CT139

Durability of Responses to SD-101 in Combination With Pembrolizumab in Advanced Metastatic Melanoma: Results of a Phase 1b, Multicenter Study

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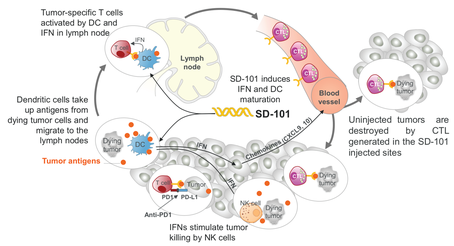
BACKGROUND

- 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, strengthening both innate and acquired immune responses (**Figure 1**).[1]
- Pembrolizumab is a PD-1 inhibitor that has been approved for treatment of unresectable or metastatic melanoma.[2]
- Preclinical studies in mice demonstrated that intratumoral injection of SD-101 in anti-PD-1 nonresponders led to a complete and durable rejection of injected tumors and a majority of uninjected, distant-site tumors.[3]
- In patients with low-grade non-Hodgkin's lymphoma, direct injection of SD-101 into tumors in combination with low dose radiation not only activated local immune responses, but also a systemic (abscopal) effect.[4]
- Previously, we presented the best overall response in evaluable melanoma patients[5]:
  - Patients naïve to anti-PD-1 therapy: ORR = 100% (2 CR, 5 PR, 2 NE)
  - Patients who previously received anti-PD-1 therapy: ORR = 17% (0 CR, 2 PR, 5 SD, 5 PD, 1 NE)

Figure 1. Both Innate and Adaptive Immune Responses Are Increased by Intratumoral Injection of SD-101. SD-101 engages TLR9 on plasmacytoid dendritic cells (pDCs) to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that is able to boost natural killer cell cytotoxic activity and induce recruitment of T cells to the tumor microenvironment. In addition, SD-101 induces DC maturation and the ability to cross-present tumor associated antigens, inducing CD8+ T cell responses.

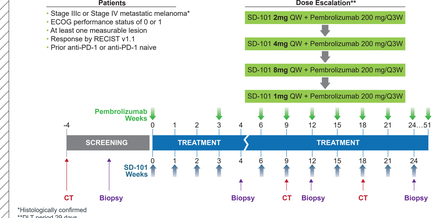


CTL= CD8+ T cell; DC = dendritic cell; IFN = interferon; NK = natural killer.

METHODS

- This is an ongoing, phase 1b/2, open-label, multicenter, dose-escalation and dose expansion study (NCT02521870). Results from the Phase 1b portion of the study are presented here.
- Safety was assessed by adverse events, immune related adverse events, and serious adverse events.
- Response was evaluated by the investigator according to RECIST v1.1.[6] Assessments were based on radiographic images (either CT or MRI) at baseline, every 9 weeks until Day 379, and every 12 weeks thereafter until confirmed progression or initiation of new anti-cancer treatment.
- To assess pharmacodynamic effects, biopsies of the injected tumor were collected at screening (prior to dosing) and post-dosing on Days 29, 85 and 169 (data from Day 29 are presented here). Biopsies were analyzed by 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.
- Baseline PD-L1 expression was measured by immunohistochemistry using the Dako 22C3 antibody in a validated assay.

Figure 2. Study Design



*Histologically confirmed
**DLT period 29 days

RESULTS

Table 1. Demographics and Baseline Characteristics

Characteristics	Naïve to Prior Anti-PD-1/L1 Therapy (N=9)	Received Prior Anti-PD-1/L1 Therapy (N=13)	Total (N=22)
Male, n (%)	6 (67)	9 (69)	15 (68)
Age (years)			
Median	67	64	64
Min, Max	46, 78	34, 77	34, 78
ECOG PS = 0, n (%)	7 (78)	9 (69)	16 (73)
Stage at Screening, n (%)			
IIIC	0	3 (23)	3 (14)
IVM1a	4 (44)	0	4 (18)
IVM1b	2 (22)	2 (23)	4 (18)
IVM1c	3 (44)	8 (54)	11 (50)
Baseline LDH (U/L), mean (SD)	397 (533)	292 (198)	335 (365)
sULN, n (%)	8 (89)	8 (62)	16 (73)
0/1/2/x3 prior lines of therapy, n	4/4/1/0	0/1/4/8	4/5/5/8
Responded to prior anti-PD-1/L1, n (%)	NA	3 (24)	NA
Prior anti-CTLA4, n (%)	4 (44)	12 (92)	16 (73)

ECOG PS = Eastern Cooperative Oncology Group performance status; NA = not applicable; SD = standard deviation; ULN = upper limit of normal.
Patients may have >1 site of tissue involvement.

