAA. Detox is a vaccine adjuvant containing: (1) monophosphoryl lipid A (MPL), an attenuated endotoxin product derived from *Salmonella minnesota;* and (2) cell wall skeleton, a complex heteropolymer isolated from *Mycobacterium phlei*. The combination of MPL and cell wall skeleton is designed to enhance the immune response to antigens present in Melanoma Lysate.

Phase 1 and 2 investigator-sponsored clinical trials of the vaccine in patients with Stage IV melanoma began in 1985 (see Appendix 1 for a summary of the clinical/regulatory history of Melacine). In 1988 the company filed an IND and began a series of uncontrolled Phase 2 and controlled Phase 3 trials of the vaccine primarily in Stage IV melanoma. Approximately 300 patients with melanoma were treated with the vaccine in these studies. Analysis of efficacy showed that a few patients treated with the vaccine achieved an objective response (complete or partial response) with long-term survival. Objective response rates ranged from 6% to 17%. Overall, the vaccine was well tolerated. The most frequently reported adverse events were flu-like symptoms (asthenia, pain, myalgia, and fever) and application site disorders (injection site pain and granulomas at the injection site). Results of these trials are summarized in Appendix 2. Based on the composite results of these trials, Melacine was approved in early 2000 in Canada for the immunotherapy of disseminated melanoma.

In 1992, clinical development of the vaccine as adjuvant immunotherapy in earlier-stage patients was initiated. The premise was that a vaccine that showed some efficacy in patients with advanced disease would be substantially more effective in patients with minimal residual disease. The Southwest Oncology Group (SWOG) conducted a randomized Phase 3 trial (SWOG-9035) of the vaccine versus observation following surgical resection in patients with Stage II melanoma, designated at that time as intermediate-thickness (1.5 to 4.0 mm or Clark's level IV if thickness unknown),

clinically or pathologically node-negative melanoma. The vaccine was administered over a two-year period. A total of 689 patients were enrolled in the study between April 1992 and November 1996.

Beginning in 1994, the SWOG-9035 protocol was amended to include HLA class I (HLA-A, HLA-B and HLA-C) serologic typing. Serologic typing was performed on the majority of patients (553 of 689) in the SWOG-9035 trial, either prospectively for patients enrolled after the amendment or retrospectively. The data were collected to test the hypothesis that response to the vaccine was related to expression of particular HLA molecules. A previous retrospective analysis of clinical responses of patients receiving this same vaccine for metastatic melanoma had found an association between certain HLA phenotypes (HLA-A2, -A28, -B44, -B45, and -C3) and clinical responses [1]. This association was especially strong for patients expressing two or three of the HLA alleles. Based upon these preliminary findings in advanced disease, it was considered to be of great interest to examine the relationship of HLA phenotypes to outcome in patients who have localized disease, a circumstance in which T-cell responses might be more effective at controlling the disease.

In the intent-to-treat analysis of all 689 patients conducted by SWOG, relapse-free survival was significantly greater for patients treated with the vaccine rather than observation (hazard ratio = 0.76, p=0.040 [Cox model], adjusted for stratification factors of gender, prior lymph node staging and primary tumor thickness; see Table 2). HLA typing was conducted for 553 (80%) of the 689 enrolled patients. The results showed that expression of two or more of the five HLA antigens originally identified by Mitchell (HLA-A2, -A28, -B44, -B45, and -C3) was associated with superior outcome. Additional analyses indicated that the major component of this effect was contributed by expression of HLA-A2 and HLA-C3. Among the 323 patients who expressed HLA-A2 and/or HLA-C3, 5-year relapse-free survival was 77% for the vaccine patients (n=178) and 64% for the observation patients (n=145, p=0.004) [2]. Of note, expression of either HLA-A2 or HLA-C3 in the absence of the vaccine was of no clinical benefit to patients, indicating that simple expression of these particular HLA genes is not a prognostic factor for positive outcome in this group of patients.

On September 19, 2000, Corixa Corporation met with the FDA to discuss the results of clinical trials with the vaccine, including the results of SWOG-9035. At that meeting, the concept of gathering an additional year's worth of data (a data sweep) was discussed. The sweep was conducted by SWOG between November 2000 and April 2001. Corixa's analyses of the 689 intent-to-treat patients in the updated database indicated that the vaccine continued to show a benefit in prolonging relapse-free survival, although the difference was no longer statistically significant. However, there remained a highly significant benefit of adjuvant therapy with the vaccine in patients who expressed HLA-A2 and/or HLA-C3. The significant benefit included not only relapse-free survival (p=0.005) but also overall survival (p=0.003).

Corixa remains interested in pursuing Melacine for market approval as adjunctive immunotherapy in patients with Stage II melanoma following surgical excision of the primary tumor. Toward that end, Corixa has had discussions with the FDA regarding

market approval for Melacine, including possible Accelerated Approval for patients with Stage II melanoma who express HLA-A2 or HLA-C3. The FDA's position remains that because the results of SWOG-9035 were robust only for the subpopulation of patients expressing HLA-A2 or HLA-C3, Accelerated Approval was deemed not an option for regulatory approval and a second pivotal trial would be required. The FDA agreed that the SWOG-9035 results would be reviewed as supportive data for approval if a second pivotal trial confirmed the significant benefit ($p<0.05$). Corixa has proposed a second randomized Phase 3 pivotal trial of the vaccine versus observation designed to reproduce the SWOG-9035 trial in patients expressing HLA-A2 and/or HLA-C3 genes.

3. RESULTS OF SWOG-9035: RANDOMIZED TRIAL OF ADJUVANT IMMUNOTHERAPY WITH MELACINE FOR PATIENTS WITH INTERMEDIATE THICKNESS, NODE-NEGATIVE MALIGNANT MELANOMA (T3N0M0)

The primary efficacy and safety data in support of the vaccine in HLA-A2 and HLA-C3 positive patients with Stage II melanoma are from the results of SWOG-9035. The study coordinators are Vernon K. Sondak, M.D. (Surgery), Jeffrey A. Sosman, M.D. (HLA Phenotyping), Raymond A. Kempf, M.D. (Medical Oncology), Ralph J. Tuthill (Pathology), and P.Y. Liu, Ph.D. (Biostatistics).

3.1 Study Design

The trial was a multi-center, open-label, randomized and controlled Phase 3 study conducted by SWOG under BB-IND 2885 held by Corixa Corporation that enrolled patients over a period of 4.5 years beginning in 1992.

The objectives of the trial were:

1) To compare disease-free survival and overall survival between patients with T3N0M0 malignant melanoma who receive adjuvant immunotherapy with an allogeneic melanoma vaccine versus no adjuvant treatment.

2) To evaluate the toxicity of adjuvant immunotherapy with an allogeneic melanoma vaccine in patients with T3N0M0 malignant melanoma.

3) To explore the interaction between the patients' defined HLA types (i.e., whether they are compatible with the HLA phenotypes of the vaccine) and the vaccine treatment effectiveness in terms of disease-free survival and overall survival.

The final objective (3) was added by a protocol amendment in September 1994.

Patients were eligible for enrollment if they were 18 years of age or older and had a completely resected clinical or pathologic T3N0M0 primary cutaneous malignant melanoma. T3 melanoma was defined as "tumor more than 1.5 mm but not more

than 4 mm in thickness and/or invades the reticular dermis (Clark's level IV – when Breslow's depth is unknown)." This corresponds to Stage IIA in the AJCC melanoma staging system in use at the time of the study (see Appendix 3 for AJCC Staging Systems). For the purposes of the study, the thickness of the tumor as measured by the method of Breslow was used to determine eligibility. In cases where thickness was unavailable for technical reasons (e.g., primary tumor not sectioned properly), patients with tumors invading into Clark's level IV were eligible for inclusion.

Performance of a regional lymph node dissection was not required for eligibility. However, all patients must have been clinically free of nodal and distant metastatic disease (N0M0) and pathologically free of nodal disease if a node dissection had been performed.

Patients had to have clinically negative regional nodes, no evidence of metastatic disease by physical examination and have been registered within 56 days of the last surgery for treatment of melanoma. Patients were required to have a Zubrod Performance Status of 0 or 1, WBC ≥ 3,000/μL, platelets ≥ 100,000/μL, creatinine and bilirubin ≤ 2x upper limit of normal, ALT and AST ≤ 3x upper limit of normal, and normal alkaline phosphatase.

Exclusion criteria included myocardial infarction within the previous year, NYHA Class III or IV heart disease, pregnancy or lactation, or any non-surgical therapy directed against their melanoma. Patients with prior malignancy were eligible only if the prior malignancy had been basal or squamous cell carcinoma of the skin, *in situ* cervical cancer, or any cancer for which the patient had been continuously disease-free for at least five years.

Data from all patients enrolled in the trial underwent retrospective, centralized pathology and surgical review to confirm patient eligibility. Patients were stratified based on gender, prior lymph node dissection/staging (no versus yes), and primary tumor thickness (T3a [1.5–3.0 mm] versus T3b [3.01–4.00 mm] versus Clark's level IV [Breslow's thickness unknown]).

Patients were then randomized to treatment with the vaccine or to observation only as the control. Patients randomized to vaccine received one dose intramuscularly (1.25 mL) as a divided dose during Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24, followed by a three-week rest period. This cycle was to be given four times for a total of 40 doses over 105 weeks.

All patients, including those assigned to observation control, were evaluated for disease relapse at Weeks 12, 24, 39, 51, 66, 78, 93, and 105 during the first two years, every four months for the next three years, and then annually until death.

The sample size and timing for final analysis were based on experience from previous studies. The medians for disease-free survival and overall survival for the control arm were estimated to be 4.4 and 7.8 years, respectively. Thus, the study was

planned to enroll approximately 600 eligible patients over four-and-a-half years. With two additional years of follow-up after the completion of enrollment, assuming uniform patient entry, exponential distribution and a two-sided log rank test at the 0.05 significance level, the power to detect a 50% increase in median disease-free survival was approximately 0.87. With two more years of follow-up (i.e., four years after completion of enrollment), the power to detect a 50% increase in median overall survival was approximately 0.82 with a two-sided 0.05 level test. Final analyses for disease-free survival and overall survival were to be determined by the SWOG Statistical Center when a specified number of events had occurred. An event was defined as death (all causes of mortality) or recurrence of melanoma.

3.2 Results

3.2.1 Patient Disposition

Six hundred eighty-nine patients (346 treated with the vaccine; 343 as observation controls) were enrolled in the trial between April 1992 and November 1996. All patients enrolled were treated on protocol based on their original entry pathology regardless of the retrospective centralized pathology and surgical review. Six patients randomized to the vaccine group did not receive vaccine. Seven patients randomized to the observation group refused their assignment and received other treatments. These 13 patients remain in the intent-to-treat (ITT) population as randomized to their respective treatment arms.

HLA typing was performed on 553 (80%) of the 689 ITT patients (294 vaccine, 259 observation). Patients were typed prospectively (n=383) on study entry from September 1994 onward, and retrospectively (n=170) for patients entered prior to that date.

Standard procedure at SWOG is to first perform statistical analyses for the eligible patient population and then on the intent-to-treat population. Eighty-nine patients were excluded from the eligible patient population. The main reason for ineligibility (76 patients) was that the central pathology review indicated the primary lesion did not represent T3N0M0 cutaneous melanoma: the lesion was too thin (42 patients), too thick (23 patients), had satellitosis or lymph node metastases (5 patients), or other ineligible pathology (6 patients). Other reasons for ineligibility were inadequate surgery (10 patients) and abnormal alkaline phosphatase (3 patients), leaving 300 eligible patients in each arm.

3.2.2 Baseline Comparability

Demographic and disease characteristics are summarized for the two treatment arms in Table 1. The treatment arms were well balanced for all three stratification factors (gender, tumor thickness and lymph node staging) and comparable in terms of the percent of patients with ulceration present in the primary tumor.

There was a trend toward higher incidence of primary tumor on the extremities in the vaccine arm (51%) than the observation arm (43%, p=0.063).

Table 1: Demographic and Disease Characteristics: ITT Population

Variable	Vaccine (n=346)	Observation (n=343)	p-value
Age			
Mean ± SEM	52.2 ± 0.74	52.6 ± 0.74	0.706
Min, Max	18, 85	20, 84	
Tumor Thickness			
T3A, 1.50 – 3.00	263 (76%)	264 (77%)	0.821
T3B, 3.01 – 4.00	69 (20%)	63 (18%)	
Clark Level IV, Breslow Depth Unknown	14 (4%)	16 (5%)	
Lymph Node Staging			
No	261 (75%)	264 (77%)	0.636
Yes	85 (25%)	79 (23%)	
Gender			
Female	137 (40%)	147 (43%)	0.384
Male	209 (60%)	196 (57%)	
Ulceration			
No	225 (65%)	203 (59%)	0.306[a]
Yes	80 (23%)	87 (25%)	
Unknown	41 (12%)	53 (15%)	
Primary Disease Site			
Extremity	177 (51%)	148 (43%)	0.063[a]
Non-extremity	167 (48%)	186 (54%)	
Unknown	2 (<1%)	9 (3%)	

[a] Missing data (i.e., "Unknown" category) excluded from analysis.

3.2.3 Summary of Relapse-Free Survival Analyses Performed by SWOG

As of February 2000, SWOG performed the primary analysis for the disease-free survival endpoint. At the data cutoff, 228 relapses or deaths had occurred. At that time, the median follow-up for all patients was 4.1 years and the minimum time since registration was 3 years.

In the ITT population, all three stratification factors (tumor thickness, gender and lymph node staging) had a significant effect on disease-free survival. When the three stratification factors plus treatment were analyzed using a Cox proportional hazards regression model, relapse-free survival was significantly greater for the

vaccine arm than for the observation arm (hazard ratio = 0.76, 95% C.I. = 0.59–0.99, p=0.040 [Cox model], adjusted for stratification factors). The relapse-free survival results are presented for the ITT population in Table 2 and Figure 1.

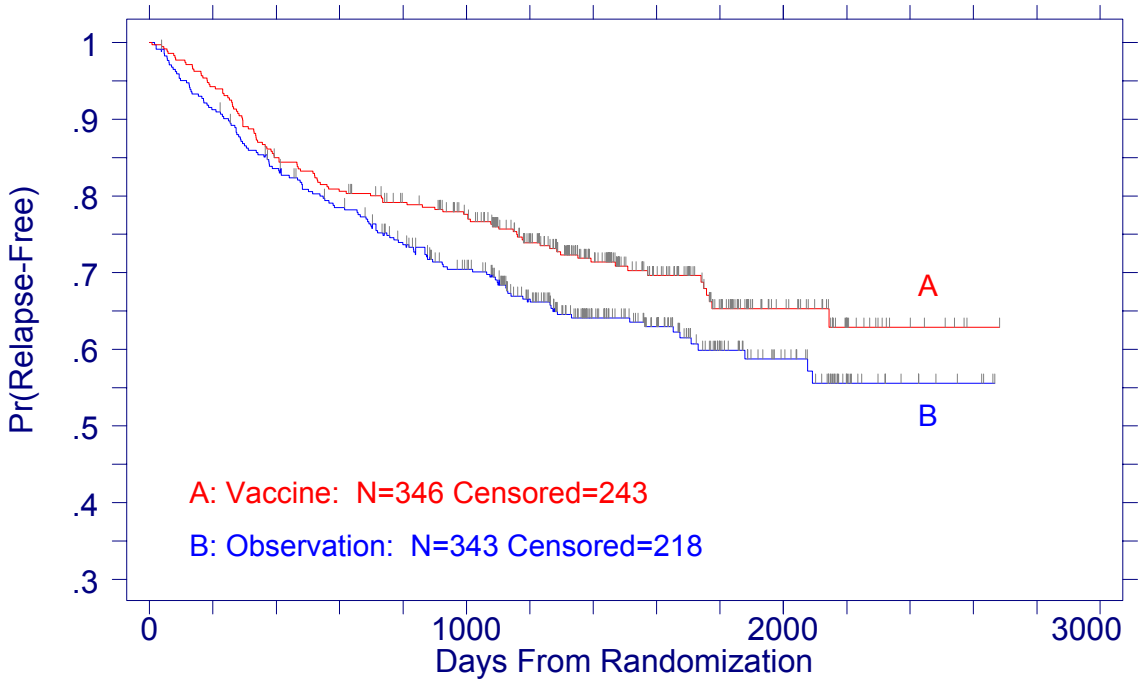
Table 2: Treatment Comparison for Relapse-Free Survival, Adjusting for Stratification Factors: N=689 ITT Patients, February 2000 Database

All Randomized Patients (n=689)[a]			
	Hazard Ratio	**95% C.I.**	**p-value**
Vaccine vs. Observation	0.76	0.59–0.99	0.040
Female vs. Male	0.58	0.45–0.77	0.0001
Tumor Thickness: ≤ 3 vs. > 3 mm[b]	0.61	0.45–0.82	0.001
Lymph Node Staging: Yes vs. No	0.67	0.48–0.94	0.019

[a] For patients who have not relapsed or died, relapse-free survival time was censored and calculated as the date of last contact minus the date of randomization.

[b] The stratum of Clark IV (thickness unknown) patients was pooled with the stratum defined by thickness ≤ 3 mm for the analysis of thickness since the centralized pathology review determined that over half of the patients actually had measurable lesions which were less than 3 mm in thickness.

Figure 1: Relapse-Free Survival by Treatment Arm: N= 689 ITT Patients, February 2000 Database



Analyses were also performed by SWOG for the eligible patient population. In the February 2000 database there were 95 (32%) patients with relapse or death among the 300 eligible patients randomized to treatment with the vaccine compared to 106 (35%) patients with relapse or death among the 300 eligible patients randomized to the observation control. After adjusting for the stratification factors (tumor thickness, gender, and lymph node staging), the effect of treatment on disease-free survival was not significant (p=0.30) for the eligible patient population. The four-year estimated disease-free survival rate was 69% for vaccine patients versus 64% for observation patients.

