Pharmacodynamic changes confirm the mechanism of action mediating SD-101 efficacy, in combination with pembrolizumab, in a phase 1b/2 study in metastatic melanoma (MEL-01)

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Abstract # LB-239

Introduction

DVG-MEL-01 (Keynote-184) is a Phase 1b/2, Open-label, Multicenter, Dose-escalation and Expansion Trial of Intratumoral SD-101 in Combination With Pembrolizumab in Patients With Metastatic Melanoma. The trial is designed to assess the safety, efficacy and pharmacodynamic effect of the combination of SD-101 and pembrolizumab.

SD-101 is a synthetic Class-C CpG-oiligosaccharide that stimulates plasmacytoid dendritic cells (pDCs) through engagement of TLR7/8. This stimulation induces pDCs to release interferon-alpha and mature into efficient antigen-presenting cells, thereby strengthening both innate and acquired immune responses (Figure 1). Pembrolizumab is a PD-1 inhibitor that has been approved for treatment of unseccessful or metastatic melanoma.

Preclinical studies have demonstrated that intratumoral injection of SD-101 in anti-PD-1 nonresponders led to a complete, durable rejection of essentially all injected tumors and a majority of unjected, distant nonresponders. In order to gain insight into the immune mechanisms underpinning the activity of SD-101 and pembrolizumab in the clinical setting and to confirm the MOA of SD-101, biomarker assessments were included in the clinical study design. Data from the dose escalation phase of the trial are presented.

Results

SD-101 induces IFN-regulated genes in the TME and in blood, confirming its predicted mechanism of action

- **Figure 2.** Data show composite scores representing the geometric mean of the induction of IFN-responsive genes. Activity in blood pre-dose and 24 hours after the second dose of SD-101. A majority of subjects demonstrated target engagement (~2 fold activity) at the 1 and 2 mg dose levels with all subjects demonstrating engagement at both 4 and 8 mg doses. Activity and number of genes responding to the 1 mg dose level were comparable to the 2 mg dose level. Data from the 8 mg dose level are not shown due to low patient enrollment and non-representative patient group.

- **Figure 3.** Patients ordered by their change in all tumor lesions. Naive = no prior checkpoint inhibitor therapy. Clinical status reflects best overall response.

- **Figure 4.** Corroborative data from NanoString (A and D) and immunohistochemistry (B, C and F) demonstrating increase CDb T cell infiltration in to the TME. Both patients were anti-PD-L1 naive.

Conclusions

- SD-101 engaged its target, TLR9, as demonstrated by the dose dependent induction of IFN-responsive genes systematically.
- SD-101 induces a sustained, local IFN response in the TME.
- SD-101 in combination with pembrolizumab generated a broad, elevated immune response in the TME by the recruitment of key cell types responsible for tumor control.
- Tumor control is generally correlated with the immune activity independent of prior checkpoint inhibitor therapy.
- Further assessments with biopsies collected at later time points are ongoing.

References


Disclosures

- Study sponsored by Dynavax Technologies Corporation and Merck & Co., Inc., Kanioorth, NJ USA.