### 16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Final v4.0, dated 05 Aug 2016

Addendum #1 to Statistical Analysis Plan Final v4.0, dated 24 Apr 2019

# STATISTICAL ANALYSIS PLAN

## Final v4.0

## A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients with a High Risk of Recurrence

***Study Drug: Seviprotimut-L (formerly POL-103A)***

***Protocol POL103A-301***

**Polynoma LLC**
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**San Diego, CA 92121**

**Date of Plan:** **Version 1 September 11, 2012**
**Version 2 December 2, 2013**
**Version 3 July 25, 2014**
**Version 4 August 5, 2016**

**CONFIDENTIAL**

**STATISTICAL ANALYSIS PLAN**

**Final v4 August 5, 2016**

# A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients with a High Risk of Recurrence

## APPROVAL SIGNATURE

_____ _____

Patrick J. Mallon — Date
Chief Operational Officer
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE(s) | Adverse event(s) |
| AJCC | American Joint Committee on Cancer |
| ALT | Alanine aminotransferase |
| ANA | Antinuclear antibodies |
| AST | Aspartate aminotransferase |
| ATAS | Adequately treated analysis set |
| CBC | Complete blood count |
| CMH | Cochran-Mantel-Haenszel |
| CRF(s) | Case report form(s) |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| ECG(s) | Electrocardiograms(s) |
| ECOG | Eastern Cooperative Oncology Group |
| Elispot | Enzyme-linked immunosorbent spot |
| ESR | Erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| FSH | Follicle-stimulating hormone |
| HIV | Human immunodeficiency virus |
| HR | Hazard Ratio |
| ITT | Intent-to-treat |
| IVRS | Interactive voice response system |
| IWRS | Interactive web response system |
| LDH | Lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OS | Overall survival |
| PHR | Proportional hazards regression |
| PT | Preferred Term |
| RFS | Recurrence-Free Survival |
| SAE(s) | Serious adverse event(s) |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TEAE(s) | Treatment-emergent adverse event(s) |
| WHO | World Health Organization |

# 1.0 INTRODUCTION

This statistical analysis plan covers the detailed procedures for performing statistical analyses and producing tables, listings, and figures in the Phase III study described in Polynoma Protocol 103A-301 (Version 10.0, dated August 5, 2016). This analysis plan has been updated after the unblinding of the Part A database. This analysis plan supplements the study protocol.

# 2.0 STUDY DESIGN

## 2.1 General Study Design and Plan

This is a multi-arm, multicenter, randomized, double-blind, placebo-controlled study composed of several parts: Part A, an open-label extension of Part A, and Parts B1 and B2

Part A is an evaluation of immunological activity and safety. The open-label extension of Part A is an evaluation of the safety and efficacy of seviprotimut-L in subjects who received placebo in Part A.

Part A is designed to evaluate the safety and biological activity of 40 µg and 100 µg of seviprotimut-L compared to placebo, and to select a dose for Part B based on immunological biomarker response. Due to variability in the vials of vaccine from different manufacturing runs, the actual doses administered could have ranged from 24 to 56 µg in the 40 µg arm and from 72 to 160 µg in the 100 µg arm. This evaluation will take place after the first 99 randomized subjects have reached Week 10 (5 doses of study treatment received). Enrollment into Part A will continue until completion of the Part A analysis. Missing or mishandled samples may result in not all dosed subjects being evaluable for the formal Part A analysis. Part A subjects are not included in the Part B primary efficacy evaluations.

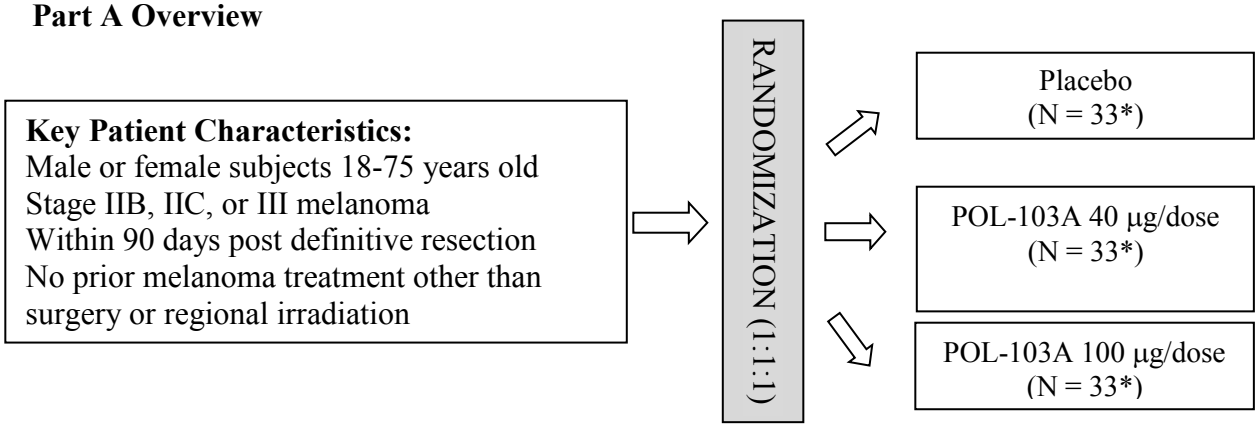
The open-label extension (Protocol 103A-301OL) is available exclusively to subjects in Part A of Protocol 103A-301 who were randomized to receive placebo.
Part B implements the clinical efficacy evaluation. Originally Part B was a single trial. This amendment splits the study into Parts B1 and B2. Part B1 is double-blind with subjects randomized in a 2:1 ratio to seviprotimut-L or placebo, respectively. Part B2 is double-blind with subjects randomized in a 1:1 ratio to seviprotimut-L or placebo, respectively. Subjects in Parts B1 and B2 will be treated for 24 months with either the dose selected for Parts B (40 µg) or placebo and followed for recurrence and survival. Due to variability among manufacturing runs of the vials of vaccine, the nominal dose of 40 µg may actually be administered as 24 to 56 µg. Individual subjects will not be unblinded at recurrence or the end of treatment in either Part B1 or B2 except to allow the subject to pursue other treatments options.

Part B1 is a clinical efficacy evaluation (with RFS as the sole primary endpoint) as well as a full safety evaluation compared with placebo in order to assess justification for Part B2. Part B1 has a relaxed type I error probability. A total of 325 subjects will be enrolled into Part B1. Clinical outcome data from Part A and the open-label extension of Part A are not used in the evaluation of clinical outcomes from Parts B1 or B2.

Part B2 is a clinical efficacy evaluation (RFS and Survival) as well as a full safety evaluation compared with placebo and will serve as the pivotal trial. 800 subjects will be randomized into Part B2. Part B2 is designed to standalone and will not use data from Parts A or B1.

**Figure 1. Study Flow Diagram**

**Part A Overview**



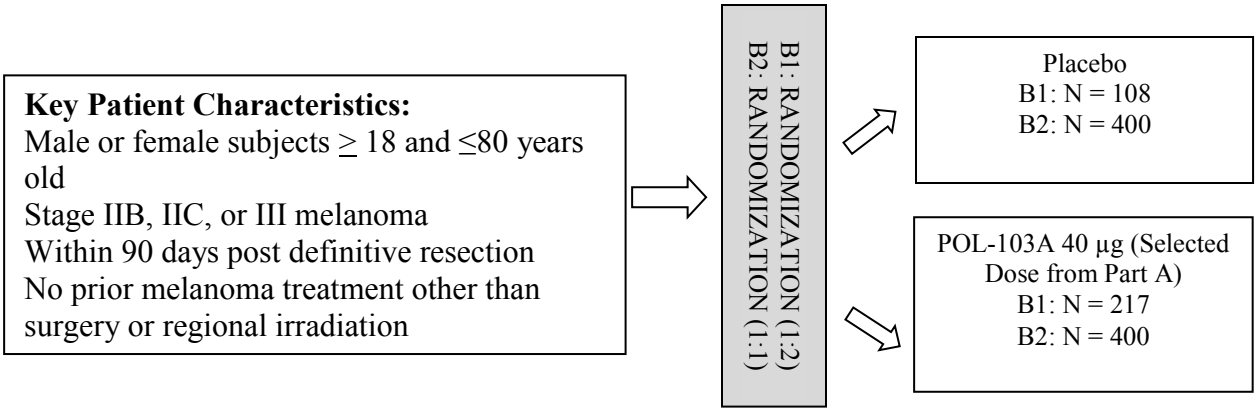

**Overall Study Design:**
Doses at W0, W2, W4, W6, W8, M3, M4, M5, M6, then every 3 months through M24**.
Key Assessments:

- Safety
- Immunological Response (measured at Week 10)
- Collection of blood samples over 3 years for later analysis of biological activity

* Enrollment in Part A is expected to exceed 99 subjects, as enrollment will continue until the 99th subject completes Week 10.

**At the completion of Part A analysis, subjects receiving 40 or 100 µg POL-103A will continue with the dose to which they have been initially randomized to (i.e., Part A subjects will not cross into Part B). Part A placebo subjects will be removed from the study and may be given the option of enrolling in open-label extension protocol 103A-301OL (Part B dose).

**Part B Overview**




**Overall Study Design:**
Doses at W0, W2, W4, W6, W8, M3, M4, M5, M6, then every 3 months through M24.

Key Assessment:

- Recurrence-Free Survival (B1 at 126 RFS events/325 B1 subjects, and for B2 at 310 RFS events/800 B2 subjects)
- Overall Survival (for B2 at 432 deaths/800 B2 subjects; survival is not a primary endpoint for Part B1, but all Part B1 subjects will be followed for survival)
- Safety

## 2.2 Randomization and Method of Treatment Assignment

Subjects in Part A will be randomized in a 1:1:1 ratio to placebo or one of two doses of seviprotimut-L. Subjects in Part B1 will be randomized in a 2:1 ratio to the dose selected from Part A or placebo. Subjects in Part B2 will be randomized in a 1:1 ratio to the dose selected from Part A or placebo. Randomization will take place across all study sites using a centralized Interactive Voice/Web Response System (IVRS/IWRS).