SWOG performed analyses to examine the importance of five specific class I antigens that had been demonstrated to be related to patients' responses to the vaccine: HLA-A2, -A28, -B44, -B45, and -C3 [1]. The SWOG analyses focused on the relationship between relapse-free survival and the number of those antigens expressed by patients. No patient in SWOG-9035 expressed more than three of the five antigens; therefore, SWOG analyses compared patients who expressed none or one, versus two or three of those five antigens. Results of the SWOG analyses were provided to FDA in September 2001. Selected analyses, adjusted for the stratification factors of gender, tumor thickness, and lymph node staging, are summarized in Table 3.

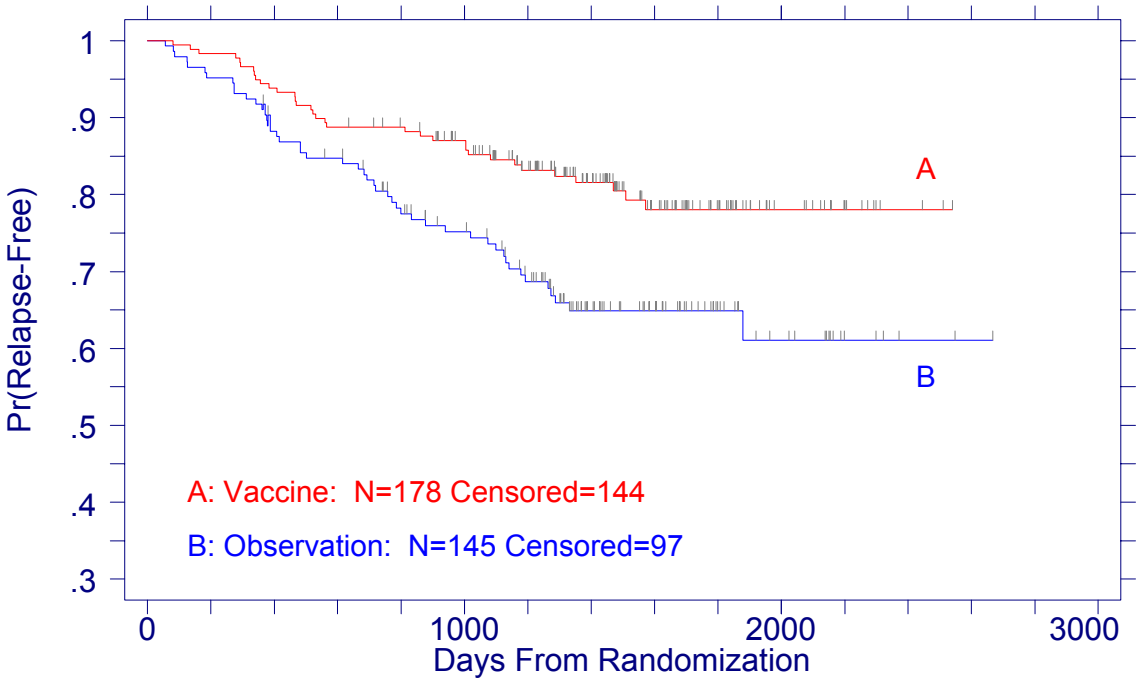
Table 3: Relationship of HLA Results and Relapse-Free Survival, February 2000 Database

Subgroup[a]	Comparison[b]	Hazard Ratio	95% C.I.	p-value
0–1 match[a] (n=402)	Vaccine (n=213) vs. Observation (n=189)	0.84	0.59–1.20	0.343
2–3 matches[a] (n=151)	Vaccine (n=81) vs. Observation (n=70)	0.25	0.12–0.51	0.0002
Vaccine patients (n=294)	2–3 matches (n=81) vs. 0–1 match (n=213)	0.39	0.20–0.75	0.004

[a] Number of matches based on specific class I antigens that had been demonstrated by Mitchell et al. [1] to be related to patients' responses to the vaccine: HLA-A2, -A28, -B44, -B45, and -C3.
[b] Comparisons include adjustment for gender, tumor thickness, and lymph node staging.

Among the 151 study patients expressing two or three antigens, the 81 vaccine-treated patients had a highly significant improvement in disease-free survival compared to the 70 observation patients. Additional analyses performed by SWOG and confirmed by Corixa indicated that the major components of this effect were contributed by two of the five class I major histocompatibility complex (MHC) molecules: HLA-A2 and HLA-C3. The relapse-free survival results are presented in Figure 2 for the 323 patients in the ITT population who expressed HLA-A2 and/or HLA-C3.

**Figure 2: Relapse-Free Survival by Treatment Arm:
N= 323 HLA-A2 and/or HLA-C3 Positive Patients, February 2000 Database**

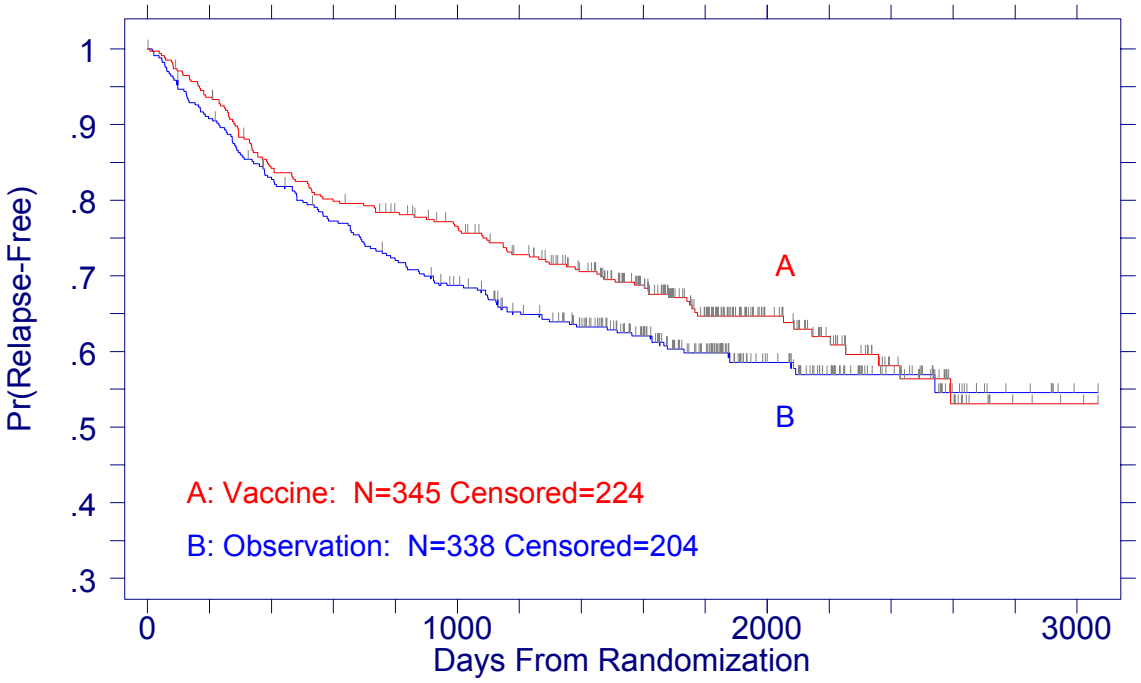


3.2.4 Relapse-Free Survival: Summary of Follow-up Analyses, May 2001: Performed by Corixa

An updated data sweep, as discussed with the FDA, was conducted by SWOG between November 2000 and April 2001, and the updated database was provided to Corixa Corporation in May 2001. Follow-up analyses of disease-free survival performed by Corixa were based on the time from date of randomization to the date of last disease assessment in the May 2001 database (rather than date of last contact as used by SWOG). Using last disease assessment date, relapse-free survival time was calculated for 683 of the 689 patients in the ITT population. Six patients (1 vaccine, 5 observation) did not have a disease assessment done after randomization and had missing relapse-free survival times. Thus, they are excluded from the analyses reported here.

In the follow-up analysis, 27 additional events were noted (18 in the vaccine arm and 9 in the observation arm). The relapse-free survival was greater for the vaccine arm than for the observation arm, but the difference was not statistically significant (hazard ratio = 0.83, 95% C.I. = 0.65–1.06, p=0.141 [Cox model], adjusted for stratification factors). The relapse-free survival results are presented in Figure 3.

Figure 3: Relapse-Free Survival by Treatment Arm: N=683 ITT Patients, May 2001 Database



3.2.5 Update on Relapse-Free Survival: Patients With HLA Typing Data

Using the May 2001 database, Corixa performed independent analyses of the relationship between relapse-free survival time and patient strata defined by the HLA type. These analyses confirmed results by Sosman et al. [2] and also confirmed that two of the antigens (HLA-A2 and HLA-C3) identified by Mitchell et al. [1] continued to be of particular importance.

HLA-A2 was the most common of the five candidate antigens, expressed by 252 (46%) of the 553 patients with HLA typing results. HLA-C3 was second most common, expressed by 158 (29%) of the HLA-typed patients. HLA-A28, -B44, and -B45 were expressed by 9%, 25%, and 1% of patients, respectively. A total of 323 (58%) of the 553 HLA-typed patients expressed either HLA-A2, or HLA-C3, or both. Patients in that category will be denoted as A2C3+; patients who expressed neither HLA-A2 nor HLA-C3 antigens will be denoted as A2C3–.

