Consistent pharmacodynamics and immunological responses to the TLR9 agonist, SD-101, following intratumoral injection in multiple cancer types

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Introduction

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, and recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

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 in a variety of cancer types.[1, 2]

DV3-LYM-01 was a multicenter phase 1/2 clinical trial that evaluated intratumoral SD-101 and low-dose radiation in patients with untreated indolent lymphoma.[3] SYNERGY-001 (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, or recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).[4]

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 design of the clinical studies. A relatively mature set of data from SYNERGY-001 and comparisons across tumor types is presented.

Figure 1. Both Innate and Adaptive Immune Responses Are Increased by Intratumoral Injection of SD-101.

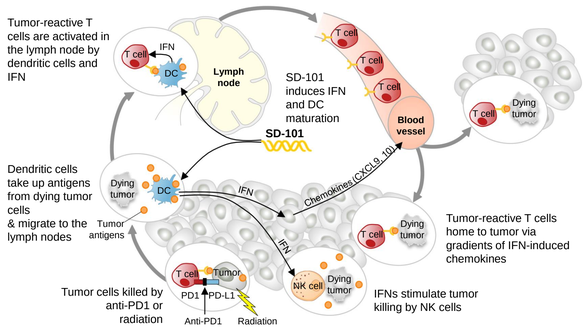


Figure 1. SD-101 induces plasmacytoid dendritic cells (DCs) to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that boosts natural killer cell cytotoxic activity and induces recruitment of T cells. In addition, SD-101 induces pDC maturation and the ability to cross-present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

Methods

To assess target engagement, peripheral blood was collected prior to dosing and 24 hours after a dose of SD-101 and was analyzed by qPCR or Nanostring to evaluate a panel of interferon (IFN) responsive genes. Interferon activity was calculated using a composite of the activity for these IFN responsive genes.

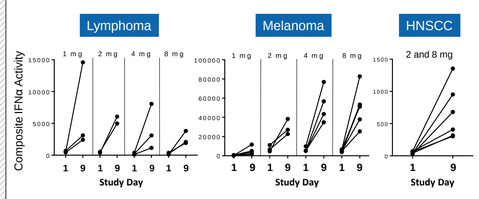
Pharmacodynamic changes in the tumor environment were assessed in fine needle aspirates from DV3-LYM-01 or biopsies from SYNERGY-001. Samples were collected prior to dosing and at various times after dosing. Biopsies were analyzed with the nCounter® PanCancer Immune Profiling Panel (NanoString Technologies, Inc., Seattle WA) to evaluate the immunophenotype of the tumor environment. Nanostring data were analyzed using the nSolver™ Analysis Software.

PD-L1 expression was conducted on biopsies collected during screening (i.e., pre-dose) and assessed using the 22C3 pharmDx assay (Agilent/Dako).

Tumor responses were assessed using RECIST v1.1.