At the time of randomization, the IVRS/IWRS will be used to stratify the population according to disease state (IIB/IIC vs. IIIA vs. IIIB/IIIC) to ensure balanced distribution between the seviprotimut-L and placebo arms. Randomization was based on permuted block design with a fixed block size that is a trial secret.

The investigator and subject will be blinded as to treatment assignment; the placebo injections will appear identical to the seviprotimut-L injections.

## 2.3 Study Procedures Part A

| Procedure | Screening | Dosing Period | | | | | | | | | | | | | | | | Pre-Recurrence | | Post-Recurrence | End of Study[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First Visit (W0) | W 2 | W 4 | W 6 | W 8 | W 10 | M 3 | M 4 | M 5 | M 6 | M 9 | M 12 | M 15 | M 18 | M 21 | M 24 | Q 3 Mos | Q 6 Mos | Q 6 Mos | |
| Baseline Documentation | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | | | | | | | | |
| Physical Exam | X | X | | | | | | X | | | X | X | X | X | X | X | X | | X | | X |
| Pathology Review | X | | | | | | | | | | | | | | | | | | | | |
| BRAF mutation status[2] | X | | | | | | | | | | | | | | | | | | | | |
| Laboratory Studies | | | | | | | | | | | | | | | | | | | | | |
| Immune Response | | X | | | | | X | | | | X | | X | | X | | X | | X[3] | | X[4] |
| LDH | X | X | | | | | | X | | | X | X | X | X | X | X | X | X | X | | X[5] |
| CBC and serum chemistry | X | X | X | X | X | X | X | X | | | X | | X | | X | | X | | X | | X |
| Urinalysis | X | X | X | X | X | X | X | X | | | X | | X | | X | | X | | X | | X |
| Pregnancy test | X | | | | | | | | | | | | | | | | | | | | X |
| Serum FSH/estradiol | X | | | | | | | | | | | | | | | | | | | | |
| ECG | X | | | | | | | X | | | | | X | | | | | | | | X |
| HIV test | X | | | | | | | | | | | | | | | | | | | | |
| ANA/ESR | X | | | | | | | | | | X | | X | | X | | X | | X | | |
| Tumor Assessments | | | | | | | | | | | | | | | | | | | | | |
| Recurrence Assessment[6] | X[7] | | | | | | | | | | X | | X | | X | | X | | X | | |
| Dosing | | | | | | | | | | | | | | | | | | | | | |
| Seviprotimut-L or placebo | | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | | | | |
| Other Clinical Assessments | | | | | | | | | | | | | | | | | | | | | |
| Survival Follow-up Contact | | | | | | | | | | | | | | | | | | | | X | |
| Autoimmune Phenomena[8] | X | | | | | | | | | | X | | X | | X | | X | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[9] | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[10] | X |

[1] At time of recurrence or study completion for subjects without recurrence
[2] BRAF tumor mutation V600E status must be either known at Screening or a tumor tissue (fresh or archived sample) must be available for testing during the Study.
[3] Blood samples for immune monitoring at visits at Months 30 and 36 only.
[4] If within 36 months of randomization into study
[5] For subjects who have not had recurrent disease
[6] See Section 9.3.1 of the Protocol for details
[7] To be performed if the protocol-specified assessments have not been performed after the surgical resection, or the data are not available to the Sponsor
[8] Include eye exam (by an ophthalmologist) and skin exam for vitiligo and rashes thereafter.
[9] Adverse events collected through 30 days after last dose.
[10] New cancer treatments only

## 2.4 Schedule of Procedures Part B (same activities for Parts B1 and B2)

| Procedure | Screening | Dosing | | | | | | | | | | | | | | | Pre-Recurrence | | Post-Recurrence | End of Study[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First Visit (W0) | W 2 | W 4 | W 6 | W 8 | M 3 | M 4 | M 5 | M 6 | M 9 | M 12 | M 15 | M 18 | M 21 | M 24 | Q 3 Mos | Q 6 Mos | Q 6 Mos | |
| Baseline Documentation | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | | | | | | | |
| Physical Exam | X | X | | | | | X | | | X | X | X | X | X | X | X | | X | | X |
| Pathology Review | X | | | | | | | | | | | | | | | | | | | |
| BRAF mutation status[2] | X | | | | | | | | | | | | | | | | | | | |
| Laboratory Studies | | | | | | | X | | | | | | | | | | | | | |
| Biomarker[3] | | X | | | | | X | | | X | | X | | X | | X | | X | | X |
| LDH | X | X | | | | | X | | | X | X | X | X | X | X | X | X | X | | X[4] |
| CBC and serum chemistry | X | X | X | X | X | X | X | | | X | | X | | X | | X | | X | | X |
| Urinalysis | X | X | X | X | X | X | X | | | X | | X | | X | | X | | X | | X |
| Pregnancy test | X | | | | | | | | | | | | | | | | | | | X |
| Serum FSH/estradiol | X | | | | | | | | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | | | | | | | | X |
| HIV test | X | | | | | | | | | | | | | | | | | | | |
| ANA/ESR | X | | | | | | | | | X | | X | | X | | X | | | | |
| Tumor Assessments | | | | | | | | | | | | | | | | | | | | |
| Recurrence Assessment[5] | X[6] | | | | | | | | | X | | X | | X | | X | | X | | |
| Dosing | | | | | | | | | | | | | | | | | | | | |
| Seviprotimut-L or placebo | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Other Clinical Assessments | | | | | | | | | | | | | | | | | | | | |
| Survival Follow-up Contact | | | | | | | | | | | | | | | | | | | X | |
| Autoimmune Phenomena[7] | X | | | | | | | | | X | | X | | X | | X | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[8] | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[9] | X |

[1] At time of recurrence or study completion for subjects without recurrence
[2] BRAF tumor mutation V600E status must be either known at Screening or a tumor tissue (fresh or archived sample) must be available for testing during the Study.
[3] Sera samples and PBMCs will be banked at these time points for biomarker analyses and Immune monitoring (Section 9.3.2 of the Protocol)
[4] For subjects who have not had recurrent disease
[5] See Section 9.3.1 of the Protocol for details
[6] To be performed if the protocol-specified assessments have not been performed after the surgical resection, or the data are not available to the Sponsor
[7] Include eye exam (by an ophthalmologist) and skin exam for vitiligo and rashes thereafter.
[8] Adverse events collected through 30 days after last dose.
[9] New cancer treatments only

## 2.5 Schedule of Procedures Open-Label Extension Study of Part A

| Procedure | Pre-Dosing | Dosing Period | | | | | | | | | | | | | | | Pre-Recurrence | | Post-Recurrence | End of Study[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First Visit (W0) | W 2 | W 4 | W 6 | W 8 | M 3 | M 4 | M 5 | M 6 | M 9 | M 12 | M 15 | M 18 | M 21 | M 24 | Q 3 Mos | Q 6 Mos | Q 6 Mos | |
| Baseline Documentation | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | |
| Physical Exam | | X[2] | | | | | X | | | X | X | X | X | X | X | X | | X | | X |
| BRAF mutation status[3] | X | | | | | | | | | | | | | | | | | | | |
| Laboratory Studies | | | | | | | | | | | | | | | | | | | | |
| LDH | | X | | | | | X | | | X | X | X | X | X | X | X | X | X | | X[4] |
| CBC and serum chemistry | | X | X | X | X | X | X | | | X | | X | | X | | X | | X | | X |
| Urinalysis | | X | X | X | X | X | X | | | X | | X | | X | | X | | X | | X |
| Pregnancy test | | | | | | | | | | | | | | | | | | | | X |
| Serum FSH/estradiol | | | | | | | | | | | | | | | | | | | | |
| ECG | | | | | | | | | | | | | | | | | | | | X |
| ANA/ESR | X[5] | | | | | | | | | X | | X | | X | | X | | X | | |
| Tumor Assessments | | | | | | | | | | | | | | | | | | | | |
| Recurrence Assessment | X[6] | | | | | | | | | X | | X | | X | | X | | X | | |
| Dosing | | | | | | | | | | | | | | | | | | | | |
| Seviprotimut-L | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Other Clinical Assessments | | | | | | | | | | | | | | | | | | | | |
| Survival Follow-up Contact | | | | | | | | | | | | | | | | | | | X | |
| Autoimmune Phenomena[7] | X[8] | | | | | | | | | X | | X | | X | | X | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[9] | | | |
| Concomitant Medications | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[10] | X |

Note: Visit windows are ± 3 days for Weeks 2, 4, 6, and 8; and ± 7 days for subsequent visits.
[1] At time of recurrence or study completion for subjects without recurrence
[2] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[3] BRAF tumor mutation V600E status must be either known at Screening or a tumor tissue (fresh or archived sample) must be available for testing during the Study.
[4] For subjects who have not had recurrent disease
[5] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[6] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[7] Include eye exam (by an ophthalmologist) and skin exam for vitiligo and rashes thereafter.
[8] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[9] Adverse events collected through 30 days after last dose.
[10] New cancer treatments only

# 3.0 STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Part A Study Objectives

Part A is designed to determine the safety profile and immunogenicity of two different doses of seviprotimut-L – 40 µg or 100 µg vs. placebo – and to determine the dose to be used in Part B. The decision to proceed to Part B will be based on evidence of immunogenicity, safety, and tolerability.

## 3.2 Open-label Extension of Part A Study Objectives

The open-label extension of Part A is to evaluate the safety of seviprotimut-L 40 µg and assess the efficacy (recurrence-free survival [RFS] and overall survival [OS]) of treatment with seviprotimut-L 40 µg in patients who received placebo in Part A.

## 3.3 Parts B1 and B2 Study Objectives

Parts B1 and B2 allow an evaluation of efficacy using the 40 µg dose of seviprotimut-L selected from Part A. The objective of the Part B1 efficacy evaluation is to assess whether subjects randomized to the active arm have superior RFS compared to subjects randomized to the placebo arm. The safety of seviprotimut-L will also be assessed. Part B1 has a relaxed type I error probability. Survival in Part B1 will be assessed as a safety outcome at the time of the final Part B1 RFS analysis. Patients enrolled in Part B1 will be followed for survival and have their vital status systematically assessed following the Part B1 RFS analysis in order to descriptively assess survival experience of Part B1 patients. The survival data from Part B1 will not be pooled with survival data from Part B2 for the formal survival analysis of Part B2.

Part B2 objectives include two primary endpoints of RFS and survival, and the statistical design is consistent with being a pivotal trial with the type I error probability shared between the two primary endpoints.

## 3.4 Part A Study Endpoints

### 3.4.1 Primary Endpoints

The following endpoints will be evaluated on data collected through Week 10 for subjects enrolled in Part A of the study.

- The biological activity of seviprotimut-L as measured by either:
  - the percentage of subjects who have generated either an IgG or IgM response to antigens contained in the vaccine at Week 10; or
  - the percentage of subjects who have generated a T-cell response (as measured by Elispot assay) to Trp-2 antigen at Week 10.

### 3.4.2 Safety Endpoints

The safety of seviprotimut-L will be evaluated by safety blood and urine laboratory measurements, physical examinations, and AE reports.

## 3.5 Open-Label Extension of Part A Study Endpoints

- The safety of seviprotimut-L evaluated by safety blood and urine laboratory measurements, physical examinations, and AE reports.
- Recurrence-free survival (RFS)
- Overall survival (OS)

## 3.6 Part B1 Study Endpoints

### 3.6.1 Primary Endpoint

- Recurrence-free survival (RFS)

### 3.6.2 Secondary Endpoint

- Survival

### 3.6.3 Safety Endpoints

The between-arm comparison of safety endpoints for Part B1 of this study are:

- The incidence of all adverse events (AEs) reported during the study, including the seriousness, severity, and assessed relatedness to study drug
- Number and percent of patients discontinued from study drug treatment due to AEs
- Change from baseline in vital signs, laboratory data, and electrocardiograms (ECGs)

## 3.7 Part B2 Study Endpoints

### 3.7.1 Primary Endpoints

- Recurrence-free survival (RFS)
- Survival

These two primary endpoints share the overall type I error probability.

### 3.7.2. Safety Endpoints

The between-arm comparison of safety endpoints for Part B2 of this study are:

- The incidence of all adverse events (AEs) reported during the study, including the seriousness, severity, and assessed relatedness to study drug
- Number and percent of patients discontinued from study drug treatment due to AEs
- Change from baseline in vital signs, laboratory data, and electrocardiograms (ECGs)

### 3.8. Exploratory Endpoints

The primary endpoints will be explored by the following baseline characteristics: stage of disease (Stage IIB vs. Stage III), gender (female vs. male), age (< 60 vs. ≥ 60), ECOG Performance Status (0 vs. 1), presence of ulceration (present vs. absent), site (extremity vs. trunk), lymph node status (sentinel LN only positive vs. other), antibody response (positive vs. negative), Elispot response (positive vs. negative), BRAF tumor mutation status, and clinical site based on region or number of patients enrolled. Other characteristics may be added as the data are evaluated.

Sensitivity analyses will be performed to investigate influences on the outcome of the primary endpoints. The details of these analyses are discussed in Section 6.8.3 "Sensitivity Analyses of Parts B1 and B2 Efficacy Endpoints." Biomarker assessment will be evaluated. Time to locoregional recurrence and time to distant recurrence will be analyzed.

## 4.0 ANALYSIS SETS

### 4.1 Intent-to-Treat (ITT) Analysis Set

The intent-to-treat (ITT) analysis set will include all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether or not patients receive the study drug to which they were randomized. The primary efficacy analysis will be based on the ITT analysis set.

### 4.2 Modified Intent-to-Treat (mITT) Analysis Set

The modified intent-to-treat (mITT) analysis set will include ITT patients with Western Blot immune response data at Baseline (prior to treatment) and at Week 10 in Part A. Due to inherent assay challenges with the Elispot assay, the extent and availability of the Elispot data lagged behind the complete set of Western Blot data available for analysis. Western Blot data will be unblinded and used to support the immune response evaluation of the dose levels of seviprotimut-L. All Elispot data will be provided when available.

### 4.3 Safety Analysis Set

The safety analysis (SA) set consists of all patients who receive at least 1 dose of study drug with treatment assignments designated according to actual study treatment received. This will be the primary population for evaluating treatment administration/compliance and safety.

### 4.4 Adequately Treated Analysis Set (ATAS)

The adequately treated analysis set (ATAS) will include all patients according to study intervention actually received, require at least 50% of intended injections of study intervention, and who have no major protocol violations. The ATAS analysis will be supportive of the primary analyses based on the ITT analysis set.

### 4.5 Treatment Misallocations

The following rules will be used for patients who were allocated to the wrong treatment group:

- If patients were *randomized but not treated*, then they will be reported under their randomized treatment group (ITT) for efficacy analyses. However, they are by definition excluded from all safety analyses.
- If patients were *randomized but took incorrect treatment*, then they will be reported under their randomized treatment group (ITT) for all efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.
- For analyses presenting the ATAS set, all patients will be presented under the treatment they actually received.

### 4.6 Handling of Dropouts or Missing Data

In general there will be no imputation of missing data, other than for partial dates, in the analysis of the primary and secondary endpoints. Imputation in other analyses will depend on the purpose of the analysis and will be described as appropriate, specifically with regards to the analysis of adverse events. Variations of analysis without imputation will be done as sensitivity analyses and as appropriate.

The data items associated with the key analyses are not generally susceptible to being missing, but there are special considerations for dates of events. The following imputation rules will be applied to missing date elements only for dates of events used in the analysis of primary and secondary endpoints:

- Dates with missing day of the month will be completed by imputing the missing day of the month as the 15th day of that month, provided another date to be used in the computation of an interval is not in the same month. If the day of the month is missing and the other date is in the same month, then the missing day of the month will be taken as half the distance to the beginning or end of the month (depending on expected sequence). If both dates to be used in the computation of an interval are missing day of the month then an interval of 15 days (plus or minus) will be used.

- Dates with both month and day of month missing will be imputed as July 1 of the known year provided another date in the same year is to be used in the computation of an interval. If both the month and day of the month are missing and another date in the same year is to be used in the computation of an interval, then the missing date components will be taken as the half the distance from the other date until the beginning or end of the year (depending on expected sequence). If both dates to be used in the computation of an interval are missing both month and day of the month then an interval of 180 days (plus or minus) will be used.

- Dates missing the year or all three components (day, month, and the year) will not be imputed.

Key analyses may depend on the date of the first occurrence of an event associated with the endpoint. When the event has yet to occur the analysis will nonetheless require an analytical date be available for the analysis. These are known as censored or truncated dates. A censored date is the date of the most recent assessment for the event for a patient for which the event of interest has yet to occur and for which additional time may lead to observation of the event of interest. A truncated date is the date of a

competing event that precludes the observation of the event of interest. The distinction between designating an analytical date as censored or truncated will depend on the purpose of the analysis and will be designated for each analysis. For example, if death is the event of interest and a patient is still alive and being followed for the date of death then the date last known alive is a censored date, whereas the date a patient withdraws consent for continued follow-up of vital status (a competing event) is a truncated date. Please note that the nature of the competing event will dictate whether the competing event is permanent. For example, the date of death for a patient who has withdrawn consent may later become known passively from governmental death records.

# 5.0 STATISTICAL CONSIDERATIONS

## 5.1 Part A

The size of Part A (33 patients per arm) was computed based on having no greater than a one-sided 20% likelihood of a false positive conclusion for the immune response statistical criterion. See the subsequent section 6.8.1 "Part A Immunological Statistical Success" for the statistical operating characteristics of the Part A statistical analysis.

Recruitment will continue in Part A until the analysis of Week 10 data has been completed on the first 99 randomized subjects. This will result in an "over enrollment" for Part A to avoid a discontinuation of recruitment and ensure a complete data set for Part A evaluation.

Patients assigned to the Placebo arm during Part A accrual will be offered the option of receiving 40 μg seviprotimut-L selected from Part A under an Open-Label Extension protocol. Patients assigned to the Part A active arms will remain on the dose assigned and be followed until the end of the study. All Part A patients will be separately tabulated and used in the assessment of safety. They may also be used in exploratory efficacy analyses, but will not be part of the primary or secondary Part B evaluations.

## 5.2 Part B

The decision regarding initiation of Part B of the study was to be based solely on biomarker and safety data from Part A, specifically not including clinical outcome data. Part A patients are not included in the primary analyses of Part B data. This revision to the SAP describes revisions to Part B leading to Part B1, an analysis of RFS, conditionally followed by Part B2, a follow-on definitive phase of the trial.

The description of the methods of analysis that follow are for all parts as applicable relative to the endpoints unless otherwise specified. Depending on the study Part an analysis may be descriptive (exploratory) or formal depending on study Part.

### 5.2.1 Part B1

Part B1 is a two-arm comparison of the efficacy of the experimental arm where the intended intervention is the experimental vaccine (Arm V) against a control arm where the intended intervention is placebo (Arm P). The primary analysis is based on recurrence-free survival (RFS). This analysis is based on the original hypothesized RFS hazard ratio and assumed control arm RFS distribution. The analysis is specified to be an intent-to-treat comparison of Arm V to Arm P using the stratified logrank

test. The major change brought about as a result of splitting the original Part B into Parts B1 and B2 is to implement a relaxed the type I error probability for Part B1.

The following table is used to specify Arm P (control arm) reference data by stage strata. The original specification of proportions expected came from a review of the articles reporting outcome from recent trials in melanoma. The empirical proportions come from trial experience to date. The stratum-specific empirical proportions are used to compute the trial size and timing as described subsequently.

| Stage | Original Proportions (%) | Empirical Proportions (%) | RFS median (y) | RFS rate |
|---|---|---|---|---|
| II | 30 | 30.9 | 4.5 | 0.154 |
| IIIA | 36 | 30.4 | 3.5 | 0.198 |
| IIIB/C | 34 | 38.7 | 1.7 | 0.409 |

The best single source of effect size data is reference (1). This article reports data from a small (38 patient) double-blind randomized trial of a similar vaccine. The estimated medians for RFS are 0.6 and 1.6 years for placebo and vaccine, respectively, providing a crude hazard ratio estimate of 0.38 (= 0.6/1.6). Therefore, Polynoma's hypothesized RFS hazard ratio is 0.625 for RFS, corresponding to a 37.5% smaller RFS hazard rate for Arm V patients. This hypothesized hazard ratio is consistent with a clinically meaningful effect, especially when weighed against the expected low adverse event profile.