Corixa analyzed relapse-free survival time by stratifying patients as A2C3+ or A2C3– within both treatment arms. Similar to the results reported by SWOG in their final analysis, the follow-up analyses using the May 2001 database confirmed that A2C3+ patients in the vaccine arm had improved relapse-free survival when compared to A2C3+ patients in the observation arm. Among the 323 A2C3+ patients, relapse-free survival was significantly longer for patients in

the vaccine arm than for observation patients (hazard ratio = 0.562; 95% C.I. = 0.376–0.838, p=0.005 [Cox model], adjusted for stratification factors). The relapse-free survival curves are presented in Figure 4.

Figure 4: Relapse-Free Survival by Treatment Arm:
N=323 HLA-A2 and/or HLA-C3 Positive Patients, May 2001 Database

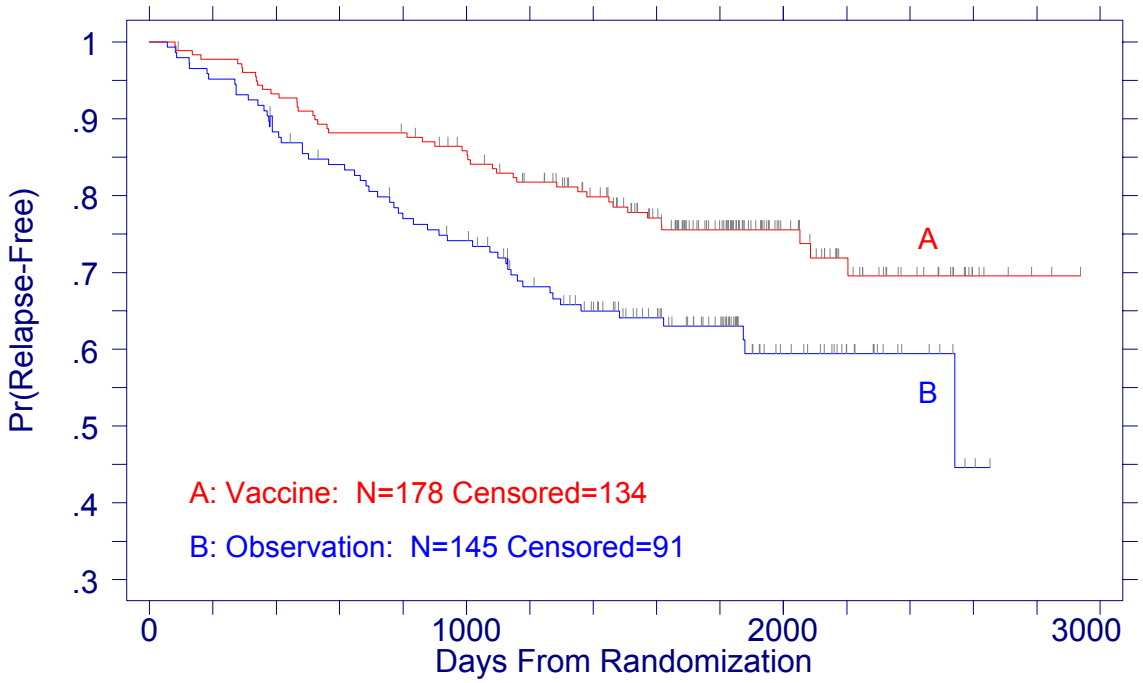


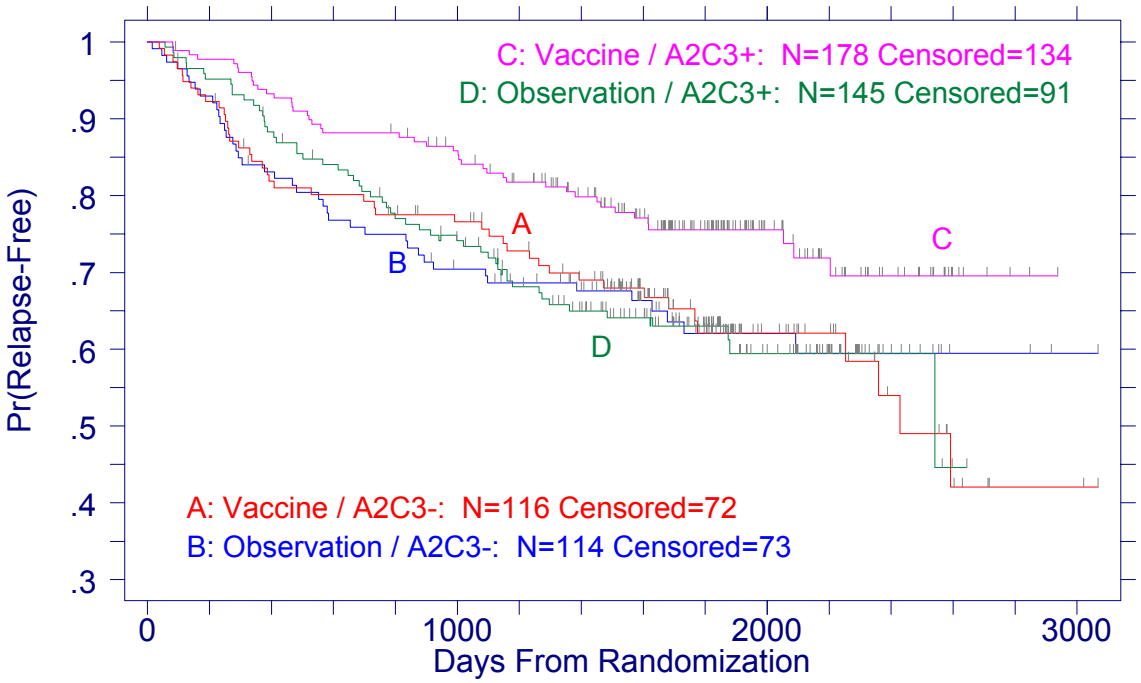
Table 4 summarizes the results of Cox model analyses of relapse-free survival for the 553 patients with HLA typing.

Table 4: Treatment Comparison for Relapse-Free Survival, Adjusting for Stratification Factors: N=553 Patients With HLA Typing, May 2001 Database

Subgroup	Comparison	Hazard Ratio	95% C.I.	p-value
Patients with HLA phenotyping	Vaccine (n=294) vs. Observation (n=259)	0.752	0.562-1.005	0.054
A2C3+ Patients	Vaccine (n=178) vs. Observation (n=145)	0.562	0.376–0.838	0.005
A2C3– Patients	Vaccine (n=116) vs. Observation (n=114)	1.065	0.694–1.634	0.773
Vaccine patients	A2C3+ (n=178) vs. A2C3– (n=116)	0.541	0.355–0.824	0.004
Observation patients	A2C3+ (n=145) vs. A2C3– (n=114)	1.010	0.672–1.517	0.963

Figure 5 shows relapse-free survival curves for the four groups of patients formed by combining treatment arm assignment with the A2C3 strata. Relapse-free survival was similar in the three groups of patients who either did not receive the vaccine or who were A2C3–, and visibly longer among A2C3+ patients in the vaccine arm. A2C3+ patients in the observation arm exhibited no greater relapse-free survival time than did patients lacking A2C3 expression, confirming that A2C3 expression alone is not associated with an improvement in relapse-free survival.

Figure 5: Relapse-Free Survival by Treatment Arm and A2C3 Status: N=553 Patients with HLA Typing, May 2001 Database