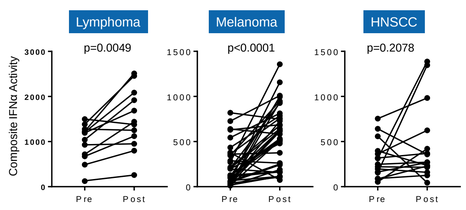
Results

Figure 2. SD-101 Engages its Target, TLR9, in Multiple Cancer Types



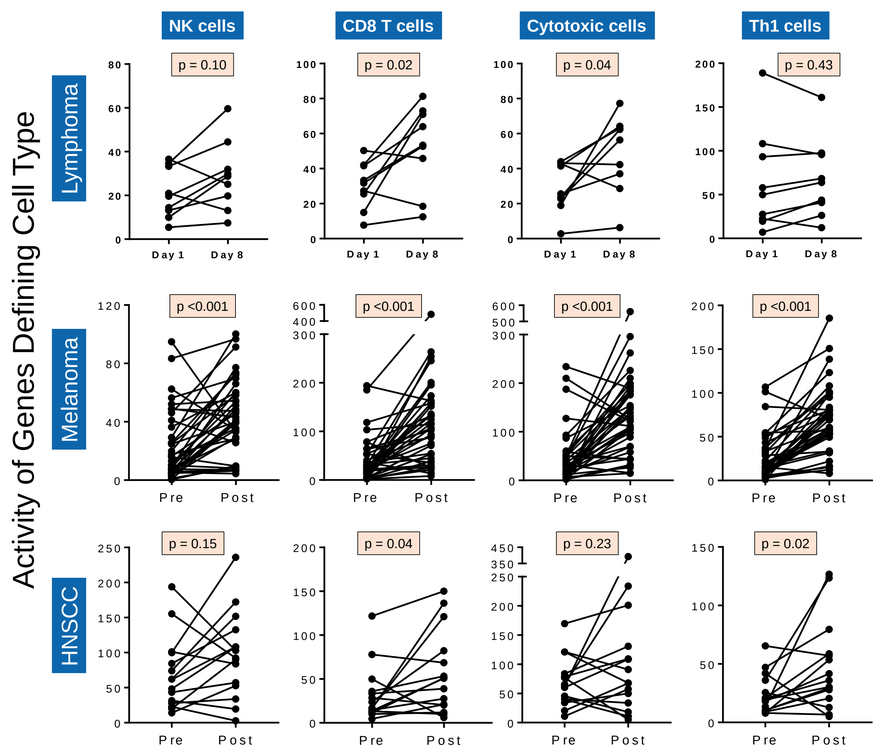
The response to SD-101 was assessed by the induction of IFN-responsive genes in peripheral blood prior to dosing (Day 1) and 24 hours after the second dose of SD-101 injection (Day 9).

Figure 3. SD-101 Induces an Increase in IFN-ɣ Gene Signature in the Tumor Environment in Multiple Cancer Types



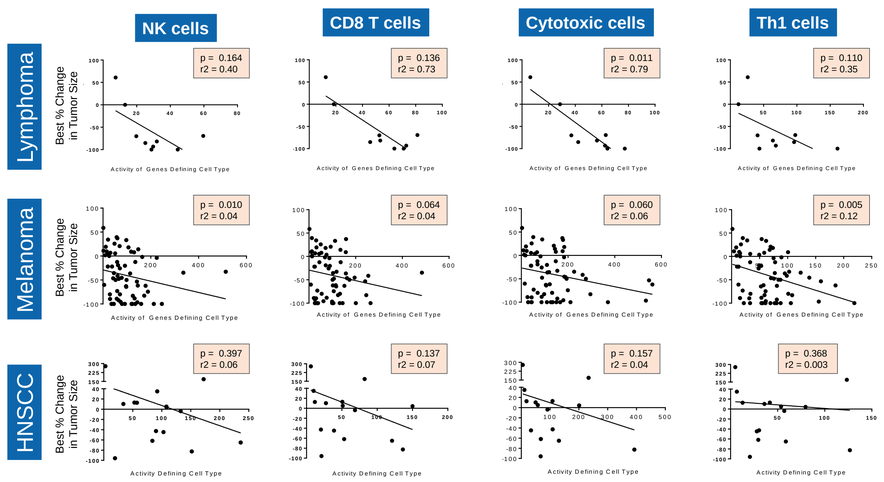
IFNɣ activity based upon a composite score as determined by RNA expression profiling of biopsies using Nanostring. Post-dose samples were collected 1 week after the 4th weekly intratumoral injection of SD-101.

Figure 4. SD-101 Increases Lymphocyte Infiltration into Multiple Tumor Types



Cell type profile determined by RNA expression profiling of pre- and post-dose biopsies by Nanostring.

Figure 5. Lymphocyte Infiltration Correlates with Changes in Tumor Burden



Reduction in tumor size inversely trends with infiltration of lymphocytes. P-values were determined with Spearman correlation.

Table 1. Clinical Responses to the Combination of SD-101 and Pembrolizumab Occur in Both PD-L1 Positive and Negative Tumors

Melanoma — Anti-PD-1/L1 Naïve — 2 mg

Subject	BOR	TPS
1	CR	0
2	CR	0
3	CR	0
4	CR	0
5	PR	0
6	PR	0
7	PR	0
8	PR	0
9	PR	0
10	PR	0
11	PR	0
12	SD	0
13	PD	0
14	DC	0
15	PR	<1
16	CR	1
17	PR	1
18	PR	1
19	PR	1
20	PD	1
21	PR	3
22	SD	3
23	PR	5
24	SD	5
25	PD	5
26	PR	10
27	PR	30
28	PR	30
29	PR	35
30	PR	45
31	PR	50
32	DC	75
33	PR	80
34	PR	95