There is evidence, both from melanoma trials and trials of therapeutic vaccines in other diseases, that there may be a delay in the effect of an experimental vaccine. Taking into account the possibility of a delay in effect precludes using trial size computation methods that assume proportional hazards because the proportional hazards assumption is no longer valid. Thus, some method other than the standard formulas for computing the required number of events must be used. For this trial simulations were used for delayed effect scenarios. An appendix to this document describes the simulation methodology.

For RFS analysis scenarios with delayed effect, the delay of effect is parameterized as follows: The RFS hazard ratio is assumed to be one until 1 month, followed by a period of 3 months over which the hazard ratio linearly decreases from one to 0.625, followed by a hazard ratio of 0.625 from 4 months forward.

The first year (January 2015 through December 2015) accrual experience in this study was 212 patients. The Part B1 RFS analysis being described is based on a total accrual of 325 patients which is projected to occur in June 2016.

This RFS analysis is based on one-sided alpha of 0.10 (equivalent to two-sided 0.20 for planning purposes) and statistical power of 80%. No interim analyses are planned for this RFS analysis.

Simulations with 10,000 replications based on the accrual of 325 patients as described above and the above specified alpha and power requires 126 RFS events and the last of these events is projected to occur 3.21 years following the start of accrual, that is, March 2018. The simulation estimate of alpha is

0.0887, the simulation estimate of power is 80.5%, and the critical RFS hazard ratio is estimated to be 0.792, corresponding roughly to a 26% longer median.

Overall survival for subjects in Part B1 will be followed and reported as a descriptive endpoint to the IND, as appropriate. Survival in Part B1 will be assessed as a safety outcome at the time of the final Part B1 RFS analysis Patients enrolled in Part B1 will be followed for survival and have their vital status systematically assessed following the Part B1 RFS analysis in order to descriptively assess the long-term survival experience of Part B1 patients. The survival data from Part B1 will not be pooled with survival data from Part B2 for the formal survival analysis of Part B2.

The original trial was planned based on accruing 960 patients in only 2 years. The above computations for Part B1 are based on accruing 325 patients in 1.5 years, a rate less than half (45%) of the originally assumed accrual rate. The original final RFS analysis was projected for 3.8 years based on the overly optimistic assumed accrual rate, or October 2018. The Part B1 analysis with a relaxed alpha of 1-sided 0.10 provides an RFS assessment at about the same time as originally projected.

### 5.2.2 Part B2

Conditional on the results from the RFS analysis from Part B1, a follow-on phase of the trial is planned that is designated as Part B2. The analysis of the B2 RFS will be supportive to the BLA to be submitted. Patients will be randomized with equal probability to a control arm for which the planned intervention is placebo, or to an experimental arm, for which the planned intervention is vaccine.

Part B2 of the trial with have co-primary endpoints of RFS followed by survival with an overall one-sided alpha of 0.025. The significance level to be used for RFS is specified to be one-sided 0.02, and the significance level to be used for the subsequent survival analysis is specified to be 0.005. (Note: The survival data from Part B1 will not be included in the analysis of survival for Part B2.) The trial is planned with power of 90% for RFS and 80% for survival.

The Part B2 trial is planned with the specific alternative RFS HR = 0.625, and the specific alternative survival HR = 0.6667 as was originally planned.

The Part B2 RFS analysis is planned using the same delayed effect specifications as were used to plan the Part B1 analysis and accrual of 800 patients in 3 years.

Simulations with 10,000 replications find a requirement for 310 RFS events and the last of these events is projected to occur 3.93 years following the start of accrual. The simulation estimate of alpha is 0.0126, the simulation estimate of power is 90.2%, and the critical RFS hazard ratio region is estimated to be $\leq 0.791$, corresponding roughly to a 26% or longer median RFS.

An interim futility and efficacy survival analysis will be performed at the time of the Part B2 RFS analysis; the final survival analysis will be done at 432 deaths. The significance levels to be used for the interim and final survival analyses are specified to be equal (not based on O'Brien-Fleming bounds) with protection of the overall one-sided 0.005 in the survival efficacy analyses. The decision to use equal significance levels at interim and final is based on increasing the chances of finding early evidence of survival efficacy.

The exact number of deaths at the time of the RFS analysis cannot be known at this time there will be an appropriate adjustment in the final efficacy significance level to be used based on the actual events at the time of the survival analysis. Assume the number of deaths at the time of the final RFS analysis is D. The information time (stated as a proportion) for the survival analysis to be done at the RFS analysis time will therefore be D/432. This proportional information time will be used to compute bounds with equal significance levels using the power method. The software suggested is SAS PROC SEQDESIGN, but other options are available.

It is projected that at the time of the analysis of RFS there will be 157 deaths in Part B2, with an information time of 36% (157 of 432). Based on the having equal significance levels for the interim and final survival analyses it is computed using SAS PROC SEQDESIGN with the power method rho specified to be 0.0003 gives significance levels of 0.002625. The survival futility analysis will be done using significance level 0.0001 and the methodology to be used for the futility analysis is described in the Appendix "Futility Analysis."

The statistical operating characteristics for the Part B2 survival endpoint assessment requires 432 deaths and the last of these events is projected to occur 13 years following the start of accrual. The simulation estimate of alpha is 0.0030, the simulation estimate of power is 80.2%, and the critical survival hazard ratio region is estimated to be $\leq 0.764$, corresponding roughly to 31% or longer experimental arm median survival.

For the Part B2 futility survival assessment, the probability of declaring futility is estimated to be 10.7% when HR = 1 with critical hazard region of $\geq 1.20$, corresponding roughly to a 17% shorter experimental arm median survival. The probability of falsely declaring superiority when HR = 1 is 0.08%.

For the superiority interim assessment, the probability of declaring superiority when HR = 0.6667 is estimated to be 21.1% with critical hazard region of $\leq 0.637$, corresponding roughly to a 57% longer experimental arm median survival. The probability of falsely declaring superiority under the null hypothesis is 0.22%.

At the projected time of the final Part B2 RFS analysis or soon thereafter the trial theoretically could be opened to the sponsor because it is projected that all patients will have completed study intervention. The study is to be conducted so that neither the patient nor the clinical site workers will be aware of the study intervention actually received, and therefore all that remains to be ascertained for patients are post-recurrence interventions and vital status updates. Because patients and clinical site workers will remain blinded to the actual individual patient study intervention, the choice of post-recurrence treatments will not influence post-recurrence interventions.

Thus, the DMC will be asked to open the trial and report the outcome of the interim survival analysis to the sponsor at the time all patients are off study intervention. The DMC can decide to postpone opening the trial to the sponsor if it judges that the integrity of a complete survival efficacy evaluation is threatened by opening the trial. Additional information for the DMC will be included in a separate DMC charter.

The decision to open the trial will mean the sponsor is free to analyze the survival data from that point onward, but not perform actionable survival analysis that would lead to a conclusion of survival efficacy until the number of deaths required for the final analysis of survival events has been realized and then using the significance level adjusted for the interim analysis as described previously. Specifically, all efficacy-oriented analyses of survival between the planned survival interim analysis at the time of the RFS analysis and the final survival analysis will not be actionable.

Having access to the survival data also means the sponsor is free to perform futility analyses and act on survival futility analyses because they will not materially affect the type I error probability of the final analysis of survival efficacy. In particular, if RFS fails to meet criterion then sponsor will want to assess whether futility exists relative to survival. See the Appendix "Futility Analyses."

See the protocol for additional details concerning the operational aspect of accrual.

### 5.3 Data Cutoff Date

Associated with each analysis is a data cutoff date which will include data for all visits up to that date. The key analyses will use the data cutoff date to censor event dates, and this may result in an event date turning into a censored date. Additional sensitivity analyses without data cutoff censoring will also be done when there has been data cutoff censoring, especially when data cutoff censoring results in loss of events.

## 6.0 STATISTICAL ANALYSIS

Categorical variables will be summarized using counts and percentages. Percentages are based on the number of patients in the analysis set for whom there are non-missing data, unless otherwise specified.

Continuous variables, including change from baseline, will be summarized using descriptive statistics [n, mean, standard deviation (SD), minimum, median, maximum].

The rates of binary endpoints will be compared using a one-sided Pearson $\chi^2$ test for unstratified analyses and Cochran-Mantel-Haenszel (CMH) test for stratified analyses. For the unstratified analyses, point estimates of the rates for each treatment arm and difference of the rates between treatment arms will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method based on the F distribution and using a normal approximation for constructing a confidence interval for differences, respectively. For the stratified analyses, the relative risk ratio estimator will be used to contrast the treatment effects on the endpoint. Both a point estimate and a 2-sided 95% confidence interval will be calculated using a normal approximation.

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence interval for each median will be provided. Cox proportional hazard models will be used to explore the potential influences of the baseline stratification factor on time-to-event endpoints. The estimated hazard ratio and 2-sided 95% confidence interval will be provided.

Stratified analyses will be conducted controlling for the randomization stratification variables of disease state (IIB/IIC vs. IIIA vs. IIIB/IIIC).

Baseline is defined as the last data point prior to randomization in Part A or Part B of the study, unless otherwise stated. Baseline is defined as the last data point prior to dosing in the open-label extension of Part A, unless otherwise stated.

Patient data listings will include all enrolled or randomized patients as applicable to Part A, open- label extension of Part A, or Part B of the study. Listings will be presented by or include part of the study where appropriate, and be sorted by treatment group, site, patient number, and date (if applicable).

Statistical analyses will be carried out using SAS statistical analysis software version 9.1.3 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

## 6.1 Patient Disposition

Patient disposition will be summarized by Part A, open-label extension of Part A, and Parts B1 and B2. The number and percent of patients who received study drug, completed each part or discontinued prematurely will be presented. The number of patients in each population, along with the number who completed the study or prematurely withdrew within each population, will be displayed. In addition, the primary reasons for early withdrawals will be summarized.

## 6.2 Protocol Deviations

All instances of protocol non-compliance will be tracked during the study and a list of protocol deviations will be finalized by a blinded Sponsor review prior to database lock. This final list of protocol deviations will be presented in a data listing and major deviations will be summarized using counts and percentages by Part A, open-label extension of Part A, and Part B.

## 6.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be presented for Parts A, open-label extension of Part A, and Parts B1 and B2 by assigned treatment. Demographics include age, gender, race, and ethnicity. Age will be calculated using the following:

Age=integer [(informed consent date – date of birth)/365.25].

Baseline characteristics include: height, weight, ECOG performance status, previous melanoma therapy, location of tumor, lymphadenectomy, pathologic staging, stage, and BRAF mutation status.

Comparability of treatment groups will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

## 6.4 Baseline History

### 6.4.1 General Medical History

Medical histories will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1 and summarized by body system using counts and percentages, for Parts A and B by assigned treatment. The number and percent of patients with ongoing conditions will be presented for each body system.

### 6.4.2 Childbearing Potential and Pregnancy Tests

Childbearing potential status and pregnancy test results will be presented for Part A, open-label extension of Part A, and Part B. All study-related procedures (other than RFS and survival follow-up) will be terminated for a female subject if she becomes pregnant.

### 6.4.3 Physical Examination

The number and percent of patients having an abnormal finding in the physical examination will be summarized at screening for each body system for Part A, open-label extension of Part A, and Part B. For those with abnormal findings, a listing of findings will be presented.

## 6.5 Concomitant and Prior Medications

All concomitant medications, including any herbal preparations, defined as non-study drug with a start date from the beginning of the Screening period through the patient's last visit in the study are to be recorded in the CRF.

Medications with partial onset dates that indicate usage from the beginning of the Screening period and medications with completely missing stop dates will be classified as concomitant.

Prior medications preceding study drug administration will be presented for Part A, open-label extension of Part A, and Part B and will be summarized for the ITT analysis set by assigned treatment. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version 01Mar2012. Levels of summarization will include global, WHO Anatomic Therapeutic Chemical (ATC) Level II drug class, and WHO generic term. At each level of summarization, a patient will be counted only once for each concurrent medication he/she has within that level. The percentage of patients having had at least one medication at each level will be calculated.

Listings will be provided for all prior and concomitant medications.

## 6.6 Concurrent Procedures

Non protocol-specified procedures performed during the study are considered as concurrent procedures. These will be recorded on the CRF from the beginning of the Screening period through the patient's last visit in the study.

The number of patients with any concurrent procedures will be summarized for Screening Parts A and B and will be summarized for the ITT analysis set by assigned treatment. The number of patients who had a concurrent procedure performed due to an adverse event, medical history, or another reason will also be summarized.

Listings will be provided for all concurrent procedures.

## 6.7 Treatment Administration/Compliance

Based on the safety analysis set, administration of study drug will be presented for Part A, open-label extension of Part A, and Part B by treatment group and will be described in terms of the total number of injections administered, expected total number of injections and compliance calculated as (total number of injections administered) / (total number of injections expected) × 100. Study drug exposure as well as reasons for modifications/interruptions/delays will be provided in data listings.

## 6.8 Part A Efficacy Endpoints

### 6.8.1 Analyses of Biological Endpoints

Complex immunological data will be collected from Part A patients. A description of these data and their processing is provided in the Endpoint Charter. The immunology data to be used in the statistical criterion for Part A come from two assessments: (1) IgG/IgM Western blot method, and (2) T-Cell Elispot method. Each method provides an immune response dichotomous outcome for each patient (0 = negative, 1 = positive). The DMC will be provided with unblinded results on these two dichotomous immune endpoints for each patient.

For the primary endpoint in Part A, a patient will be regarded as having a positive immune response if the IgG/IgM Western blot is positive. For the secondary endpoint in Part A, a patient will be regarded as having a positive immune response if the T-Cell Elispot method is positive.

The proportion of positive immune responses for each arm and combined seviprotimut-L will be computed and used to assess Part A immune response. The proportions will be notated as $P_0$, $P_1$, and $P_2$, where the subscript designates the arm (0, 1, and 2 denoting placebo, 40 μg seviprotimut-L, and 100 μg seviprotimut-L, respectively). Data will be summarized for the proportion of patients having a positive or negative response for the IgG/IgM Western blot, the T-Cell Elispot, and either the IgG/IgM Western blot or T-Cell Elispot.

### 6.8.2 Immunological Statistical Success

Immunological statistical success is defined as either one of Arm 1 or Arm 2 having a higher proportion of positive immune response (defined above) being significant at the one-sided 0.10 level of significance. A relaxed significance level is justified because a high false positive probability is acceptable for this immune response evaluation. Fisher's exact test is to be used to perform these two tests. The overall likelihood of a false positive conclusion for these two comparisons will not exceed 0.20 adjusting for two tests (0.10 = 0.20/2). The following table shows approximate critical values of the difference being tested for various values of probability of success in Arm 0:

| Arm 0 Success Probability | Critical Difference |
|---|---|
| 0.10 | 0.155 |
| 0.15 | 0.170 |
| 0.20 | 0.175 |
| 0.25 | 0.185 |
| Critical difference = this value or greater will be significant at the one-sided 0.10 level. | |

If only one of the two comparisons (Arm 0 versus Arm 1 or Arm 0 versus Arm 2) meets the statistical criterion then the dose associated with this arm may become the candidate dose for Part B. If both arms meet the statistical criterion, then the candidate dose may be selected based on the relative size of the proportion difference.

The dose to be used in the initiation of Part B will be based on all aspects of the analysis of the data collected and available from Part A. The primary consideration will be the statistical criterion specified above. Failure to meet statistical criteria for either Arm 1 or Arm 2 will not automatically preclude the initiation of Part B, however. The DMC is chartered to make a recommendation regarding initiation of Part B based in part on toxicity of the vaccine treatment compared to current FDA-approved treatment for resected melanoma (see DMC Charter).

The seviprotimut-L dose selected for the initiation of Part B is 40 μg.

The analysis of other immunological data will be open-ended with the goal of identifying any immunological changes associated with the initiation of vaccine therapy.

## 6.9 Parts B1 and B2 Efficacy Endpoints

### 6.9.1 Overall Survival (OS)

The survival analysis objective is to ascertain whether the survival time distribution for patients randomized to the experimental arm is consistent with longer survival as compared to patients randomized to the control arm. All randomized patients will be included in the primary survival analysis in Part B2 or the descriptive secondary analysis of survival in Part B1 according to the randomized arm (intent-to-treat).

The following dataset variables (actual variable names may be different in the analysis datasets) are to be derived from the study database associated with a data cutoff date and used to perform the analysis of survival associated with that data cutoff:

| Variable Name | Label | Definition |
|---|---|---|
| **strat** | Randomization Stratum | A variable having a unique value for each possible combination of factors used in the stratified randomization scheme. |
| **randd** | Date of Randomization | Date patient is randomized. |
| **expi** | Experimental Arm Indicator | **expi** = 1 if patient is randomized to the experimental arm.<br>**expi** = 0 if patient is randomized to the control arm. |
| **di** | Death Indicator | • **di** = 1: The patient is known to be dead. The value of **dd** (see below) is the date of death.<br>• **di** = 0: The patient is not known to be dead and is not known to have had a competing event. The value of **dd** is the date the patient is last known to be alive for a patient that has yet to experience either death or a competing event (see below). **di** = 0 indicates that **dd** is a censored date. |

| | | |
|---|---|---|
| | | • **di** = -1: The value of **dd** is the date the patient was classified as having a competing event. **di** = -1 indicates that **dd** is the date of a competing event. |
| **dd** | Date of Death | The date of death (**di** = 1) or the date last known to be alive (**di** = 0) or the date of competing event (**di** = -1). See data imputation rules previously specified. |
| **dt** | Time to Death | **dt** = **dd - randd** |

Imputation of missing dates will follow the rules previously specified. Competing events for death are "definite" lost to follow-up and withdrawal of consent for continued vital status assessments. While both of these competing events are subject to revision for an individual patient with the passage of time it is considered unlikely. The primary analysis will consist of executing two SAS procedures, a stratified logrank test for the test of the hypothesis and a proportional hazard regression to estimate the hazard ratio and its 95% confidence interval. Model SAS code for these two procedures is as follows:

```
proc lifetest;
  strata strat / group=expi test=logrank;
  time dt*di(0,-1);
run;

proc phreg;
  class strat;
  strata strat;
  model dt*di(0,-1)=expi / rl ties=exact;
run;
```

The significance of the logrank test will be assessed in Part B2 by referring the one-sided stratified logrank test P value to the significance criterion applicable to the analysis. The one-sided stratified logrank test P value, $P_1$, is to be computed as follows from the hazard ratio estimate from the proportional hazard regression, HR, and the two-sided P value from stratified logrank test, $P_2$: If HR < 1 then $P_1 = P_2/2$. If HR ≥ 1 then $P_1 = 1 - P_2/2$. The analysis of survival for Part B1 will be descriptive and use the same methods, with a focus on confidence intervals of estimates.

Notes:

- These analyses must be stratified (3).

- When there are competing events then censoring competing events provides a between-arm test of the event of interest (4).

### 6.9.2 Recurrence-free Survival (RFS)

The recurrence-free survival (RFS) analysis objective is to ascertain whether the RFS time distribution for patients randomized to the experimental arm is consistent with longer RFS as compared to patients randomized to the control arm. All randomized patients will be included in the primary RFS analysis according to the randomized arm (intent-to-treat).

The following dataset variables are to be derived from the study database associated with a data cutoff date and used to perform the analysis of RFS associated with that data cutoff:

| Variable Name | Label | Definition |
|---|---|---|
| **strat** | Randomization Stratum | A variable having a unique value for each possible combination of factors used in the stratified randomization scheme. |
| **randd** | Date of Randomization | Date patient is randomized. |
| **expi** | Experimental Arm Indicator | **expi** = 1 if patient is randomized to the experimental arm.<br>**expi** = 0 if patient is randomized to the control arm. |
| **rdi** | Recurrence or Death Indicator | • **rdi** = 1: The patient is known to have recurred or be dead without recurrence. The value of **rdd** (see below) is the date of recurrence or death.<br>• **rdi** = 0: The patient is not known to have recurred and is not dead and is not known to have had a competing event. The value of **rdd** is the date the patient was last assessed for recurrence for a patient that has yet to experience, death, or a competing event (see below). **rdi** = 0 indicates that **rdd** is a censored date.<br>• **rdi** = -1: The value of **rdd** is the date the patient was classified as having a competing event. **rdi** = -1 indicates that **rdd** is the date of a competing event. |
| **rdd** | Date of Recurrence or Death | The date of recurrence or death (**rdi** = 1) or the date last assessed for recurrence for a patient that has yet to experience death (**rdi** = 0) or the date of competing event (**rdi** = -1). See data imputation rules previously specified. |
| **rdt** | Time to Death | **rdt** = **rdd - randd** |

Imputation of missing dates will follow the rules previously specified. Competing events for RFS are "definite" lost to follow-up and withdrawal of consent for continued study participation. Both of these competing events are subject to revision for an individual patient with the passage of time.
The primary analysis will consist of executing two SAS procedures, a stratified log-rank test for the test of the hypothesis and a proportional hazard regression to estimate the hazard ratio and its 95% confidence interval.

```
proc lifetest;
  strata strat / group=expi test=logrank;
  time rdt*rdi(0,-1);
run;

proc phreg;
  class strat;
  strata strat;
  model rdt*rdi(0,-1)=expi / rl ties=exact;
run;
```

The significance of the logrank test will be assessed by referring the one-sided stratified logrank test P value to the significance criterion applicable to the analysis. The one-sided stratified logrank test P value, $P_1$, is to be computed as follows from the hazard ratio estimate from the proportional hazard regression, HR, and the two-sided P value from stratified logrank test, $P_2$: If HR < 1 then $P_1 = P_2/2$. If HR ≥ 1 then $P_1 = 1 – P_2/2$.

Notes:

- These analyses must be stratified (3).
- When there are competing events then censoring competing events provides a between-arm test of the event of interest (4).

The RFS data will be plotted as either Kaplan-Meier or cumulative incidence distribution estimate depending on the amount of competing events. The cumulative incidence estimates and not the Kaplan-Meier estimates will be plotted if the percent of patients with competing events in either arm exceeds 10%. (When there are competing events then the Kaplan-Meier estimate is not an estimate of the probability free of event (5)).

### 6.9.3 Sensitivity Analyses of Efficacy Endpoints

#### 6.9.3.1 Sensitivity Analyses of Overall Survival (OS)

The following sensitivity analyses for OS will be performed:

- The primary OS analysis will be performed using the ATAS.
- Deaths that occur after the cutoff will not be censored.
- Clinical site homogeneity will be assessed by testing the arm by site or site class interaction. This open-ended exploration will assess homogeneity across sites using the following clumping of sites: Clinical sites with patients fewer than K patients in either arm will be pooled into a single pseudo clinical site. K will be varied in the range of 2 to 8. Classes of clinical sites will be analyzed according to characteristics such as region, type of facility, or homogeneity of medical practice for treating melanoma.
- The proportional hazard regression (PHR) will be re-run without the strata statement and with the treatment arm by stratum interaction term added to the model statement in order to assess the interaction between the treatment arms and the disease states at randomization.
- Effect modifier analyses will be performed for base attributes and particularly putatively prognostic factors, including those explored previously in the literature as well as those hypothesized to be predictive in the context of this study. These are listed subsequently. Effect modification will be assessed one factor at a time in stratified PHR models. Each factor will be analyzed as either a natural dichotomy, a dichotomized ordered categorical with cutpoint chosen based on biologic considerations, or a continuous variable dichotomized at the overall median, and possibly tertiles, quartiles or quintiles. A separate hazard ratio estimate for arm and its 95% confidence interval will be computed for each level of the categorical attribute

using contrast statements in SAS PROC PHREG. Kaplan-Meier estimates of combinations of arm by factor will be plotted on.

- Proportional hazard regression models with multiple added prognostic covariates will be estimated. The covariates to be added will include those explored previously in the literature as well as those hypothesized to be predictive in the context of this study. Interactions will also be explored for contribution to the model.

#### 6.9.3.2 Sensitivity Analyses of Recurrence-free Survival (RFS)

The following sensitivity analyses for RFS will be performed:

- The same sensitivity analyses specified for as sensitivity analyses of survival will be done for RFS.
- Sensitivity analyses of alternative coding of the date of recurrences and censoring will be performed. These analyses will follow the suggestions in the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 (Appendix 3).

All secondary efficacy analyses and sensitivity analyses will be presented by randomized treatment, based on the ITT analysis set, unless otherwise specified.

### 6.9.4 Base Attributes to be Assessed

As specified under sensitivity analyses for RFS and Survival analyses the relationship between outcomes and base attributes are planned to be conducted. These base attributes include but are not limited to:

- Stage of disease (Stage IIB v Stage III)
- Sex (F vs. M), age ($< 60$ vs. $\geq 60$)
- ECOG Performance Status (0 vs. 1)
- Presence of ulceration (present vs. absent)
- Site (extremity vs. trunk)
- Lymph node status (sentinel LN only positive vs. other)
- Antibody response (positive vs. negative)
- Elispot response (positive vs. negative)
- BRAF tumor mutation status

- Source of the patient (clinical site or various site classes)

## 6.10 Exploratory Analyses

### 6.10.1 Time-to-Event Endpoints

Additional exploratory time-to-event endpoints including time to locoregional recurrence and time to distant recurrence will be analyzed as described for RFS, including the sensitivity analyses. These analyses will be interpreted using two-sided 0.05 P values.

### 6.10.2 Exploratory Analyses of Other Time-Dependent Outcomes

Other time-dependent outcomes include serially assessed biomarker status, laboratory assessments, and the use of other anti-cancer interventions. These will be analyzed longitudinally using MMRM methods or as time-to-event as appropriate. In addition, the relationship between these other time-dependent outcomes and the primary outcomes will be analyzed using proportional hazard regression with time-dependent covariates.

## 6.11 Safety Endpoints

### 6.11.1 Adverse Events (AEs)

Adverse events will be coded using the MedDRA Version 14.1. Coding includes system organ class (SOC) and preferred term (PT). All verbatim descriptions and coded terms will be listed for all AEs. All adverse event tables will be presented by treatment received, based on the Safety population. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (NCI-CTCAE v4) [NCI, 2009] as defined below.

| Grade | Degree of Severity |
|---|---|
| 1 | Mild, with no or mild symptoms; not interventions required |
| 2 | Moderate; minimal intervention indicated; some limitation of activities |
| 3 | Severe but not life-threatening; hospitalization required; limitation of patient's ability to care for him/herself |
| 4 | Life-threatening; urgent intervention required |
| 5 | Death related to adverse event |

A summary of adverse events, including any AEs of special interest, will be presented for Part A, open-label extension of Part A, and Part B. A summary of AEs by PT and maximum CTCAE grade will also be presented for Parts A and B.

*Treatment-emergent AEs (TEAEs)*

The following AEs will be defined as TEAEs:

- AEs occurring between study drug administration and 30 days following the last dose of study drug;

- AEs started prior to study drug administration but worsened in severity following study drug administration;
- AEs with partial onset dates if the stop date is after the first study drug administration and the dates do not definitively place the AE before the start date of study drug;
- AEs with completely missing onset dates.

All AEs will be listed by patient and AE line number.

The frequency and percentage of subjects with at least one TEAE will be summarized by SOC and PT. At each summary level, a subject will be counted only once if he/she experiences one or more TEAE. The percentage of subjects having had at least one TEAE at each level will be calculated.

Tabular summaries for Part A, open-label extension of Part A, and Part B will include all TEAEs, TEAEs related to study drug, TEAEs by severity grade, serious TEAEs, serious TEAEs related to study drug and TEAEs and related TEAEs leading to permanent discontinuation of study drug. All deaths will be presented in a listing that includes the AE leading to death, demographic data, details of study treatment, and relationship to the study drug of the AE leading to death.

In instances where a subject may have multiple AEs with differing levels of severity grade or relatedness, the most severe grade or most related event, respectively, will be reported for the severity grade and relatedness tables. For the purpose of analysis, AEs with a relatedness of Probable, Possible or missing relatedness will be considered related; AEs with a relatedness of Unlikely will be considered not related. AEs with missing severity will be presented as severe in the tables but will have severity grade listed as missing.

### 6.11.2 Physical Examination

In addition to the baseline complete physical examination, physical examinations will be performed and be summarized descriptively for Part A, open-label extension of Part A, and Part B at each scheduled visit and timepoint collected (screening, Visit 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, and every 6 months thereafter until recurrence or end of study).

### 6.11.3 Autoimmune Monitoring

Autoimmune monitoring will be performed and be summarized descriptively for Part A, open-label extension of Part A, and Part B (Safety Population) at each scheduled visit and timepoint collected (screening, Week 0, Month 6, Month 12, Month 18 and Month 24). For laboratory measures mean and mean change from baseline values will be presented for each timepoint collected. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. Results from eye and skin exams will be listed.

### 6.11.4 Laboratory Parameters

Clinical laboratory parameters for LDH, CBC, serum chemistry and urinalysis will be summarized descriptively for Part A, open-label extension of Part A, and Part B (Safety Population). Mean and

mean change from baseline values will be presented at each study visit. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

Each laboratory result will be classified as low (L), normal (N), and high (H) at each visit according to the laboratory-supplied normal range. The shift from baseline will be presented for each post-baseline visit for Part A, open-label extension of Part A, and Part B. In addition, for Part B, toxicity grade of lab result will be presented in a shift table for each post-baseline visit for the change from baseline.

### 6.11.5 Electrocardiograms

Electrocardiograms (ECGs) will be collected during Screening, Month 3, Month 12, and at the end of study in Part A, at the end of study in open-label extension of Part A, and at Screening and the end of the study in Part B. Counts and percentages for ECG diagnosis (normal or abnormal) will also be presented. If the diagnosis was abnormal, counts and percentages for clinical significance will be presented.

### 6.11.6 Vital Signs

Vital signs (pulse, temperature, systolic and diastolic blood pressure) and weight will be summarized descriptively for Part A, open-label extension of Part A, and Part B at each scheduled visit and timepoint collected (screening, Visit 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, and every 6 months thereafter until recurrence or end of study).

