Abstract # LB-239

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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Introduction

DV3-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-oligodeoxynucleotide that stimulates plasmacytoid dendritic cells (pDCs) through engagement of Toll-like receptor 9 (TLR9). This stimulation causes 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 unresectable 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 uninjected, distant-site tumors.[1]

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.

Both Innate and Adaptive Immune Responses Are Increased by Intratumoral Injection of SD-101.

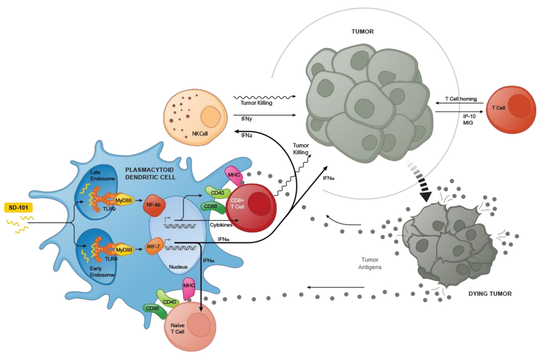

Figure 1. SD-101 induces plasmacytoid dendritic cells (pDCs) to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that boosts natural killer cell cytotoxic activity and induces recruitment of T cells. In addition, SD-101 induces pDC maturation and the ability to cross-present tumor associated antigens, promoting CD8+ T-cell responses.

Methods

The dose escalation phase of this trial was a modified 3 + 3 design with 4 dose levels of SD-101 (1, 2, 4, and 8 mg) in combination with pembrolizumab. SD-101 was injected into a single tumor lesion qw X 4 followed by q3w X 7. Pembrolizumab was administered at 200 mg IV q3w concurrently with SD-101. A total of 22 patients were enrolled in the dose escalation phase.

Peripheral blood was collected immediately before and 24 hours after the second dose and was analyzed by qPCR with a panel of interferon (IFN) responsive genes (GBP-1, IFIT2, CCL2 and MxB) to assess target engagement. The geometric mean of the fold activity for the 4 genes was calculated (composite activity score) for each subject.

Biopsies of the injected tumor were collected at screening (prior to dosing) and post-dosing on Days 29, 85 and 169. Biopsies were analyzed by immunohistochemistry (Acteris, Inc.) and the nCounter® PanCancer Immune Profiling Panel (NanoString Technologies, Inc., Seattle WA) to evaluate the immunophenotype of the tumor environment. Nanostring data were analyzed using the nSolver™ Analysis Software.

Tumor responses were assessed using RECIST v1.1.

Results

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

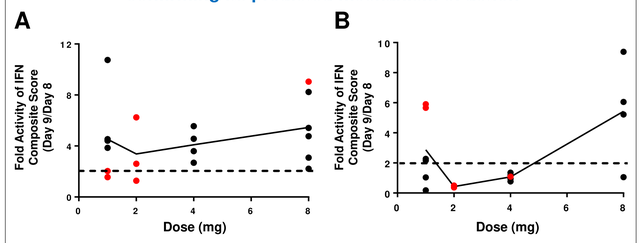

Figure 2. Data show composite scores representing the geometric mean of the induction of IFN responsive genes. A. Activity in blood pre-dose and 24 hours after the second dose of SD-101. A majority of subjects demonstrated target engagement (> 2 fold activity) at the 1 and 2 mg dose levels with all subjects demonstrating engagement at the 4 and 8 mg doses. Activity and number of subjects demonstrating engagement shows dose-dependency. Target engagement is independent of prior anti-PD-1 treatment (naïve patients are indicated in red).
B. Activity in the TME 7 days after the 4th intratumoral injection of SD-101 demonstrates sustained IFN activity in a subset of patients.

Increased immune activity following administration of SD-101 and pembrolizumab in a subset of patients

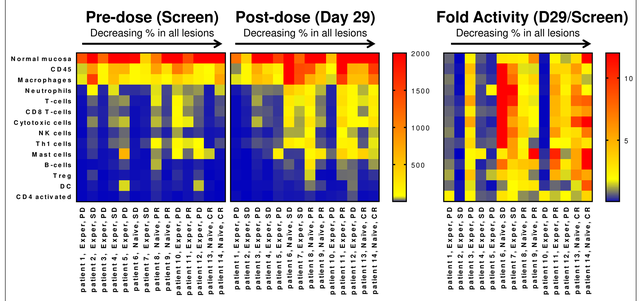

Figure 3. Patients ordered by their change in all tumor lesions. Naïve = no prior checkpoint inhibitor therapy; Exper = prior checkpoint inhibitor therapy. Clinical status reflects best overall response.

CD8 T cell infiltration following administration of SD-101 and pembrolizumab

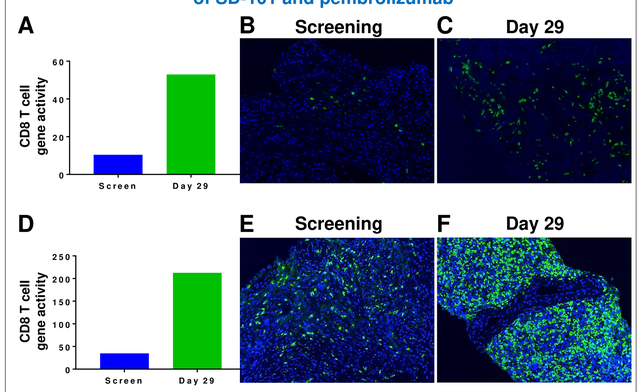

Figure 4. Corroborative data from Nanostring (A and D) and immunohistochemisty (B, C, E and F) demonstrating increase CD8 T cell infiltration in to the TME. Both patients were anti-PD-L1 naïve.