Melanoma — Anti-PD-1/L1 Naïve — 8 mg

Subject	BOR	TPS
35	PR	0
36	PR	0
37	PR	0
38	SD	0
39	SD	0
40	SD	0
41	SD	0
42	irAE	0
43	PD	0
44	PD	0
45	DC	0
46	DC	0
47	PR	<1
48	PD	<1
49	PD	<1
50	PD	1
51	PR	2
52	SD	3
53	CR	5
54	PR	10
55	PR	20
56	PR	25
57	PR	30
58	SD	30
59	PD	30
60	SD	80
61	CR	90
62	PR	90

Melanoma — Prior anti-PD-1/L1 Therapy

Subject	Dose	BOR	TPS
63	8	PR	0
64	4	SD	0
65	4	SD	0
66	8	SD	0
67	1	SD	0
68	8	SD	0
69	4	PD	0
70	8	PD	0
71	8	PD	0
72	8	PD	0
73	8	PR	<1
74	8	SD	<1
75	4	PD	<1
76	8	clPD	<1
77	8	SD	1
78	8	SD	1
79	8	PD	1
80	8	PD	1
81	8	CR	3
82	8	PR	10
83	8	PR	10
84	1	PD	60
85	8	PD	90

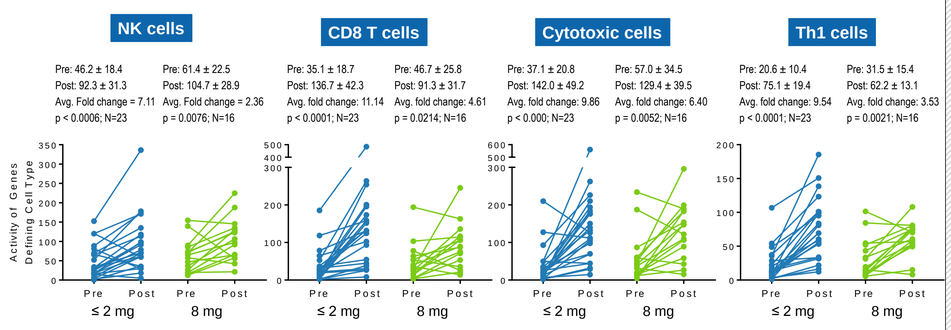
Head and Neck — Anti-PD-1/L1 Naïve — 8 mg

Subject	BOR	TPS
1	PD	0
2	PD	0
3	PR	<1
4	SD	2
5	PD	5
6	PD	10
7	PD	10
8	PD	15
9	PR	30
10	PR	40
11	PD	60
12	PR	90
13	PD	95

BOR = best overall response, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, DC = discontinued prior to first scan, irAE = immune-related adverse event, iCPD = immune confirmed progressive disease.

Figure 6. Dose-related Changes in Lymphocyte Infiltration in the Tumor Microenvironment

The ORR in anti-PD-1/L1 naïve patients receiving 2 mg per dose is 70% when compared to patients receiving 8 mg per dose who have an ORR of 48% (ESMO 2018, LBA45). Trends in immune infiltrate changes between the 2 mg and 8 mg groups are consistent with the higher response rate in the 2 mg group.



Lymphocyte infiltration into the tumor as determined by RNA-expression profiling by Nanostring. Values above the graphs represent the means and 95% confidence intervals

Conclusions

- SD-101 engaged its target, TLR9, across multiple tumor types as demonstrated by the induction of IFN-responsive genes systemically
- Increases in Th1 cells and an IFN-γ–related gene expression signature is consistent with the induction of a type I IFN response in the tumor microenvironment
- Increases in recruitment of key cell types responsible for tumor control are orchestrated by SD-101 alone in lymphoma and in combination with pembrolizumab in melanoma and head and neck tumor lesions.
- Tumor control is generally correlated with increased immune activity following SD-101 treatment
- Antitumor responses occurred in patients with negative or positive baseline PD-L1 expression
- SD-101 shows strong parallels in the pharmacodynamic responses and mechanism of action across three tumor types
- Trends in immune infiltrate changes between the 2 mg and 8 mg groups are consistent with the higher response rate in the 2 mg group

References

1. Wang, S, Campos, J, et al. Intratumoral injection of a CpG oligonucleotide reverts resistance to PD-1 blockade by expanding multifunctional CD8+ T cells. (2016) Proc Natl Acad Sci U S A. 13(46):E7240-E7249.
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Disclosures

- This study was sponsored by Dynavax Technologies Corporation in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA.