Final analysis of relapse-free survival in a multicenter, double-blind, placebo-controlled trial of seviprotimut-L polyvalent melanoma vaccine after resection of high-risk melanoma

CL.Slingluff Jr[1], B Blumenstein[2], K Lewis[3], RHI Andtbacka[4], JR Hyngstrom[4], MM Milhem[5], S Markovic[6], O Hamid[7], LF Hernandez-Aya[8], TL Bowles[9], P Philips[10], S Jang[11], J Lutzky[12], A Bar[13], P Beitsch[14],.

[1]University of Virginia, [2]Tri Arc Consulting, [3]Anschutz Cancer Pavilion, [4]Huntsman Cancer Institute, [5]University of Iowa, [6]Mayo Clinic Rochester, [7]The Angeles Clinic, [8]Washington University, [9]Intermountain Medical Center, [10]University of Louisville, [11]Inova Medical and Skin Cancer Center, [12]Mount Sinai Medical Center, [13]Oregon Health and Science University, [14]Dallas Surgical Group..

Introduction

Many patients with resected stage IIB-III melanoma relapse after surgery. For Stage IIB-C patients, the only FDA-approved treatment is high-dose interferon, which has limited effectiveness and frequent toxicity. New therapies are needed for these high-risk patients.

Seviprotimut-L (formerly POL-103A) is an investigational, polyvalent melanoma vaccine that contains multiple melanoma-associated antigens that are shed from 3 human melanoma cell lines, admixed with alum as the adjuvant. Prior formulations showed promising immunogenicity for T cell and antibody responses. An earlier formulation enhanced survival in a small randomized phase II clinical trial in 38 advanced stage III melanoma patients, in which the recurrence-free survival of the vaccine-treated subjects was over twice that of placebo vaccine-treated subjects (p=0.03) [1].

Part B1 of MAVIS (Melanoma Antigen Vaccine Immunotherapy Study, a three-part, Phase III clinical program), was a multicenter, double-blind, placebo-controlled trial to assess the efficacy of seviprotimut-L, with the primary endpoint of relapse-free survival (RFS) in patients at high risk of recurrence after definitive surgical resection.

Methods

The Melanoma Antigen Vaccine Immunotherapy Study (MAVIS) has 3 parts:

Part A (n = 99): 40 μg and 100 μg of seviprotimut-L vs placebo
- safety & biological activity
- select dose for Part B based on immune (antibody & T-cell) response.

Part B1 (n = 325) seviprotimut-L 40 μg vs placebo (2:1)
- recurrence-free survival

Part B2 (n = 800) seviprotimut-L 40 μg vs placebo (1:1)
- survival and recurrence-free survival co-primary endpoints

For MAVIS Part B1, patients with AJCC v7 stage IIB-III cutaneous melanoma, after surgical resection, age 18-75, ECOG PS 0-1, were randomized 2:1 to seviprotimut-L 40 mcg or placebo, administered intradermally at 4 skin sites every 2 weeks x 5, then monthly x 4, then every 3 months to month 24.

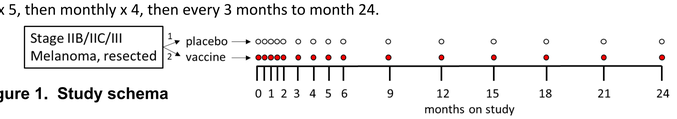


Figure 1. Study schema

Patients were stratified by stage (IIB/C, IIIA, IIIB/C). Target enrollment was 325. The study was powered for assessment of RFS, with target hazard ratio (HR) of 0.625, one-sided alpha 0.10, power 80%. Final data are presented.

Endpoints addressed in this report: *Primary Endpoint*: Recurrence-free survival (RFS);
Secondary Endpoints: Incidence and severity of AEs, overall survival (OS)

Results

347 subjects at 65 centers in the U.S. and Canada were enrolled and randomized. Arms were well-balanced (**Table 1**). Treatment-emergent adverse events (AEs) were similar for seviprotimut-L and placebo patients: there were no grade 4-5 treatment-related AEs and no treatment-related SAEs (**Table 1**).

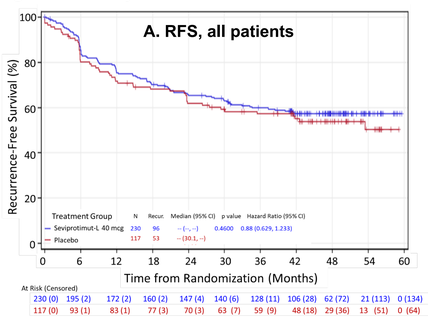
Results (cont.)