3.2.6 Preliminary Findings on Survival: Patients With HLA-A2 and/or HLA-C3 Phenotypes

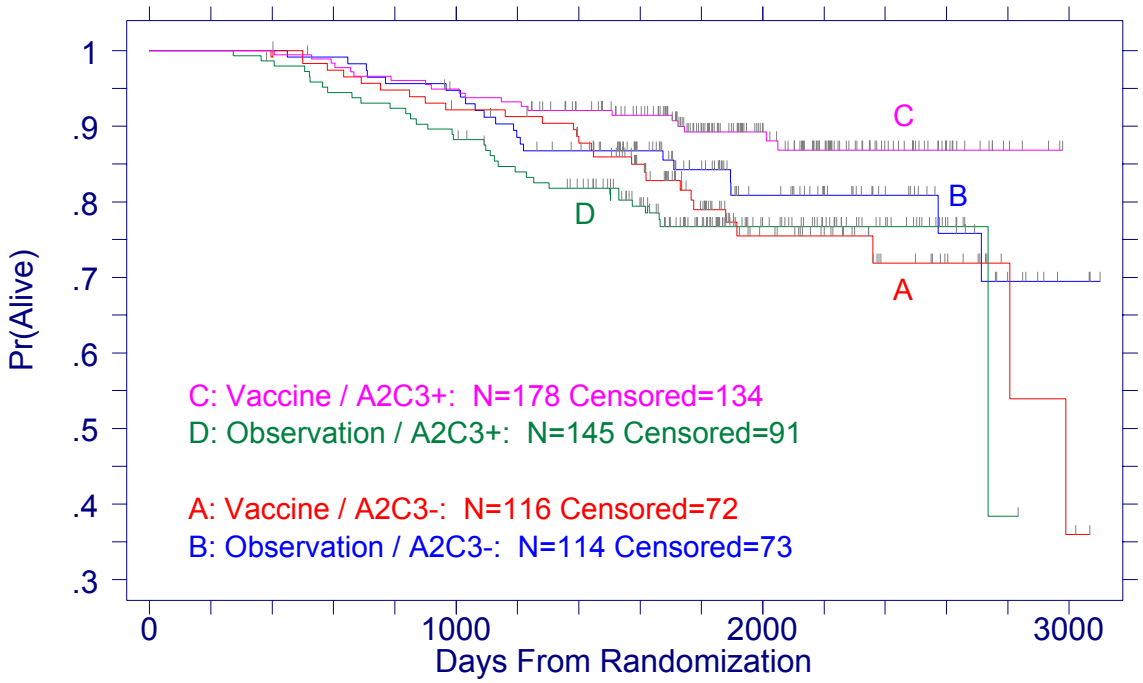
To confirm the importance of the finding for patients who have the HLA-A2 or HLA-C3 phenotypes, Corixa analyzed the overall survival time for these patients. Table 5 and Figure 6 summarize results of Cox model analyses for overall survival for the 553 HLA-typed patients, stratifying patients in terms of their A2C3 status within both treatment arms.

Table 5: Treatment Comparison for Overall Survival: Adjusting for Stratification Factors: N=553 Patients With HLA Typing, May 2001 Database

Subgroup	Comparison	Hazard Ratio	95% C.I.	p-value
Patients with HLA phenotyping	Vaccine (n=294) vs. Observation (n=259)	0.737	0.498–1.090	0.126
A2C3+ Patients	Vaccine (n=178) vs. Observation (n=145)	0.429	0.245–0.749	0.003
A2C3– Patients	Vaccine (n=116) vs. Observation (n=114)	1.360	0.766–2.417	0.294
Vaccine patients	A2C3+ (n=178) vs. A2C3– (n=116)	0.469	0.261–0.843	0.011
Observation patients	A2C3+ (n=145) vs. A2C3– (n=114)	1.402	0.805–2.443	0.233

A2C3+ patients in the vaccine arm had significantly longer overall survival times than A2C3+ patients in the observation arm (p=0.003; Cox model, adjusted for stratification factors).

Figure 6: Overall Survival by Treatment Arm and A2C3 Status: N=553 Patients with HLA Typing, May 2001 Database



In summary, Corixa's follow-up analysis of the HLA-typing results indicated a significant improvement in both relapse-free survival (p=0.005) and overall survival (p=0.003) among patients who expressed either HLA-A2 or HLA-C3 and who received the vaccine.

3.2.7 Safety

Adverse events were assessed for patients in the vaccine arm using the SWOG Toxicity Criteria. Adverse events were not recorded for the observation control patients. Investigators were instructed not to record symptoms that were "certainly or most likely due to disease or other non-treatment cause" on the adverse event case report form. Adverse events are summarized in this section for the 339 patients in the intent-to-treat population who received at least one dose of the vaccine.

At least one adverse event was reported by 325 of 339 patients (96%) who received at least one dose of the vaccine. The majority of patients treated with the vaccine experienced mild to moderate toxicity. There were 74 patients (23%) with maximum Grade 1 toxicity and 219 (65%) who experienced a maximum Grade 2 toxicity. Thirty-two patients (9%) experienced a maximum Grade 3 toxicity. The adverse events reported by three or more patients were severe local reactions (11 patients), and malaise/fatigue/lethargy, diarrhea, vision abnormalities, and fever in absence of infection (3 patients each). No patient experienced a Grade 4 (life-threatening) toxicity.

Adverse events that occurred in more than 15% of the population (in decreasing order of incidence) included local reactions (87%), granuloma (43%), abscess (38%), malaise/fatigue/lethargy (36%), fever in absence of infection (33%), myalgia/arthralgia (29%), chills (24%), pain (17%), nausea (16%), headache (16%), and erythema (15%).

3.3 Conclusions

The SWOG-9035 results are highly encouraging for patients with melanoma and for cancer vaccines in general. The results are particularly intriguing in regard to entering the post-genomic era where one of the outcomes of the genomic revolution is that patient responses to therapies can be tailored to the patient's genetic capabilities to respond to such treatments. Patient responses to the vaccine would appear to be linked to particular MHC genes, also called HLA in humans. MHC genes, often called immune response genes, are highly polymorphic from individual to individual and are known to be responsible for many of the differences observed in immune responses between individuals.

4. ISSUES FOR FURTHER DEVELOPMENT OF MELACINE AS ADJUVANT THERAPY FOR STAGE II MELANOMA

Since SWOG-9035 was initiated in 1992, there have been three pertinent changes in standard practice that confound attempts to precisely repeat SWOG-9035.

(1) Interferon alfa-2b (Intron® A) has been approved by the FDA as an adjuvant to surgical treatment in patients with melanoma who are free of disease but at high risk for systemic recurrence.

(2) A new American Joint Committee on Cancer (AJCC) Staging System for melanoma has been proposed and appears to be more relevant, both clinically and prognostically [4-5].

(3) The use of lymphatic mapping and sentinel lymph node biopsy mapping as a means to pathologically stage patients has become more widespread.

Thus, the approval and efficacy of Interferon alfa-2b, the new AJCC Staging System and sentinel node biopsies need to be taken into account in designing a second pivotal trial to confirm the results observed in the SWOG-9035 trial for approval of Melacine as adjuvant therapy for patients expressing HLA-A2 and/or HLA-C3.

4.1 Adjuvant Intron A

According to the package insert, "Intron A Interferon alfa-2b is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery."

The term "high risk" was not defined, but according to the package insert: "The safety and efficacy of Intron A Interferon alfa-2b, recombinant for Injection was evaluated as adjuvant to surgical treatment in patients with melanoma who were free of disease (post-surgery) but at high risk for systemic recurrence. These included patients with lesions of Breslow thickness > 4 mm, or patients with lesions of any Breslow thickness with primary or recurrent nodal involvement." [References 6 and 7 discuss adjuvant Intron A for melanoma.]

4.2 Changes in AJCC Staging System

The AJCC Staging System (edition 4) used for patient entry into SWOG-9035 is presented in Appendix 2. A new AJCC Staging System (edition 6) is currently being used [5] and will become official with the publication of the 6th Edition of the AJCC Staging Manual this year (2002). See Appendix 3 for both Staging Systems. The new AJCC Staging System (edition 6) will be used for patient entry into the proposed confirmatory trial.

The pertinent changes in the new AJCC Staging System (edition 6) are summarized below:

- Melanoma thickness and ulceration, but not level of invasion are to be used in the T category (except for T1 melanomas);
- The number of metastatic lymph nodes rather than their gross dimensions and the delineation of clinically occult (i.e., microscopic) versus clinically apparent (i.e., macroscopic) nodal metastases will be used in the N category;
- An upstaging of all patients with Stage I, II, and III disease when a primary melanoma is ulcerated;
- A new convention for defining clinical and pathologic staging so as to take into account the staging information gained from intraoperative lymphatic mapping and sentinel node biopsy.

4.3 Lymphatic Mapping and Sentinel Node Biopsy

Lymphatic mapping and sentinel node biopsy allows detection of microscopic nodal metastasis without the need for an extensive lymph node dissection. The use of sentinel node biopsy then divides the previous clinically staged lymph node negative patients into two categories: (1) pathologically staged lymph node negative and (2) pathologically staged lymph node positive patients. The pathologically staged lymph node positive patients can be subcategorized according to the number of lymph nodes positive and whether the nodes have microscopic or macroscopic disease.

4.4 Summary of Issues

Intron A was not an approved therapy at the time of initiation of SWOG-9035. Now Intron A has been approved for melanoma patients at "high risk for systemic recurrence." The product information is silent on the definition of "high risk of recurrence," but the general assumption is that Intron A has been approved for and is appropriate for patients with lesions > 4 mm without or with lymph node involvement. The corollary assumption is that Intron A has not been approved for patients with lesion of < 4 mm without lymph node involvement. It is not clear as to whether Intron A is appropriate for "low risk" and "intermediate risk" lesions. The terms "low risk" and "intermediate risk" are not well defined. Thus, it is not clear as to what categories of patients are "low risk" and "intermediate risk" according to the new AJCC Staging System.

SWOG-9035 entered patients with primary lesions of 1.5–4.0 mm. The new AJCC Staging System has determined that the break point is at 1.00 mm rather than 1.5 mm.

Ulceration was not a stratification factor in SWOG-9035. The new AJCC Staging System recognizes that ulceration is a poor prognostic factor and upstages patients with ulcerated primary lesions.