Mean and mean change from baseline values will be presented. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

All vital signs will be presented in data listings by patient and timepoint.

## 7.0 TABLES, FIGURES, AND DATA LISTINGS

This SAP includes mockups of tables, figures, and data listings (in separate documents) that will be generated.

## 8.0 REFERENCES

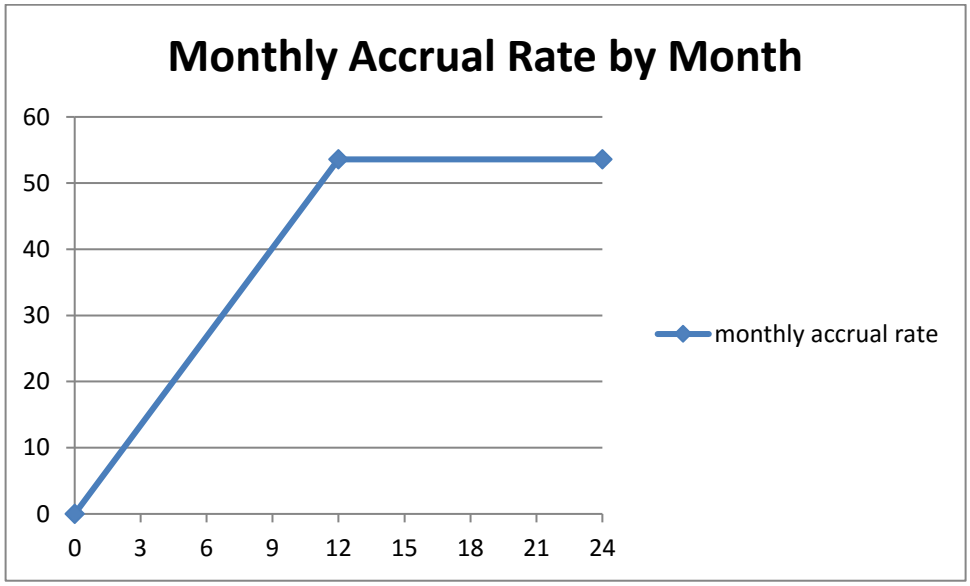
1. Bystryn J-C, Zeleniuch-Jacquotte A, Oratz R, Shapiro RL, Harris MN, Roses DF. Double-blind trial of a polyvalent, shed antigen, melanoma vaccine. Clin Cancer Res. 7:1882-1887, 2001.
2. SAS Institute Inc., SAS 9.1.3 Help and Documentation, Cary, NC: SAS Institute Inc., 2000-2004.
3. Anderson GL, LeBlanc M, Liu PY, Crowley J. On the use of covariates in randomization and analysis in clinical trials. In: Handbook of Statistics in Clinical Oncology, 2nd Edition, Crowley J & Ankerst DP editors. Boca Raton: CRC Press. 2006, 617 pages.
4. Prentice RL, Kalbfleisch JD, Peterson A, Flournoy N, Farewell V, Breslow N. The analysis of failure times in the presence of competing risks. Biometrics 1978; 34:541-554.
5. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new presentation of old estimators. Stat. Med. 1999; 18:695-706.

# APPENDICES

## APPENDIX 1: ACCRUAL RATE

The simulation software used to plan the trial requires specification of the number of subjects to be accrued and the period of time over which accrual is to take place (as is usual with trial planning software). These simple specifications would generate an accrual distribution that is uniform, that is, a constant accrual rate. But since it is unrealistic to assume uniform accrual the software also allows specification of an arbitrary accrual distribution through the specification of intervals and accrual in each interval. An additional feature, and the one used in these computations, allows specification of a linear ramp time for the accrual distribution from which the accrual distribution is generated. The linear ramp time must be less than or equal to the total accrual time. Given the linear ramp time the accrual distribution is generated by assuming zero accrual at time zero and a constant accrual rate increase from time zero through the time specified by the linear ramp time, after which the accrual rate is uniform from the linear ramp time until the end of accrual. The rate of accrual increase during the ramp time and the constant accrual rate after the linear ramp time are derived from the total accrual, the total accrual time, and the linear ramp time. For example, for the computations done in this SAP the following specifications were used: total accrual time of 2 years for 960 patients and with a linear ramp time of 1 year. Figure 1 illustrates accrual rate by month.

**Figure 1: Accrual Rate**



## APPENDIX 2: FUTILITY ANALYSIS METHODOLOGY

The following are the specifications for futility analyses. The futility null hypothesis is $H_0$: $\Delta \leq HR_A$ where $HR_A$ is the hypothesized specific alternative hazard ratio for the test of the efficacy null hypothesis. The futility alternative hypothesis is $H_A$: $\Delta > HR_A$. The testing of the futility null hypothesis can be formulated as follows. The futility null hypothesis can be written as

$H_0$: $\ln(\Delta) \leq \varphi$, or $H_0$: $\beta_{arm} \leq \varphi$ , or $H_0$: $\beta_{arm} - \varphi \leq 0$.

where $\varphi = \ln(HR_A)$ and $\beta_{arm}$ is the "true" logarithm of the hazard ratio associated with the arm variable in the model previously defined. Thus, the test is that $\beta_{arm} - \varphi$ is zero is a test of the futility null hypothesis. The futility null hypothesis is tested using SAS PHREG using the OFFSET option. When using the OFFSET option the estimated coefficient of the arm variable will be an estimate of $\beta_{arm} - \varphi$. If the estimated coefficient of the arm variable is greater than 0 then the associated two-sided P value should be divided by 2 and reported as the one-sided futility P value for assessing whether the futility null hypothesis can be rejected, otherwise the futility null hypothesis is not rejected.

The one-sided futility P value will be compared to the applicable significance level $P_F$. If the futility P value is less than or equal to $P_F$ then the survival futility boundary will be regarded as having been crossed.

## APPENDIX 3: DELAYED EFFECT SIMULATION METHODOLOGY

Following is a description of the simulation methodology used to evaluate the statistical operating characteristics of trials where the intervention under study is subject to a delay of effect. The text that follows is based on a methodological manuscript submitted for publication.

The reasons for a delayed effect include: (1) Randomization of patients with advanced disease for which experimental intervention is "too late". (2) The experimental intervention has a delayed onset of benefit. One or both of these mechanisms could apply.

Assume a two-arm randomized clinical trial and that individuals entering this trial are to be randomized to one of two groups designated as arms 1 and 2, where arm 1 is to receive control intervention (perhaps a placebo) and arm 2 is to receive experimental intervention. Assume that the outcome of interest is time to a failure event or time to the last date when this event has yet to be observed. Assume it is hypothesized that the experimental intervention induces a distribution of event times that is more favorable, that is, shifted to the right, as compared to the distribution of event times associated with the control intervention. Assume competing events are either nonexistent or negligible.

Trials of this type are typically planned by computing the required number of events under the assumption of proportional hazard rates, specific type I and II error probabilities, and a hypothesized clinically consequential ratio of the arm 2 (experimental) hazard rate to the arm 1 (control) hazard rate. Let $h_A$ be the hypothesized consequential hazard ratio.

Let the hazard ratio function $h(t) = \lambda_1(t)/\lambda_2(t)$ where $\lambda_1(t)$ and $\lambda_2(t)$ are hazard rate functions for arm 1 and 2, respectively. The proportional hazard rates assumption means that $h(t) = \lambda_1(t)/\lambda_2(t) = h$ (a constant).

After computing the required number of events, projections for the timing of analyses are usually made based on assuming exponential distributions for the arms with hazard rates $\lambda_1(t) = \lambda_1$ and $\lambda_2(t) = \lambda_2 = h_A\lambda_1$. Thus, when there is no delayed effect the survival functions for arm 1 and arm 2 are usually specified to be

$$F_1(T \le t) = \exp(-\lambda_1 t)$$

$$F_2(T \le t) = \exp(-\lambda_2 t) = \exp(-h_A\lambda_1 t).$$

The delayed effect simulation methodology described here is based on assuming that the control arm survival distribution is exponential. It is possible to generalize this methodology to other types of control arm survival distributions.

Now, assume that the experimental intervention has a lag in realization of effect so that the arm 2 hazard rate is initially $\lambda_1$ and only later becomes $h_A\lambda_1$. This delay of effect assumes the arm 2 hazard rate function is

$$\lambda_2(t) = (\lambda_1 - \lambda_2)g(t) + \lambda_2, \ (t \ge 0),$$

where g(t) is a function with the following properties: g(0) = 1, g(t) is non-increasing, and either g(t) = 0 for some t' where $t \ge t' > 0$ or $g(t) \to 0$ as $t \to \infty$. This implementation of delayed effect specifies that ultimately the hazard ratio becomes proportional or approaches proportionality.

In order to do simulations under delayed effect the survival function $F_2(t)$ must be derived. This survival function is obtained using the relationship

$$F_2(t) = \exp(-H_2(t))$$

where $H_2(t)$ is the integral of $\lambda_2(t)$ from 0 to t (integrated hazard function). Depending on the function g(t) the integral $H_2(t)$ may have an analytic form; if not then numerical integration can be used.

A segmented linear form of g(t) will now be described (other forms of g(t) are possible). The segmented linear form of g(t) has two parameters, d and r, where $d \geq 0$ and $r > 0$. The parameter d is the delay in the start of the effect of the experimental intervention and r is the time it takes to realize full effect from the start of realization of effect. The function g(t) is specified linear and descending between d and d + r.. Specifically, g(t) is defined as follows

$g(t) = 1$ for $t < d$

$g(t) = (d + r – t)/r$ for $d \leq t < d + r$,

$g(t) = 0$ for $t \geq d + r$.

It follows that

$H_2(t) = (\lambda_1 - \lambda_2)t + \lambda_2 t = \lambda_1 t$ for $t < d$

$H_2(t) = (\lambda_1 - \lambda_2)\{d + [(d + r)(t – d) –(t^2 – d^2)/2]/r\} + \lambda_2 t$ for $d \leq t < d + r$,

$H_2(t) = (\lambda_1 - \lambda_2)(d + r/2) + \lambda_2 t$ for $t \geq d + r$.

Pseudo random survival times from $F_2$ can be generated by tabling its inverse and using a uniform pseudo random generator.

