A multicenter, double-blind, placebo-controlled trial of seviprotimut-L polyvalent melanoma vaccine in post-resection melanoma patients at high risk of recurrence.

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Abstract

Background: Seviprotimut-L is a vaccine prepared from antigens shed by 3 human melanoma cell lines, administered with alum. Prior formulations showed promising immunogenicity for T cell and antibody responses and improved survival in a small phase II clinical trial. 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: 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 every 2 weeks x 5, then monthly x 4, then every 3 months to month 24. 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 of 0.10, and power 80%.

Results: 347 patients were randomized, and arms were well-balanced. Treatment-emergent adverse events (AEs) were similar for seviprotimut-L and placebo patients. By intent-to-treat (ITT) analysis, RFS was not significantly enhanced for seviprotimut-L in the full study population but trended slightly higher. Analysis of subgroups based on pre-planned stratification suggested enhanced RFS for seviprotimut-L among Stage IIB/IIC patients (HR 0.59, 95% CI[0.33,1.07]). Age has been identified as a cause of decreased immune competence; thus, outcomes were assessed as a function of age as an effect modifier. Effect estimates for age <60 are favorable to seviprotimut-L (HR = 0.61, 95% CI [0.36, 1.05] and HR = 0.239, 95% CI [0.083, 0.69], respectively).

Conclusions: Seviprotimut-L is very well tolerated. Subgroup efficacy analyses identified two populations who may benefit from Seviprotimut-L: those with AJCC stage IIB/IIC melanoma and those under age 60. These data support proceeding to the definitive final part of the MAVIS phase III trial testing seviprotimut-L for stage IIB/C patients, in particular those under age 60.

Introduction

Many patients with resected stage IIB to 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. Thus, 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.

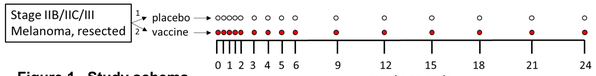

Figure 1. Study schema

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 of 0.10, and power 80%.

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 2**).

Table 1. Demographics

	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%

Results (cont.)

Table 2. Enrollment and adverse events

	Seviprotimut-L	Placebo	Total
N	230	117	347
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 in the full study population, RFS was not significantly enhanced for seviprotimut-L but trended slightly higher (**Figure 2A**).

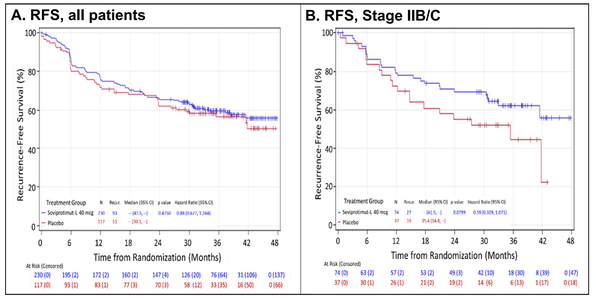

Figure 2. RFS by treatment

However, analysis of subgroups based on pre-planned stratification suggested enhanced RFS for seviprotimut-L among Stage IIB/IIC patients (HR 0.59, 95% CI[0.33,1.07], **Figure 2B**): Stage IIB/C patients were well-matched between arms (**Table 3**). Definitive assessment of overall survival is not yet possible, as there have been too few events, but preliminary data favor seviprotimut-L (HR 0.47 (0.15, 1.46), not shown) for overall survival.

Table 3. Demographics: Stage IIB/C

	Seviprotimut-L	Placebo	Total
N	74	37	111
Age: Median (Q1, Q3)	60 (50, 69)	61 (51, 68)	61 (51, 69)
Sex: % female / % male	35% / 65%	32% / 68%	34% / 66%
Race: % White (Caucasian)	99%	100%	99%
Ethnicity: % Hispanic or Latino	4.1%	2.7%	3.6%
ECOG PS = 0	86.5%	86.5%	86.5%
Tumor location: Extremity/Head-neck/Trunk	34% / 37% / 26%	27% / 32% / 41%	32% / 35% / 31%

Age has been identified as a cause of decreased immune competence[2]; thus, outcomes were assessed as a function of age as an effect modifier. **Figure 3** shows all randomized patients (**Figure 3A**) and Stage IIB/IIC subset (**Figure 3B**) by arm and age, split at <60 versus ≥60. Interaction P values of 0.0641 and 0.0266 (not shown), respectively, provide evidence of effect modification. Effect estimates for age <60 are favorable to seviprotimut-L (HR = 0.61, 95% CI [0.36, 1.05] for all patients and HR = 0.239, 95% CI [0.083, 0.69], for stage IIB/C patients).

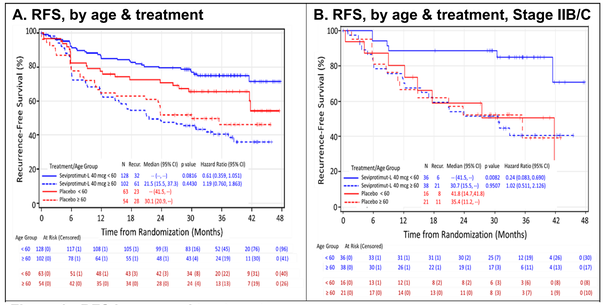

Figure 3. RFS by age and treatment

Conclusion

Seviprotimut-L treatment is very well tolerated. Subgroup efficacy analyses identified two populations who may benefit from Seviprotimut-L: those with AJCC stage IIB/IIC melanoma and those under age 60. These data support proceeding to the definitive final part of the MAVIS phase III trial testing seviprotimut-L for stage IIB/C patients, in particular those under age 60.

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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