In SWOG-9035, 75% of patients were staged clinically and only 25% were staged pathologically. The current practice is to perform lymphatic mapping and sentinel node biopsy whenever possible. A proportion of the clinically staged patients in SWOG-9035 would most likely have had positive lymph nodes detected by sentinel node biopsy and would have therefore been excluded from the trial. Moreover, the common use of sentinel node biopsy identifies many patients with one microscopically positive lymph node. The extent to which detection of one microscopically positive sentinel lymph node changes prognosis is not clear, and thus the need for adjuvant interferon in these patients is not certain. Data on prognosis and survival of melanoma are presented in references 4 and 5. Data from reference 5 on survival as related to stage are presented in the next section (see Table 6 below.)

5. A PROPOSED SECOND RANDOMIZED PIVOTAL TRIAL OF MELACINE AS ADJUVANT THERAPY FOR STAGE II MELANOMA

Based on the regulatory pathway suggested by FDA for approval of Melacine, a second Phase 3 trial (schema below) was designed to compare the vaccine versus observation alone in a patient population similar to that studied in SWOG-9035 and who express HLA-A2 or HLA-C3 genes in order to confirm the vaccine is effective in prolonging disease-free survival.

5.1 Patient Population

SWOG-9035 included patients with T3N0M0 melanoma tumors, where T3 was defined as "tumor more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark's level IV – when Breslow's depth is unknown)" (i.e., defined as Stage IIA by the old AJCC Staging System). Stage IIB tumors (i.e., tumors > 4 mm) were excluded.

The proposed patient population will be based on pathologic staging as described by the new AJCC Staging System (edition 6). The patient population includes patients with Stage IIA (T2b and T3a) and IIB (T3b) tumors. Stage IIB (T4a) and Stage IIC (T4b) tumors are > 4 mm and would be excluded. The new AJCC Staging System and the projected 5-year survival for each group are presented in Table 6 below. All patients will be HLA-A2 and/or HLA-C3 positive.

The included patients are deemed to be at "intermediate risk" for relapse. Patients with higher stages will be excluded since they were not represented in SWOG-9035 and the risk of recurrence may be too high. Patients with Stage IA and IB will be excluded, since they were largely not represented in SWOG-9035 and the risk of relapse may be too low.

Table 6: Patients Included and Excluded in Proposed Trial

SWOG-9035 – Old AJCC Staging System			Proposed Second Pivotal Trial – New AJCC Staging System						
Stage	**TMN**	**Description**	**Pathological Stage[1]**	**TMN**	**Thickness (mm)**	**Ulceration**	**Nodes**	**5-year[1] survival (%)**	**Include or Exclude**
IA	T1N0M0	≤ 0.75 mm or Clark's level II	IA	T1aN0M0	≤ 1.0	No	0	95	Exclude
IB	T2N0M0	0.76–1.5 mm or Clark's level III	IB	T1bN0M0	≤ 1.0	Yes	0	91	Exclude
				T2aN0M0	1.01–2.0	No	0	89	Exclude
IIA[2]	T3N0M0	1.5–4.0 mm or Clark's level IV	IIA[3]	T2bN0M0	1.01–2.0	Yes	0	77	Include
				T3aN0M0	2.01–4.0	No	0	79	Include
			IIB	T3bN0M0	2.01–4.0	Yes	0	63	Include
IIB	T4N0M0	> 4.0 mm or Clark's level V		T4aN0M0	> 4.0	No	0	67	Exclude
			IIC	T4bN0M0	> 4.0	Yes	0	45	Exclude
III	(Any T, N1-2, M0)	Nodal or in-transit metastasis	IIIA	N1a	Any	No	1 micro	70	Exclude
				N2a	Any	No	2–3 micro	63	Exclude
			IIIB	N1a	Any	Yes	1 micro	53	Exclude
				N2a	Any	Yes	2–3 micro	50	Exclude
				N1b	Any	No	1 macro	59	Exclude
				N2b	Any	No	2–3 macro	46	Exclude
			IIIC	N1b	Any	Yes	1 macro	29	Exclude
				N2b	Any	Yes	2-3 macro	24	Exclude
				N3	Any	Any	4	27	Exclude
IV	(Any T, any N, M1-2)	Any patient with distant metastasis	IV	M1a M1b M1c	Any	Any	Any	7–19	Exclude

[1] Pathological Stage Groupings and 5-year survival rates from Balch et al., J Clin Oncol 19:3635-3648 2001.

[2] Patients in Pathological Stage IIA were eligible for entry into SWOG-9035, but Clark's level IV patients were eligible only if the tumor thickness was 1.5–4.0 *or* the tumor thickness was indeterminate. The shaded areas represent patients on SWOG-9035 and proposed patients for the second pivotal trial.

[3] Patients in Pathological Stages IIA and IIB will be eligible for entry into the proposed confirmatory trial in HLA-A2 and HLA-C3 patients, but Stage IIB patients with tumors > 4.00 mm (T4bN0M0) will be excluded.

5.2 HLA Typing

All patients will be HLA-A2 and/or HLA-C3 positive.

5.3 Sentinel Node Sampling

Pathological staging using lymphatic mapping and sentinel lymph node sampling techniques will be required for all patients. The only exclusions are patients with midline lesions, prior non-melanoma surgery in the area of regional nodes, and lymph node dissections without prior sentinel node biopsy.

5.4 Stratification

Patients will be stratified for the following major prognostic factors [based on Balch et al., reference 4; see Appendix 4]:

- Pathologic Stage (T2b [1.0–2.0 mm, ulcerated primary] versus T3a [>2.0–4.0 mm, nonulcerated primary] versus T3b [>2.0–4.0 mm, ulcerated primary]).
- Gender (male versus female)
- Site of primary (head and neck and trunk versus extremities)

5.5 Randomization

Following stratification, patients will be randomized in a 1:1 ratio to treatment with the vaccine (40 doses over 105 weeks using the same dose, route, and schedule as used in SWOG-9035) versus observation alone.

5.6 Objectives

The primary objective will be to compare the vaccine arm and the observation arm in terms of disease-free survival. Secondary objectives include comparing the treatment arms in terms of overall survival time and the incidence of adverse events.

5.7 Sample Size and Time

A total of 700 patients, approximately 350 patients in each of the two treatment arms, will be enrolled and randomized into the study. The estimated 5-year relapse-free survival is expected to be 70% in the observation arm and 80% in the vaccine arm. Enrollment will occur over 3-4 years and the data cutoff date for the primary analyses will occur approximately 5 years after enrollment of the last patient. It is assumed that no more than 5% of patients will be randomized but not complete treatment. The

sample size of 700 patients will result in >80% power using a two-sided (alpha = 0.05) test.

The trial may take approximately 3 years to accrue patients and 5 years of follow-up after enrollment of the last patient until enough events have occurred to allow analysis.

5.8 Efficacy Endpoints

The primary efficacy endpoint will be the intent-to-treat comparison of relapse-free survival between patients randomized to vaccine and patients randomized to observation. The primary efficacy analysis will be based on the Wald chi-square statistic from a Cox proportional hazards regression model, adjusted for each of the stratification factors. A similar analysis using overall survival as an endpoint will be performed. Disease-specific mortality will also be analyzed.

5.9 Eligibility Criteria

1) Patients must have histologically diagnosed, surgically removed, Stage IIA (T2b and T3a) or IIB (T3b) cutaneous malignant melanoma.
2) Patients must be HLA-A2 and/or HLA-C3 positive.
3) Resection must meet described surgical criteria.
4) Patients must have had lymphatic mapping and sentinel node biopsy whenever possible.
5) Patients must have no evidence of residual or metastatic melanoma as demonstrated by the following:
    a) Physical examination documenting complete resection of the primary AND no evidence of regional lymphadenopathy or distant metastases within 28 days prior to registration.
    b) Chest x-ray demonstrating no evidence of metastatic disease within 56 days prior to registration.
6) Patients must not have received prior chemotherapy, hormonal therapy, radiation therapy or biologic response modifier therapy for melanoma.
7) Patients must not have received or be receiving Intron A therapy.
8) Patients must be registered within 56 days after last surgery.
9) Patients must have reached their 18th birthdays.
10) Patients must have WBC ≥ 3,000/μL and platelets ≥ 100,000/μL within 28 days prior to registration.
11) Patients must have performance status 0–1 according to Southwest Oncology Group criteria.

12) Patients must have serum creatinine and bilirubin ≤ 2x the institutional upper limits of normal, SGOT or SGPT ≤ 3x the institutional upper limits of normal, and alkaline phosphatase within institutional normal limits within 28 days prior to registration.

13) Patients with a history of myocardial infarction during the year prior to registration or with NYHA Class III or IV heart disease are not eligible.

14) Pregnant or nursing women are not eligible. Men and women with reproductive potential are not eligible unless they have agreed to use an effective contraceptive method (including abstinence).

15) Patients who require or are expected to require treatment with corticosteroids are not eligible.

16) There must be no plans for the patient to receive concurrent chemotherapy, hormonal therapy, immunotherapy, interferon, radiotherapy, surgery or other treatment directed at the primary tumor while on protocol treatment.

17) No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for five years.