Table 2. Overview of Safety

Event, n (%)	Total (N=22)
All TEAEs	22 (100)
Grade 3–4	14 (64)
irAEs	3 (14)
Treatment-related AEs	21 (96)
Grade 3–4	7 (32)
Chills	3 (14)
Myalgias	3 (14)
Injection-site pain	3 (14)
Fatigue	2 (9)
Headache	2 (9)
TEAEs leading to d/c of either or both drugs	5 (23)
SAEs	9 (41)
Death	0

AE = adverse event; d/c = discontinuation; irAE = immune-related adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 3. Efficacy

	Anti-PD-1 Naïve (N=9) % (n/N)	Anti-PD-1 Experienced (N=13) % (n/N)
ORR (ITT)	78% (7/9)	15% (2/13)
Median time to response (weeks) (range)	18 weeks (8–44 weeks)	14 weeks (9–18 weeks)
Duration of response		
Median (range)	NR	4 months (2–6 months)
Ongoing responses at 18 months	86% (6/7)	0
Progression free survival		
Median	NR	2 months
12-month	88% (7/8)	8% (1/13)
Overall survival		
12-month	89% (8/9)	UNK

NR = not reached; UNK = unknown.

Figure 3. Duration of Response and Subject Status by Prior Anti-PD-1/L1 Treatment

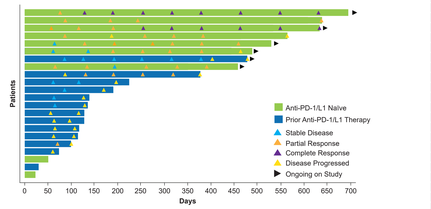


Figure 4. Percent Change From Baseline in Tumor Burden (All Target Lesions) in Patients Who Had No Prior Anti-PD-1/L1 Therapy (*left*) and Who Had Prior Anti-PD-1/L1 Therapy (*right*)

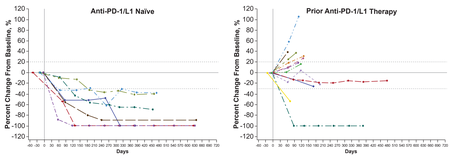


Figure 5. Antitumor Response Occurred in Both Injected and Non-Injected Target Lesions

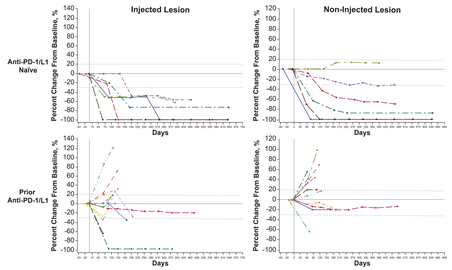


Figure 6. Correlation of Response Between Injected and Non-Injected Lesions (All Phase 1b Patients)

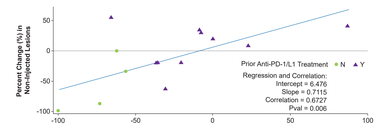


Figure 7. Antitumor Response in Anti-PD-1/L1 Naïve Patients by Organ System

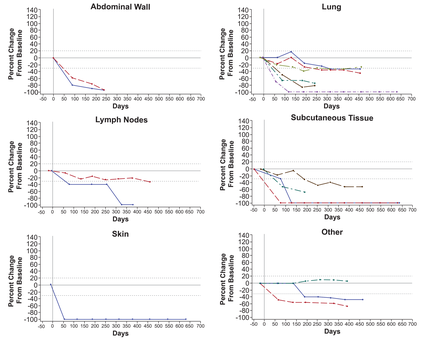
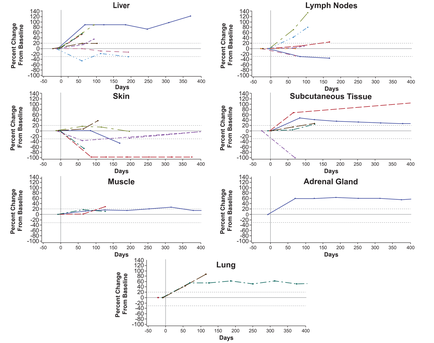


Figure 8. Antitumor Response in Patients Who Had Prior Anti-PD-1/L1 Therapy by Organ System



Biomarker Analyses

Table 4. SD-101 in Combination with Pembrolizumab Led to Durable Responses in Patients With Negative or Positive Tumor PD-L1 Expression at Baseline. Data sorted by PD-L1 expression. PD-L1 expression was assessed by immunohistochemistry using a validated assay with the DAKO 22C3 antibody.