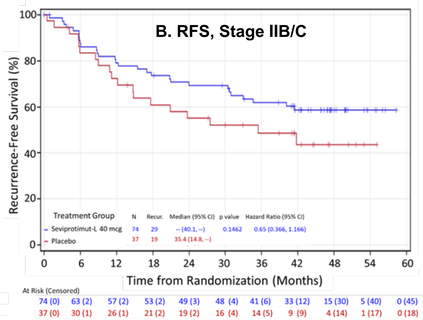
Table 1. Demographics, Enrollment, and adverse events

	Seviprotimut-L	Placebo	Total
N	230	117	347
Age: Median (Q1, Q3)	58 (48, 67)	56 (45, 67)	58 (47, 67)
Race: % White (Caucasian)	99%	100%	99%
Sex: % female / % male	42% / 58%	44% / 56%	43% / 57%
Ethnicity: % Hispanic or Latino	3%	3.4%	3.2%
AEs	96%	97%	96%
Grade 3 AEs	12%	9%	11%
Rx-related AEs	70%	73%	71%
AEs leading to d/c study drug	0.9%	0.9%	0.9%
Rx-related AEs leading to d/c study drug	0.4%	0%	0.3%
Rx = *treatment*			

By intent-to-treat (ITT) analysis overall, RFS was not significantly enhanced for seviprotimut-L but trended higher (**Figure 2A**). However, subgroup analysis for planned randomization stratum stage IIB/IIC revealed trends to longer RFS (HR 0.65 [0.37,1.17], **Figure 2B**) & OS (HR 0.37 [0.13, 1.06], **Figure 3**) with vaccine.

Figure 2. RFS by treatment





Stage IIB/C patients were well-matched by treatment arms (**Table 2**).

Table 2. Demographics: Stage IIB/C

	Seviprotimut-L	Placebo
N	74	37
Age: Median	60	61
Sex: % female	35%	32%
Race: % White	99%	100%
Ethn: % Hispanic	4.1%	2.7%
ECOG PS = 0	86.5%	86.5%
Tumor site: Extremity/ Head-neck/Trunk	34% / 37% / 26%	27% / 32% / 41%

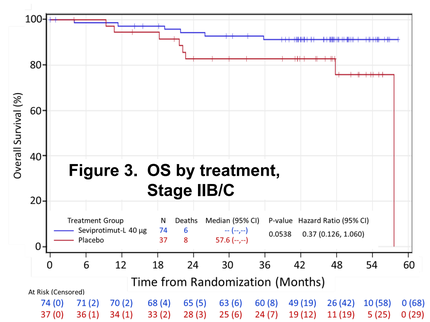
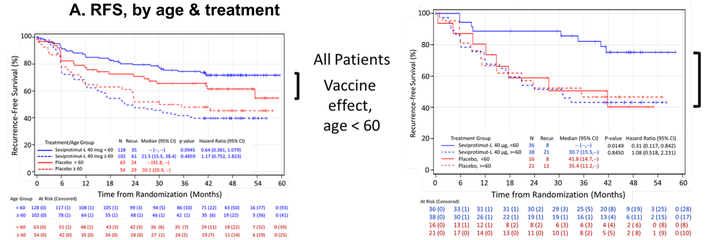


Figure 3. OS by treatment, Stage IIB/C

Age can decrease immune competence; thus, outcomes were assessed by age (<60 and ≥60), for all randomized patients (**Figure 4A**) and the Stage IIB/IIC subset (**Figure 4B**). RFS was longer with vaccine for all patients age <60 (N = 191, HR 0.64, 95% CI [0.38, 1.08]) and among stage IIB/C patients (N = 52, HR = 0.31, 95% CI[0.12, 0.84]). The effect modification p value for age for stage IIB/IIC patients was 0.56.

Figure 4. RFS by age and treatment



In a multivariable RFS model, the HR for the 38 IIB/IIC patients <60 with ulceration was 0.209 (95% CI [0.07,0.61]). The survival HR for the 191 patients <60 was 0.41 (19 deaths, 96% CI [0.33,1.14]) and for the 156 patients ≥ 60, the HR was 0.92 (24 deaths, 95% CI [0.39,2.12]).

Conclusion

Seviprotimut-L treatment is well-tolerated. Subgroup efficacy analyses identified populations who may benefit from Seviprotimut-L: those with AJCC stage IIB/IIC melanoma, those under age 60, and those with ulcerated melanomas. These data support proceeding to the definitive part B2 of the MAVIS phase III trial to test seviprotimut-L for stage IIB/C patients, with stratification by age and ulceration.

Acknowledgements

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Registration: This trial was registered at ClinicalTrials.gov: NCT01546571.
The study was approved by the Ethics Board at each participating institution.

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