The combination of SD-101 and pembrolizumab induces broad immune activity and a Th1 response in the TME

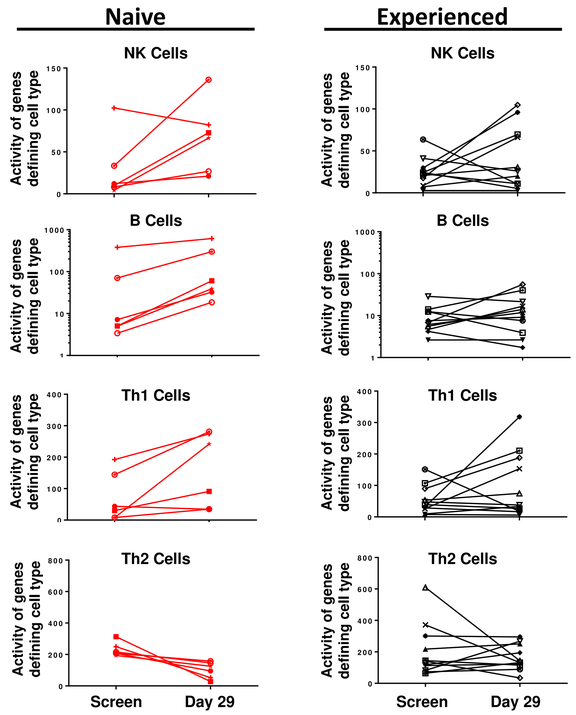

Figure 5. Comparison between checkpoint therapy naïve and experienced patients in the TME prior to dosing and one week after the 4th dose of SD-101 on study day 29.

Tumor response: all target lesions

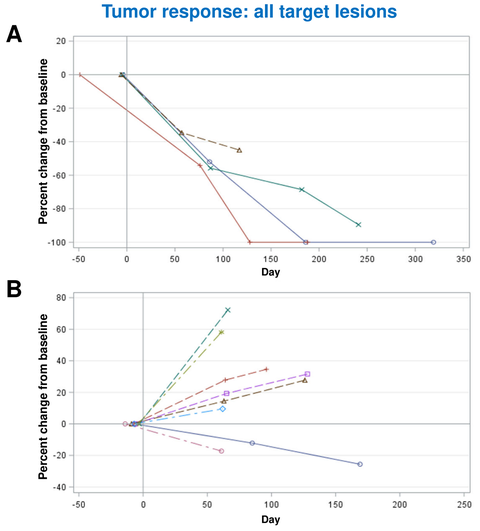

Figure 6. A. Anti-PD-L1 naïve patients. B. Anti-PD-L1 experienced patients.

Correlation of immune response and tumor control

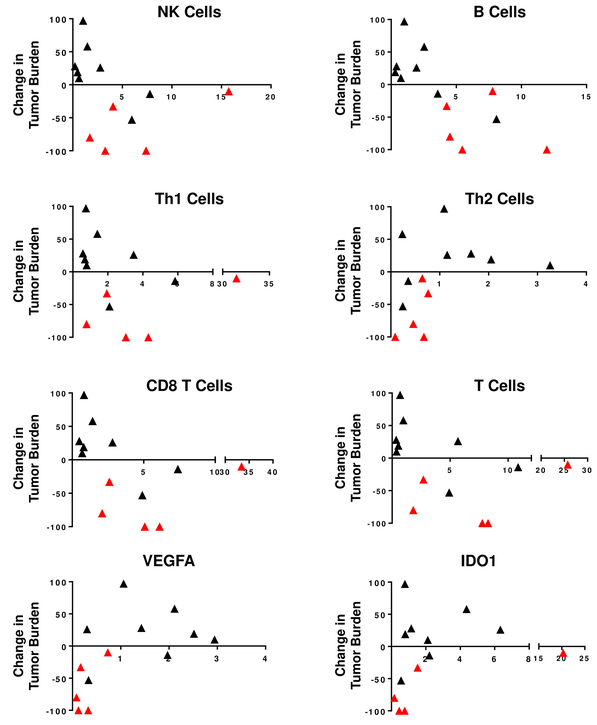

Figure 7. Changes in tumor burden are significantly correlated with increased changes in NK, B cells and CD8 T cells and a decrease in VEGFA ($p < 0.05$, Spearman).

Conclusions

- SD-101 engaged its target, TLR9, as demonstrated by the dose dependent induction of IFN-responsive genes systemically.
- 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

1. Wang et al. Intratumoral injection of a CpG oligonucleotide reverts resistance to PD-1 blockade by expanding multifunctional CD8+ T cells. Proc Natl Acad Sci U S A. 2016 Nov 5;113(46):E7240-E7249).

Disclosures

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