Subject ID	Prior Anti-PD-1/L1 Therapy	BOR	PD-L1 Expression (%)	TTP (day)
104-203	Yes	SD	0	120
104-205	Yes	SD	0	127
101-005	No	CR	0	Ongoing (743+)
110-401	No	PR	0	463
104-202	Yes	PD	<1	64
110-305	Yes	PR	10	64
110-404	No	PR	30	Ongoing (463+)
105-406	Yes	PD	60	64

BOR=best overall response; TTP=time to disease progression

Figure 9. Increased Post-Dose Immune Activity in the Tumor Microenvironment is Associated With a Better Clinical Response. A composite score of the fold change (Day 29/ screening) in relevant immune cell types binned according to best overall response. Cell types included NK cells, CD8 T cells, dendritic cells, CD45, T cells cytotoxic cells, Th1 cells and CD4 activated cells.

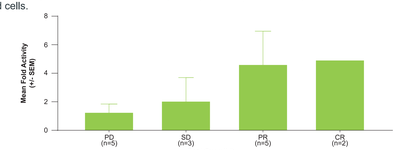
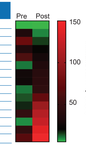


Figure 10. Increased Immune Cellularity Is Associated With a Durable Clinical Response and Is Independent of Pre-Existing Immune Infiltration. Heat map of immune activity score sorted by post-dose activity, with time to disease progression (TTP). The immune activity score is a composite of relevant immune cell types including NK cells, CD8 T cells, DC, CD45, T cells, cytotoxic cells, Th1 cells and CD4 activated cells.

Pt ID	Prior Anti-PD-1/L1 Therapy	BOR	TTP (day)
104-202	Yes	PD	64
104-203	Yes	SD	120
105-406	Yes	PD	64
104-205	Yes	SD	127
102-303	Yes	PD	64
104-201	Yes	PD	64
102-301	Yes	PD	67
102-004	No	PR	Ongoing (788+)
106-204	No	CR	Ongoing (652+)
101-403	Yes	SD	463
101-005	No	CR	Ongoing (743+)
101-405	Yes	PR	358
110-401	No	PR	463
110-305	Yes	PR	85
110-404	No	PR	Ongoing (484+)



CONCLUSIONS

- The combination of SD-101 and pembrolizumab is well tolerated.
  - Most common adverse events related to SD-101 treatment were transient, mild to moderate flu-like symptoms (fatigue, malaise, chills, headache and myalgia) and injection-site reactions that responded to over-the-counter medications.
  - No increase in the frequency of immune-related adverse events over individual monotherapies reported in previous studies,[7,8] nor was there evidence of a unique safety signal for the combination.
- Antitumor responses occurred in patients naïve to or who had received prior anti-PD-1/L1 therapy.
  - Responses were durable in patients who were naive to anti-PD-1 therapy, with the 12-month PFS higher than with pembrolizumab monotherapy.[7]
  - Responses were observed in the injected lesion and in distant lesions, including visceral metastases in the lung.
  - Responses in the injected lesion correlated with responses in non-injected lesions.
  - Patients with durable responses included those with negative or positive baseline PD-L1 expression.
- Clinical responses were supported by mechanistic data consistent with the anticipated activity of SD-101.[2]
  - The combination induced immune stimulation in both patient groups.
  - Increased immune activity was variable, but was generally associated with increased clinical response.
  - Increase in immune cell infiltrate was independent of baseline infiltration.
- These early data demonstrate that the combination of SD-101 and pembrolizumab was well tolerated, induced immune activation at the tumor site, and resulted in durable tumor responses. Combining an intratumoral TLR9 innate immune stimulant with PD-1 blockade can potentially increase clinical efficacy with minimal additional toxicity relative to PD-1 blockade alone.

REFERENCES

1. Guiducci et al. *J Exp Med*. 2006;203(8):1999-2008.
2. Merck & Company, Inc. KEYTRUDA (pembrolizumab). Prescribing information. 2016. Whitehouse Station, NJ.
3. Wang S et al. PNAS 2016;113:E7240-E7249.
4. Levy R et al. ASH 2016. Abstract 2974.
5. Leung ACF et al. ASCO 2017. Abstract 193149.
6. Eisenhauer EA et al. *N Eur J Cancer* 2009;45:228–47.
7. Robert C et al. *New Engl J Med* 2015;372:2521-2532.
8. Specenier P. *Expert Opin Biol Ther*. 2017;17(6):765-780.

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