18) All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.10 Treatment Plan

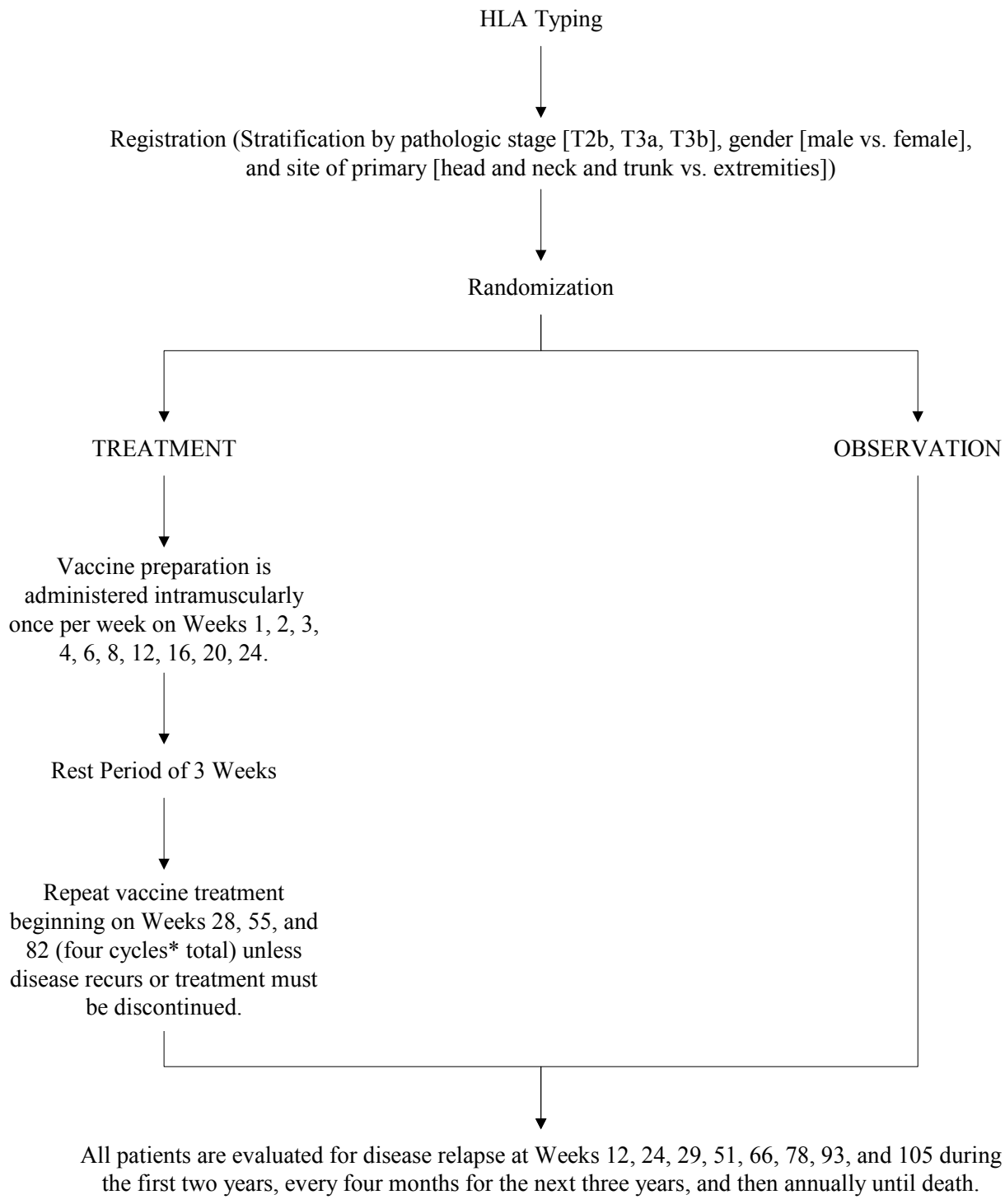
One treatment consists of two intramuscular injections of the vaccine preparation (1.25 mL split between two injection sites) performed during one visit. Each cycle of treatment consists of 10 separate treatments (20 injections) given on Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 followed by a three-week rest period. Each cycle is therefore 27 weeks long. A total of four cycles of treatment will be given.

5.11 Treatment Schedule

Agent	Dose	Route	Weeks
Vaccine	1.25 mL vaccine	IM	Administration once per week during weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, followed by a 3-week rest period. This cycle will be repeated three times.
Observation	None		

All patients will be evaluated at comparable intervals regardless of assigned treatment arm.

SCHEMA



* A cycle is a period of 24 weeks of treatment (Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24) followed by three weeks of rest (i.e., 27 weeks total).

6. ISSUES FOR ODAC AND THE FDA

The proposed second Phase 3 trial is designed to compare Melacine vaccine versus observation alone in a patient population similar to that studied in SWOG-9035 and who express HLA-A2 and/or HLA-C3 genes in which the vaccine was significantly effective in prolonging both disease-free survival and overall survival. However, several confounding problems are posed by changes in standard practice since initiation of SWOG-9035 in 1992. Corixa seeks the advice of ODAC and the FDA on the trial in general and on these issues specifically.

1) Is it agreed that treatment with Intron A is not necessary for the proposed "intermediate risk" patient population that includes patients with Stage IIA (T2b and T3a) and IIB (T3b) tumors?

2) Can/should patients with Stage IIIA (N1a) tumors, especially if < 4 mm, but with one positive microscopic lymph node detected by sentinel node biopsy, be included in the proposed trial? The projected 5-year survival for the proposed Stage IIA and IIB patient population is 63–77%. The projected 5-year survival for patients with Stage IIIA (N1a) tumors is 70%, thus indicating that these patients fall within the "intermediate risk" category. Moreover, many of the patients with clinical Stage IIA but presumed surgical Stage IIIA disease were included in SWOG-9035, before the widespread use of sentinel node biopsy.

7. REFERENCE LIST

1. Mitchell MS, Harel W, Groshen S. Association of HLA phenotype with response to active specific immunotherapy of melanoma. J Clin Oncol 10:1158-1164, 1992.

2. Sosman JA, Unger JM, Liu PY, Flaherty LE, Park MS, Kempf RA, Thompson JA, Terasaki PI, Sondak VK. for the Southwest Oncology Group. Adjuvant Immunotherapy of Resected, Intermediate-Thickness Node-Negative Melanoma with an Allogeneic Tumor Vaccine. II. Impact of HLA Class I Antigen Expression on Outcome. J Clin Oncol 1992 (in press).

3. SondakVK, Liu PY, Tuthill RJ, Kempf RA, Unger JM, Sosman JA, Thompson JA, Weiss GR, Redman BG, Jakowatz JG, Noyes RD, Flaherty LE for the Southwest Oncology Group. Adjuvant Immunotherapy of Resected, Intermediate-Thickness Node-Negative Melanoma with an Allogeneic Tumor Vaccine. I. Overall Results of a Randomized Trial of the Southwest Oncology Group. J Clin Oncol 1992 (in press).

4. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, Urist M, McMasters KM, Ross MI, Kirkwood JM, Atkins MB, Thompson JA, Coit DG, Byrd D, Desmond R, Zhang Y, Liu PY, Lyman GH, Morabito A. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622-34, 2001.

5. Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, Fleming ID, Gershenwald JE, Houghton A Jr, Kirkwood JM, McMasters KM, Mihm MF, Morton DL, Reintgen DS, Ross MI, Sober A, Thompson JA, Thompson JF. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 19:3635-48, 2001.

6. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 14:7-17, 1996.

7. Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, Smith TJ, Rao U, Steele M, Blum RH. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 18:2444-58, 2000.

Appendix 1: Summary of Clinical/Regulatory History of Melacine

1985–1988	Initial Phase 1 (1985–1986) and 2 (1987–1988) trials conducted under an investigator-sponsored IND (M. Mitchell, M.D., Univ. Southern California) in 49 Stage III/IV patients. (Study # 1901 and 2206)
1988	RIBI Immunochem Research, Inc. files IND for Melacine. (BB-IND 2885)
1988–1999	Seven open-label Phase 2 trials conducted in 139 patients with Stage III/IV melanoma. (Study # 2885-01, -03, -06, -08, -09, -10, and -11)
1989	Melacine granted Orphan Drug status for disseminated melanoma.
1991–1993	Controlled Phase 3 trial of Melacine vs. Combination Chemotherapy (DTIC + cisplatin +BCNU + tamoxifen) in 140 patients with Stage IV melanoma. (Study # 2885-12)
1992–2001	Controlled Phase 3 trial of adjuvant immunotherapy with Melacine vs. Observation in 689 patients with Stage II melanoma. Patients continue to be followed by SWOG for overall survival. (SWOG-9035)
1994	End-of-Phase 3 meeting with FDA to discuss results of Study# 2885-12 (Melacine vs. Combination Chemotherapy, Stage IV). FDA requested a second Phase 3 trial in Stage IV patients using a control treatment that is less toxic than combination chemotherapy (e.g., Intron A).
1995–2000	Controlled Phase 3 trial of Melacine + Intron A vs. Intron A in 253 patients with Stage IV melanoma.
1997	RIBI Immunochem Research, Inc. submits New Drug Submission for Melacine in disseminated melanoma to the Canadian Health Protection Branch.
Oct. 1999	Corixa acquires RIBI Immunochem Research, Inc., and Melacine IND assumed by Corixa.
Jan. 2000	New Drug Submission approved in Canada.
Sep. 2000	End-of-Phase 3 meeting with FDA to discuss results of SWOG-9035 (adjuvant Melacine in Stage II). Corixa and FDA agreed to an additional data sweep.
June 2001	Additional data sweep results from SWOG-9035 submitted to FDA.
Oct. 2001	Discussion with FDA regarding submission of Biologics License Application for adjuvant immunotherapy with Melacine in HLA-A2/C3 patients (based on SWOG-9035). FDA requests a second Phase 3 trial; final definition of patient cohort requires advice from expert advisory panel.