Thus, if $F_1$ is exponential (as usual) and $F_2$ is defined as above then pseudo random samples of survival times from $F_1$ and $F_2$ can be generated for specified values of $\lambda_1$, $\lambda_2$, d and r. These survival times can be converted to clinical trial data based on specification of accrual distribution and follow-up intervals.

The net effect of delayed effect is a reduction in projected statistical power relative to no delayed effect. Specifically, events occurring prior to the time of realization of the specified effect $h_A$ will be less differentiating than events that occur after full realization of the specified effect size $h_A$, and therefore only the events occurring after the time of realization of effect fully contribute to statistical power. Thus, if a trial is planned without taking into account delayed effect then the projected power of the trial will be overestimated if delayed effect is present in the data.

Statistical operating characteristics for a specific set of trial specifications, including parameters specifying a delayed effect, are estimated from replicating the generation trial data for the control arm and the experimental arm, that is, from replicates of the simulated trial data. Thus, for specified significance criteria the statistical operating characteristics of the test of the null hypothesis for superiority of the experimental intervention can be estimated using the logrank test on the simulated trial replicates. The following statistical operating characteristic estimates are most often of interest:

One-sided type 1 error probability: The proportion of replicates for which the test of the null hypothesis is rejected using the one-sided logrank test and when the experimental arm data are generated with $\lambda_2 = \lambda_1$.

- Power: The proportion of replicates for which the test of the null hypothesis is rejected using the one-sided logrank test and when the experimental arm data are generated with $\lambda_2 = h_A\lambda_1$.

  These estimates also can be made for interim analyses based on event time or calendar time,

and the cumulative estimates (trial-wise) are those that take into whether and when specific trial replicates meet interim analysis criteria.

The statistical operating characteristics of futility tests can also be estimated using simulation. An additional parameter $\Omega$ is specified for the generation of experimental arm data replicates so that $\lambda_2 = \Omega\lambda_1$. For futility testing the logrank test is modified with an offset corresponding to $h_A$ so that the futility null hypothesis is for a hazard ratio equal or less than $h_A$ against a hazard ratio larger than $h_A$. The following estimates are of interest when assessing the statistical operating characteristics of futility tests:

- False futility probability (futility test type I error probability): The proportion of replicates for which the test of the futility null hypothesis is rejected using the futility logrank test and $\Omega = h_A$.
- Probability of futility conditional on $\Omega$: The proportion of replicates for which the test of the futility null hypothesis is rejected using the futility logrank test and $\Omega \neq h_A$, usually $\Omega > h_A$.

When delayed effect is specified the false futility probability cannot be regarded as the test size because the logrank test when $\Omega = h_A$ will be on based on data that inherently violates proportional hazards. When delayed effect is specified and $\Omega = 1$ then the estimate of the probability of futility can be regarded as unbiased because in fact there will be no delayed effect. However, when delayed effect is specified and $\Omega \neq 1$ then the accuracy of the estimated probability of futility will depend on how closely the parameters specifying the delayed effect in the simulations correspond to the actual delayed effect applicable at the time of the futility test. Therefore, when assessing the statistical operating characteristics of a trial with a conjectured delayed effect it is important to generate statistical operating characteristics for a range of possibilities.

# ADDENDUM #1

*to* STATISTICAL ANALYSIS PLAN

Final v4.0

A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients with a High Risk of Recurrence

*Study Drug: Seviprotimut-L (formerly POL-103A)*

*Protocol POL103A-301*

Polynoma LLC
11230 Sorrento Valley Rd.
Suite 215
San Diego, CA 92121

Date of Plan: Version 1 September 11, 2012
Version 2 December 2, 2013
Version 3 July 25, 2014
Version 4 August 5, 2016

# ADDENDUM #1

*to* STATISTICAL ANALYSIS PLAN

Final v4.0

A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients with a High Risk of Recurrence

**APPROVAL SIGNATURES**

Patrick J Mallon

Patrick J. Mallon
Chief Operational Officer
Polynoma LLC

24 APRIL 2019
Date

# ADDENDUM #1

## Section 1.0

Add the following text after the first paragraph:

*Pre-Unblinding SAP modifications and extensions are specified based on realization of a need for clarification of the SAP, recognition of additional useful sensitivity and challenge analyses, a need to conform to precedents set by other similar studies, and a need to facilitate the understanding of results from this study in the context of other contemporary similar studies. The study remains blinded as this addendum is written. The primary statistical criteria are not changed as a result of this addendum.*

*The details of AESIs, concomitant medications of interest, treatment effect on non-melanoma and melanoma precursors are added as a separate document.*

*Note: This trial is double blind and therefore the following considerations apply to the time when the data can be unblinded. An unblinded analysis based on a January 1, 2019 cutoff and an April 25, 2019 soft lock will be prepared for a highly selected distribution. Immediately after release of the randomization file (consisting of two main items: patient identifier and actual assigned arm) this file will be sent to the consulting statistician. Following this transmission, and during the time when the final analysis SDTM datasets are being validated, the consulting statistician will use a merge of this randomization file with the blinded datasets already in possession of the consulting statistician to refine the study presentation slides working together with selected others. (The results are expected to be close to the final results.) The study presentation will be finalized after the validated SDTM datasets are sent to the consulting statistician.*

## Section 4.1

Delete the following sentence at the end of the first paragraph:

*The primary efficacy analysis will be based on the ITT analysis.*

Add the following text to the end of the first paragraph:

*The ITT analysis set is to be considered as all patients randomized without regard to having initiated study intervention and free of pre-randomization findings of not meeting inclusion/exclusion criteria and not randomized in error, the existence of which must be discovered based on post-randomization review of data collected pre-randomization.*

*The analysis set used for the primary analysis will be a modified ITT analysis set and will be referred to as the Full Analysis Set (FAS). The FAS is the terminology preferred in ICH Topic E9 and is the ITT analysis set with deletion of patients not initiating study intervention. The FAS is unbiased in the sense that the ITT analysis set is unbiased because this study is blinded. Analyses based on the ITT analysis set become sensitivity analyses. The rationale for this change is to conform to previously published similar*

*studies, the very low frequency of deletions from the ITT analysis set to create the FAS, and changes in the perception of the status of RFS relative to patient benefit.*

**Section 6.9.1**

Add the following text in the Table where "randd" is defined:

*The randomization date is that from the IVRS system.*

Add the following text in the Table where "strat" is defined:

*The stage used as a stratification factor in the primary analysis and related analyses is that collected from the IVRS system.*

Add the following text after the paragraph before and in the Box providing template code for use of the LIFETEST and PHREG procedures:

*When using SAS PROC LIFETEST quantile confidence intervals will be computed using the option CONFTYPE=LINEAR in order to invoke the Brookmeyer-Crowley method. When using PROC PHREG use the option TIES=EXACT.*

**Section 6.9.2**

Add the following text after the first paragraph:

*RFS Variable: The following variables play a role in the ascertainment of recurrence and is used for the primary analysis of recurrence as well as the recurrence sensitivity analysis to be described subsequently:*

1. *The first assessment date for each patient is to be the date of randomization.*
2. *In dataset CE, variable CEOCCUR (and its associated date) flags a suspicious finding on the associated date.*
3. *In dataset FA, variable FAORRES for the code variable FATESTCD with values ABCT, CHESTCT, CHESTX, and PCT are missing if not reported or flag negative (N) or positive (Y) finding for the respective radiological findings on the associated date.*
4. *In dataset FA variable FAORRES for code BMRI is missing if a brain MRI is not reported or flag negative (N) and positive (Y) brain MRI finding on the associated date.*
5. *In dataset FA variable FAORRES for code BIOPSY is missing if not reported or flag negative (N) or positive (Y) biopsy finding on the associated date.*
6. *In dataset FA variable FAORRES for code CONFIRM is missing if not reported or flag negative (N) or positive (Y) confirmation of a suspicion (see above) on the associated date, which should be a date with a suspicion flag on the same date. Note: A brain MRI or biopsy positive finding may not induce a confirmation of a suspicion.*

7. *A recurrence is indicated for the date of a first confirmation, brain MRI, or biopsy positive finding. Note: A positive brain MRI finding does not require a biopsy, whereas a radiological or other suspicious finding (physical exam, for example) does require a positive biopsy though this check does not need to be coded. Therefore, there may be exceptions so a confirmation without any other positive finding is technically possible. Also note: A recurrence should always be associated with a suspicion, but not all suspicions will be confirmed.*
8. *Assessment modalities such as radiology are involved only as an auditing aids and play no role in detecting the presence of recurrence.*
9. *For endpoints with censoring based on date last known alive:*
    a. *If censor date is after the cutoff date then the censor date should be adjusted to the cutoff date.*
    b. *If event date is after the cutoff then change the event to a censor on cutoff date.*
10. *For endpoints with censoring based on assessment date:*
    a. *If censor date is after the cutoff date then adjust censor date to previous assessment.*
    b. *If date of event is after the cutoff then change the patient to being censored of the previous assessment date.*

Add the following text in the Table where "randd" is defined:

*The randomization date is that from the IVRS system.*

Add the following text in the Table where "strat" is defined:

*The stage used as a stratification factor in the primary analysis and related analyses is that collected from the IVRS system.*

Replace the text in the Table for the definition of "rdi" with the following text/definition:

*The definition of rdi is specified prior to this table as one of the created from RFS variables.*

Replace the text in the Table for the definition of "rdd" with the following text/definition:

*The definition of rdd is specified prior to this table as one of the created from RFS variables. The value of rdd is the date last known alive for a patient without recurrence or death.*

Add the following text after the paragraph before and in the Box providing template code for use of the LIFETEST and PHREG procedures:

*When using SAS PROC LIFETEST quantile confidence intervals will be computed using the option CONFTYPE=LINEAR in order to invoke the Brookmeyer-Crowley method. When using PROC PHREG use the option TIES=EXACT.*

**Section 6.9.3.2**

Add the following text as a bullet point after the first two bullet points in the first paragraph:

*An RFS sensitivity analysis with the event defined as the date of recurrence or if there is no observed recurrence then date of death up to 120 days since last recurrence assessment. Censoring for this analysis will be the date of last recurrence assessment.*

**[ End of Addendum #1 ]**