Appendix 2: Overview of Other Clinical Trials with Melacine

The proposed second pivotal trial is based on the results of SWOG-9035 in Stage II patients. There have been two additional Phase 3 studies evaluating the vaccine for treatment of patients with melanoma:

- One as first line therapy in Stage IV patients (Study Protocol 2885-12), and
- One as combination therapy with Intron A in Stage IV patients (Study Protocol 2885-14).

Both trials were in Stage IV patients, neither had an observation alone control, and both failed to achieve their primary endpoints.

Phase 1/2 Studies Evaluating the Immunologic Effect of the Vaccine in Patients with Stage III or IV Melanoma (Studies #1901 and 2206)

Two single-center, uncontrolled studies were conducted by Dr. Malcolm Mitchell from 1985 to 1989 (under an investigator-sponsored IND) to evaluate the safety, immunologic and clinical effects of the vaccine. Forty-seven Stage III and Stage IV melanoma patients were enrolled. Nine of 47 patients (19%) had objective tumor responses following treatment, three complete responses (CR) and six partial responses (PR).

Approximately 60% of patients treated with the vaccine in Phase 1/2 trials had a rise in frequency of cytotoxic cells specific for melanoma cells. All patients who demonstrated an objective clinical response also had an increase in cytotoxic cells. In both studies patients with increased levels of cytotoxic cells after administration of the vaccine lived longer than patients whose levels of cytotoxic cells did not increase.

Uncontrolled Phase 2 Trials of the Vaccine (Study #2885-01, -03, -06, -08, -09, -10 and -11)

One hundred thirty-nine patients were enrolled in seven Phase 2 studies of the vaccine conducted between 1988 and 1992. All were open-label, uncontrolled, single-site trials in patients with Stage III or Stage IV melanoma. Results were analyzed for the 106 patients with Stage IV disease and measurable lesions. Two patients (2%) achieved a CR and five patients (5%) achieved a PR.

A Phase 3 Clinical Trial Conducted with the Vaccine in Patients with Stage IV Melanoma (Study #2885-12: A Randomized Phase 3 Trial of Melacine versus Chemotherapy in Patients with Disseminated Malignant Melanoma)

One hundred forty patients were enrolled in this randomized study to receive either the vaccine or combination chemotherapy (70 randomized to the vaccine arm and 70 randomized to the chemotherapy arm). The combination chemotherapy was (DTIC + cisplatin + BCNU + tamoxifen), referred to as the “Dartmouth Regimen.” There was no

statistically significant difference in survival between the two treatment arms (p=0.24, log rank test). Median survival times were 281 days (95% C.I.: 222–337 days) for vaccine-treated patients and 362 days (95% C.I.: 309–441 days) for chemotherapy-treated patients.

Quality of Life was a secondary efficacy objective. The three primary endpoints were symptom distress, physical functioning and mental health scores. Results showed a significant advantage for the vaccine over chemotherapy for Weeks 2–7 (p=0.011).

Independent Review of Objective Responders in Company-Sponsored Clinical Studies using the Vaccine as a Single Agent

One hundred ninety-eight patients with advanced melanoma were enrolled in the above Phase 2 studies and the initial Phase 3 study (Protocol 2885-12). The investigators identified 12 patients (6%) who were considered objective responders (5 were CR, 7 were PR). Duration of response ranged from 7 weeks to over 10 years. Patients who achieved a complete response to the vaccine had the most durable responses. Based on the most recent follow-up, four patients were still alive; all four had achieved a complete response and have maintained that status for 7 to 10 years. Partial responses were less durable (7 weeks to 17 months).

In order to validate these responses, an independent review of the source documentation was conducted by Cato Research (Durham, N.C.). Source documentation for 11 of 12 patients was considered evaluable for objective response determination. This independent review confirmed all CR or PR responses for the 11 patients evaluated.

Based on results of the above studies, Melacine has been approved for sale in Canada for the treatment of Stage IV melanoma.

Study #2885-14: Phase III Trial of Melacine Plus Interferon alfa-2b versus Interferon alfa-2b in Patients with Disseminated Malignant Melanoma

This study was a multi-center, open-label, randomized, controlled Phase 3 trial of the vaccine plus Intron A versus Intron A alone for the treatment of Stage IV disseminated melanoma. Between January 1996 and January 2000, 253 patients were enrolled.

The primary objective was to compare survival of patients treated with the vaccine plus Intron A versus Intron A alone. There was no statistically significant difference in survival between the two treatment arms (p=0.45). The median survival time for patients treated with the vaccine plus Intron A was 332 days (95% C.I.: 269–428 days) compared to 251 days for patients treated with Intron A alone (95% C.I.: 194–384 days).

The secondary objectives included a comparison of the frequency of durable complete responses (i.e., CR ≥ 6 months duration) and objective clinical responses in the two treatment arms. The number of complete responders was too small for statistical comparison. There were three patients in the vaccine arm with durable complete responses and one patient in the arm treated with Intron A alone. Thirteen patients (10%)

treated with the vaccine plus Intron A and 10 patients (8%) treated with Intron A alone had an objective tumor response (CR or PR). The median duration of response for the vaccine plus Intron A group was approximately 7.5 months longer than the Intron A only group (p=0.038).

There were no apparent differences between the treatment arms with respect to the incidence of adverse events, with the exception of more frequent injection site disorders in the vaccine plus Intron A group.

Study # 6875-01: Phase 3 Randomized Multi-Center Trial of Melacine and Interferon alfa-2b (Intron A) versus Interferon alfa-2b as Adjunctive Therapy for Resected Stage III Melanoma

This study is an ongoing, investigator-sponsored trial being conducted under an IND held by Malcolm Mitchell, M.D. (Karmanos Cancer Institute, Detroit, MI). This study compares the effect of high-dose Intron A versus lower-dose Intron A plus the vaccine in patients with Stage III melanoma. The patients have not been HLA typed.

Appendix 3: AJCC Staging Systems

A. AJCC Staging System for Melanoma (edition 4)

Stage	TNM	Description
IA	T1N0M0	Localized melanoma ≤ 0.75 mm or Clark's level II
IB	T2N0M0	Localized melanoma 0.76–1.5 mm or Clark's level III
IIA	T3N0M0	Localized melanoma 1.5–4.0 mm or Clark's level IV*
IIB	T4N0M0	Localized melanoma > 4.0 mm or Clark's level V
III	Any T, N1-2, M0	Nodal or in-transit metastasis
IV	Any T, any N, M1-2	Any patient with distant metastasis

* Patients in Stage IIA were eligible for entry into SWOG-9035, but Clark's level IV patients were eligible only if the tumor thickness was 1.5–4.0 mm *or* the tumor thickness was indeterminate.

B. Proposed New AJCC Staging System for Melanoma (edition 6)

(from Balch et al, J Clin Oncol 19:3635-48, 2001).

Stage	TNM	Description
IA	T1aN0M0	Localized non-ulcerated melanoma ≤ 1.00 mm and Clark's level II or III
IB	T1bN0M0	Localized melanoma ≤ 1.00 mm, ulcerated or Clark's level IV
	T2aN0M0	Localized non-ulcerated melanoma 1.01–2.00 mm
IIA	T2bN0M0*	Localized ulcerated melanoma 1.01–2.00 mm
	T3aN0M0*	Localized non-ulcerated melanoma 2.01–4.00 mm
IIB	T3bN0M0*	Localized ulcerated melanoma 2.01–4.00 mm
	T4aN0M0	Localized non-ulcerated melanoma > 4.00 mm
IIC	T4bN0M0	Localized ulcerated melanoma > 4.00 mm
IIIA	Any T, N1-2aM0	1–3 microscopic nodal metastases
IIIB	Any T, N1-2bM0	1–3 macroscopic nodal metastases
IIIC	Any Tb, N1-2bM0	1–3 macroscopic nodal metastasis, ulcerated primary
	Any T, N3M0	Satellite/in-transit metastases
IV	Any T, any N, M1	Any patient with distant metastasis

* Patients in Stages IIA and IIB will be eligible for entry into the proposed confirmatory trial in HLA-A2 and HLA-C3 patients, but Stage IIB patients with tumors > 4.00 mm (T4bN0M0) will be excluded.